Formal Total Synthesis of Manzacidin B via Sequential Diastereodivergent Henry Reaction

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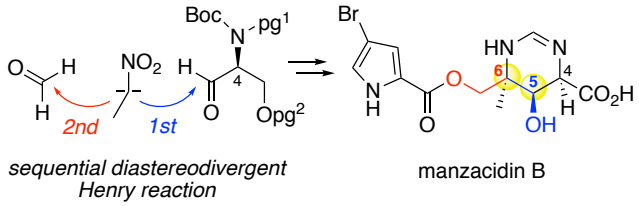
Supporting Information



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.

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] Therefore, a number of synthesis, targeting manzacidins A and C,[7] have been developed based on variety of methodologies constructing β,β-disubstituted β-aminoalcohol[8] moiety composed of the nitrogen-containing tetrasubstituted carbon.

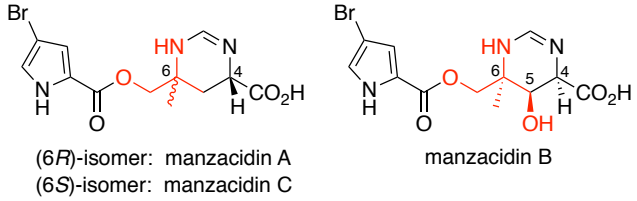
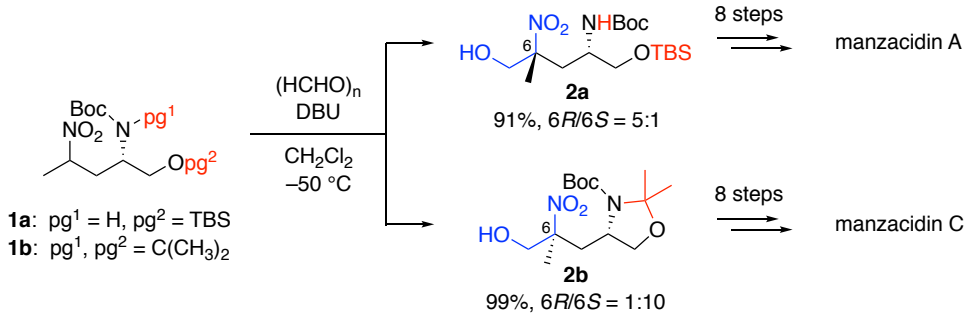


Figure 1. Manzacidins A, B and C



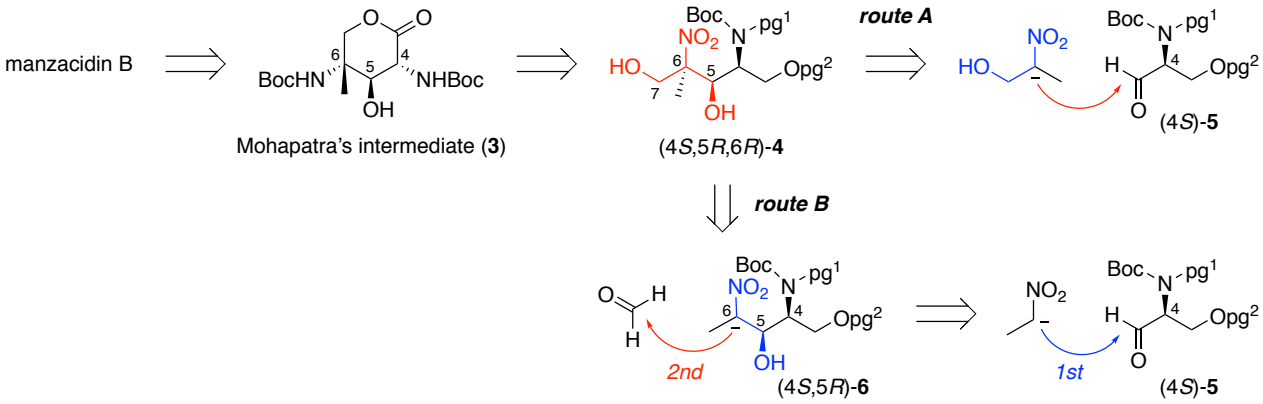
Scheme 1. Synthesis of manzacidins A and C based on diasterodivergent Henry reaction (our previous work)[9]

Recently, we also have achieved stereoselctive synthesis of manzacidins A and C based on Henry reaction of chiral nitroalkane **1**.[9,10] In this study, we have found that in the key Henry reaction, the use of different protecting groups diastereodivergently produces both isomers of tertiary nitroalkanes **2a** and **2b**, which could be converted to manzacidins A and C respectively (Scheme 1).

In contrast to manzacidins A and C, only two groups have reported the stereoselective synthesis of manzacidin B,[11] which has an additional hydroxy group at C5 position as a part of three contiguous stereogenic center and a characteristic β,β-disubstituted γ-hydroxy-β-aminoalcohol structure. Considering this β-aminoalcohol motif as a Henry retron, we envisioned that this natural product could also be synthesized via Henry reaction as in our synthesis of manzacidin A and C.[9] Herein, we report a formal total synthesis of manzacidin B based on the substrate-controlled diastereoselective Henry reaction.

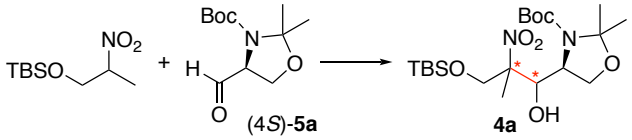
Scheme 2 shows our plan for the synthesis of manzacidin B. We set Mohapatra's synthetic intermediate **3**[11c] as the target compound, since **3** can be readily converted to manzacidin B. Compound **3** is retrosynthetically converted to tertiary β,β'-dihydroxynitroalkane (4*S*,5*R*,6*R*)-**4** via 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 center 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 stepwisely controlled. Since the route A is more straightforward than the route B, our study commenced with an investigation of the Henry reaction in route A.

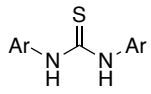
RESULTS AND DISCUSSION



Scheme 2. Retrosynthesis of manzacidin B

Table 1. Henry Reaction of 7 with (4*S*)-5a



catalyst, conditions, results		
DBU (90 mol%)	THF[a] –50 °C, 19 h	22% yield[c] dr 1.6:1.6:1.2:1[d]
Et_3N +  [Ar = 3,5-$(CF_3)_2C_6H_3$] (30 mol% each)	solvent-free[b] 0 °C, 2 h	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 ^1H NMR analysis.

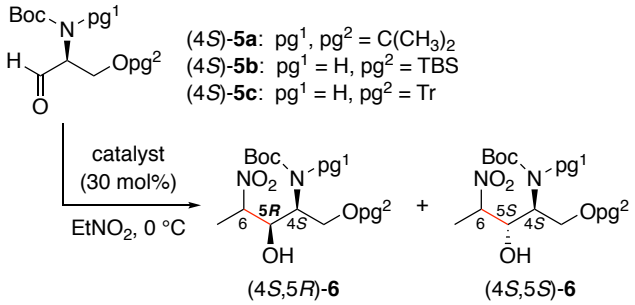
Table 1 shows our study on the Henry reaction of TBS-protected 1-hydroxy-2-nitropropane with (4*S*)-**5a**.[12] When the reaction of the nitroalkane (3 equiv) with (4*S*)-**5a** was conducted in the presence of DBU (90 mol%),[10] a significant amount of the nitroalkane was decomposed, and only 22% yield of adduct **4a** was obtained as a mixture of four diastereomers (dr 1.6:1.6:1.2:1). 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).

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*)-**6**, a 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%),[13]

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%),[14] 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).

Although the stereoselectivity at C5 was high in the first Henry reaction, adduct **6c** was obtained as a ca. 1:1 diastereomeric mixture at C6. However, we did not make efforts to control the C6-stereochemistry at this stage, since it would be lost at the second Henry reaction. C6-diastereomers of **6c** (named as **6ca** and **6cb**) were separable on silica gel column chromatography, and **6ca** and **6cb** were isolated in respective yields of 44 and 46%.[15]

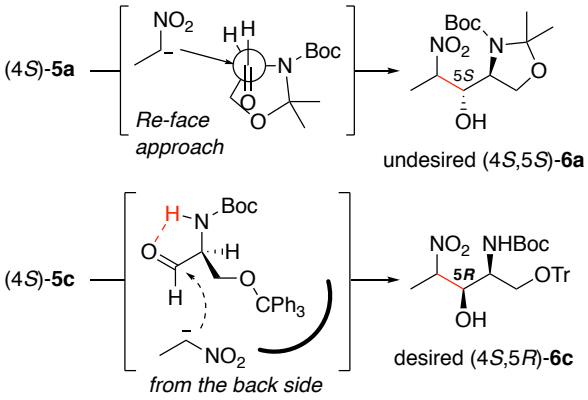
Table 2. Investigation of the 1st Henry Reaction[a]



entry	5	catalyst	yield (%)[b]	5*R*/5*S*[c]
1[d]	**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[e,f]	**5c**	$^{n}Bu_4PBr$, KF	**6c**, 90	**11**:1

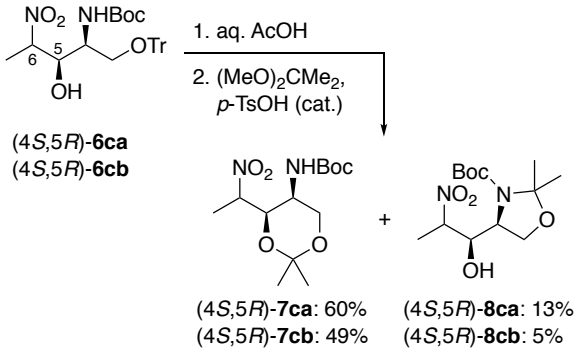
[a]The reaction of (4*S*)-**5** (0.2 mmol) was conducted in the presence of a catalyst (30 mol%) in $EtNO_2$ at 0 °C for 1.5–24 h. [b]Isolated yield. [c]Evaluated by ^1H NMR analysis. [d]The reaction was conducted with $EtNO_2$ (5 equiv) in the presence of KF (20 mol%) in *i*-PrOH–benzene (10:1). [e]The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

Here we propose mechanisms for the first Henry reaction with (4*S*)-**5** (Scheme 3). The stereoselectivity of the reaction with (4*S*)-**5a** could be explained by the polar Felkin–Anh model[16] 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).[17] 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 was considered to be the fact that these aprotic and sterically hindered countercations did not disrupt the formation of the intramolecular hydrogen bonding.



Scheme 3. Proposed transition-state assemblies

Before the second Henry reaction, 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 4). 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 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%.



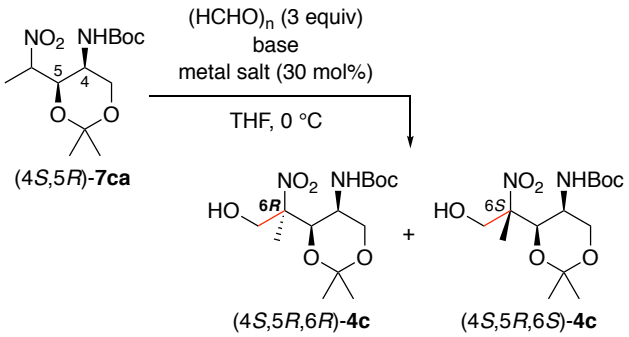
Scheme 4. Synthesis of secondary nitroalkane (4*S*,5*R*)-7c

With chiral nitroalkane (4*S*,5*R*)-**7c** in hand, we investigated the second Henry reaction constructing the nitrogen-containing tetrasubstituted carbon (Table 3). Since 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 results, 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).

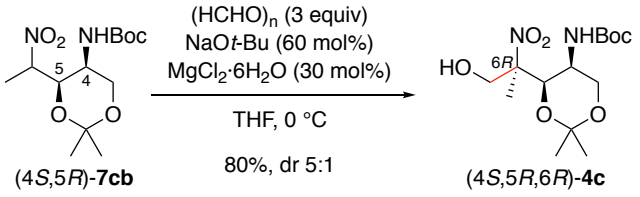
Diastereomeric (4*S*,5*R*)-**7cb** was also converted to desired (4*S*,5*R*,6*R*)-**4c** under the same conditions in 80% yield with a 5:1 diastereomeric ratio (Scheme 5).

Table 3. Investigation of the 2nd Henry reaction[a]



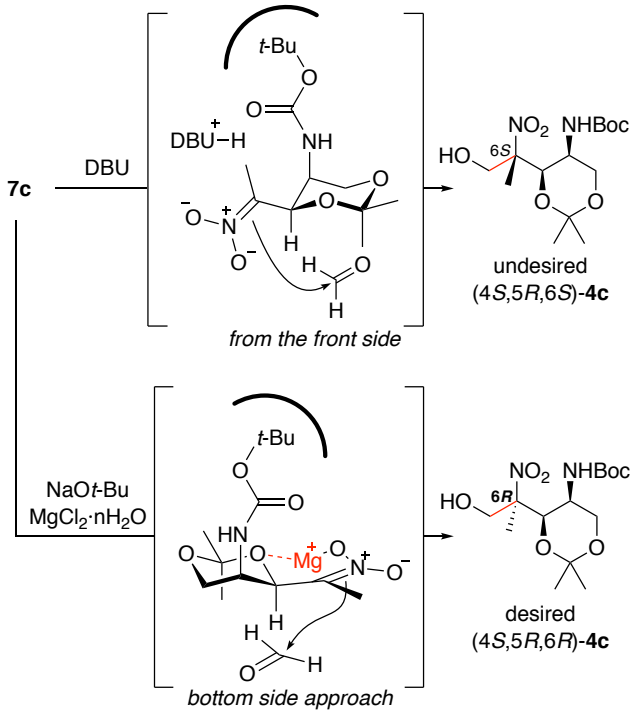
entry	base	metal salt	yield (%)[b]	6*R*/6*S*[c]
1[d]	DBU (200 mol%)	—	89	1:>**20**
2	NaO*t*-Bu (30 mol%)	—	81	4.0:1
3	NaO*t*-Bu (60 mol%)	$BaCl_2$	91	3.7:1
4	NaO*t*-Bu (60 mol%)	$CaCl_2$	81	4.3:1
5[e]	NaO*t*-Bu (60 mol%)	$MgCl_2{\cdot}6H_2O$	83	4.5:1
6[f]	NaO*t*-Bu (60 mol%)	$MgCl_2{\cdot}6H_2O$	92	**6.0**:1
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 five minutes.



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

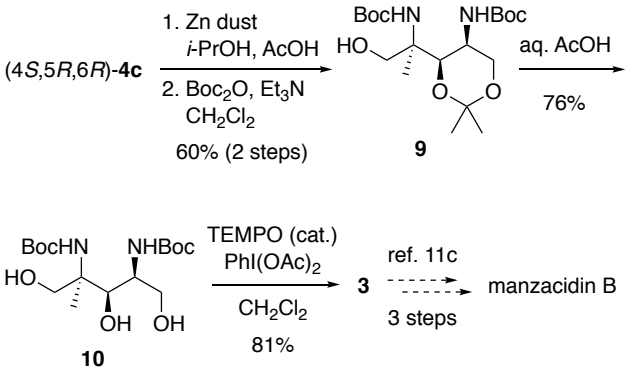
The diastereoselectivity of the second Henry reaction could be explained with the following models (Scheme 6). In the DBU-promoted reaction, the nitronate intermediate would have a conformation in which the allylic strain is the smallest in energy (upper scheme). The *N*-Boc group would shield the back 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, 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 6. Proposed transition state-assemblies

With compound (4*S*,5*R*,6*R*)-**4c**, which bears all of the stereogenic center 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 7). Reduction of the nitro group of (4*S*,5*R*,6*R*)-**4c** using Zinc dust[18] 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 $PhI(OAc)_2$[11c] in 81% yield. The spectral data of synthetic **3** were identical to the reported data.[11c] Thus, our diastereoselective Henry reaction-based synthetic approach allowed us to achieve a stereoselective formal total synthesis of manzacidin B.



Scheme 7. Formal total synthesis of manzacidin B

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** has 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 C5- and C6-diastereomers of manzacidin B diastereoselectively. Since the substrate-controlled reaction sequence is practical and economical, it should provide us an opportunity for the scalable production of manzacidin B.

EXPERIMENTAL SECTION

General Experimental Information. All reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents, unless noted. All reagent and starting material 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. ^1H 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 = qualtet; 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 digital polarimeter Horiba SEPA-300 using a 3.5 mm × 0.5 dm pyrex cell. TLC analyses were performed on Merck precoated TLC plates (silica gel 60 F_{254} 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 (4*S*)-5a.

*tert-Butyl (4S)-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 Mg_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 **4a** (69.7 mg, 0.155 mmol, 70%) as a diastereomeric mixture (relative stereochemistry was not determined).

Diastereomeric ratio of **4a** (1.7:1.6:1.1:1) was determined by ^1H 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): colorless oil; IR (film) 3493, 3020, 2931, 2858 1693, 1548, 1392, 1367, 1255, 1215, 840, 756 cm^{-1}; ^1H 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) were 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 Mg_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 **4a** (29.1 mg, 64.9 μmol, 22%) as a diastereomeric mixture. Diastereomeric ratio (1.6:1.6:1.2:1) was determined by ^1H NMR as above.

The 1st Henry reaction.

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

*(4R)-tert-Butyl-4-((1S)-hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4S,5S)-**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 same temperature for 24 h, the mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite®. After 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)

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). 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 minor diastereomer were described): colorless oil; IR (film) 3440, 3021, 2981, 1690, 1651, 1552, 1367cm^{-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 ((2S,3R)-1-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-4-nitropentan-2-yl)carbamate [(4S,5R)-**6b**] and*

*tert-Butyl ((2S,3S)-1-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-4-nitropentan-2-yl)carbamate [(4S,5S)-**6b**]*

To a solution of (4*S*)-**5b**[19] (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 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*S* =2:1). **6ba** and **6bb** are stereoisomers at C6, but relative stereochemistry was not determined.

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). 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{^{1}H} 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 ((2S,3R)-3-Hydroxy-4-nitro-1-(trityloxy)pentan-2-yl)carbamate [(4S,5R)-**6c**] and*

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

To a solution of (4*S*)-**5c**[20] (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 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.

Diastereomeric ratio of **6cb** (5*R*/5*S* =5:1) was determined by ^{1}H NMR analysis comparing the characteristic peaks observed at δ 5.06 (d, 1H, 5*R* isomer) and δ 4.96 (d, 1H, 5*S* isomer).

6ca: Colorless solid; mp 62–64 °C; $[\alpha]^{27}_D$ –30.2 (c 0.50, $CHCl_3$); IR (film) 3428, 3059, 2978, 2880, 1713, 1549, 1165, 750 cm^{-1}; ^{1}H 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{^{1}H} 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}; ^{1}H 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{^{1}H} 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 ((4R,5S)-2,2-Dimethyl-4-(1-nitroethyl)-1,3-dioxan-5-yl)carbamate [(4S,5R)-**7c**] and*

*(4S)-tert-Butyl-4-((1R)-1-hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4S,5R)-**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 mol) was added at ambient temperature. After being stirred for 3.5 h at 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; $[\alpha]^{27}_D$ –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; $[\alpha]^{27}_D$ –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 ((4R,5S)-2,2-Dimethyl-4-(1-nitroethyl)-1,3-dioxan-5-yl)carbamate [(4S,5R)-**7cb**] and*

*(4S)-tert-Butyl-4-((1R)-1-hydroxy-2-nitropropyl)-2,2-dimethyloxazolidine-3-carboxylate [(4S,5R)-**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; $[\alpha]^{27}_D$ –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{^{1}H} 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; $[\alpha]^{27}_D$ –26.1 (c 0.35, $CHCl_3$); IR (film) 3337, 2980, 2942, 1715,1694, 1557, 1393, 1165, 872 cm^{-1}; ^{1}H 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{^{1}H} 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.

The 2nd Henry reaction.

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

*tert-Butyl ((4R,5S)-4-((S)-1-Hydroxy-2-nitropropan-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl)carbamate [(4S,5R,6S)-**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 five minutes (*Note: the appearance of $MgCl_2 \cdot 6H_2O$, which was initially a*

colorless solid, was changed to white solid during this step). After cooling down to ambient temperature, the flask was purged with nitrogen. To the flask was added NaO*t*-Bu (10.6 mg, 0.110 mmol) and THF (0.500 mL), and resulting mixture was stirred at ambient temperature for 30 minutes 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 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 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%, 6*R*/6*S* = 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; $[\alpha]^{24}_D$ –16.2 (c 0.50, $CHCl_3$); IR (film) 3445, 2982, 2942, 1694, 1549, 1505, 1368, 1163, 1099, 764 cm^{-1}; ^1H 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; $[\alpha]^{24}_D$ –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 ((4R,5S)-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 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 dissoleved 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; $[\alpha]^{23}_D$ –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 ((2R,3R,4S)-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 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; $[\alpha]^{20}_D$ –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 ((3R,4R,5R)-4-Hydroxy-5-methyl-2-oxotetrahydro-2H-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 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; $[\alpha]^{20}_D$ –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); $^{13}C\{^1H\}$ 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXXX.

Copies of ^1H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Tanaka, N.; Kusama, T.; Kashiwada, Y. Kobayashi, J. Bromopyrrole Alkaloids from Okinawan Marine Sponges *Agelas* spp. *Chem. Pharm. Bull.* **2016**, *64*, 691–694.

(2) Walker, R. P.; Faulkner, D. J.; Engen, D. V.; Clardy, J. Sceptrin, an antimicrobial agent from the sponge *Agelas sceptrum*. *J. Am. Chem. Soc.* **1981**, *103*, 6772–6773.

(3) Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. Dispacamides, anti-histamine alkaloids from Caribbean *Agelas* sponges. *Tetrahedron Lett.* **1996**, *37*, 3587–3590.

(4) Inaba, K.; Sato, H.; Tsuda, M.; Kobayashi, J. Spongiacidins A–D, New Bromopyrrole Alkaloids from *Hymeniacidon* Sponge. *J. Nat. Prod.* **1998**, *61*, 693–695.

(5) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. Manzacidins A–C, Novel Tetrahydropyrimidine Alkaloids from the Okinawan Marine Sponge *Hymeniacidon* sp. *J. Org. Chem.* **1991**, *56*, 4574–4576.

(6) (a) Hashimoto, T.; Maruoka, K. Syntheses of manzacidins: a stage for the demonstration of synthetic methodologies. *Org. Biomol. Chem.* **2008**, *6*, 829–835. (b) Ohfune, Y.; Oe, K.; Namba, K.; Shinada, T. Total Synthesis of Manzacidins. An Overview and Perspective. *Heterocycles* **2012**, *85*, 2617–2649.

(7) (a) Zwick, C. R., III; Renata, H. Remote C–H Hydroxylation by an α-Ketoglutarate-Dependent Dioxygenase Enables Efficient Chemoenzymatic Synthesis of Manzacidin C and Proline Analogs. *J. Am. Chem. Soc.* **2018**, *140*, 1165–1169. (b) Zwick, C. R., III; Renata, H. Evolution of Biocatalytic and Chemocatalytic C–H Functionalization Strategy in the Synthesis of Manzacidin C. *J. Org. Chem.* **2018**, *83*, 7407–7415. (c) Liu, Y.; Ruan, Z.; Wang, Y.; Huang, S.-H.; Hong, R. Stereoselectivity in a nitroso-ene cyclization: Formal synthesis of *rac*-manzacidins A and C. *Tetrahedron* **2019**, *75*, 1767–1773, and references cited therein.

(8) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. Total Synthesis of Natural *tert*-Alkylamino Hydroxy Carboxylic Acids. *Chem. Rev.* **2005**, *105*, 4537–4558.

(9) Kudoh, T.; Araki, Y.; Miyoshi, N.; Tanioka, M.; Sakakura, A. Diastereodivergent Henry Reaction for the Stereoselective Construction of Nitrogen-Containing Tetrasubstituted Carbons: Application to Total Synthesis of Manzacidins A and C. *Asian. J. Org. Chem.* **2017**, *6*, 1760–1763.

(10) Luzzio, F. A. The Henry reaction: recent examples. *Tetrahedron* **2001**, *57*, 915–945.

(11) (a) Shinada, T.; Ikebe, E.; Oe, K.; Namba, K.; Kawasaki, M.; Ohfune, Y. Synthesis and Absolute Structure of Manzacidin B. *Org. Lett.* **2007**, *9*, 1765–1767. (b) Shinada, T.; Oe, K.; Ohfune, Y. Efficient total synthesis of manzacidin B. *Tetrahedron Lett.* **2012**, *53*, 3250–3253. (c) Sankar, K.; Rahman, H.; Das, P. P.; Bhimireddy, E.; Sridhar, B.; Mohapatra, D. K. Practical Syntheses of Proposed and Revised Manzacidin B and Their Congeners. *Org. Lett.* **2012**, *14*, 1082–1085.

(12) Garner, P.; Park, J. M. 1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3- OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE. *Org. Synth.* **1992**, *70*, 18.

(13) Fioravanti, S.; Marchetti, F.; Pellacani, L.; Ranieri, L.; Tardella, P. A. Stereoselective aza-MIRC reactions on optically active (*E*)-nitro alkenes. *Tetrahedron Asymmetry* **2008**, 19, 231–236.

(14) (a) Hanessian, S.; Devasthale, P. V. Generation of functional diversity via nitroaldol condensations of α-aminoacid aldehydes – A new and stereocontrolled route to acyclic 1,3-diamino-2-alcohols. *Tetrahedron Lett.* **1996**, 37, 987–990. (b) Corey, E. J.; Zhang, F.-Y. *Re*- and *Si*-Face-Selective Nitroaldol Reactions Catalyzed by a Rigid Chiral Quaternary Ammonium Salt: A Highly Stereoselective Synthesis of the HIV Protease Inhibitor Amprenavir (Vertex 478). *Angew. Chem. Int. Ed.* **1999**, *38*, 1931–1934.

(15) The absolute stereochemistry at C6 was not determined.

(16) Evans, D. A.; Cee, V. J.; Siska, S. J. Asymmetric Induction in Methyl Ketone Aldol Additions to α-Alkoxy and α,β-Bisalkoxy Aldehydes: A Model for Acyclic Stereocontrol. *J. Am. Chem. Soc.* **2006**, *128*, 9433–9441.

(17) Jung, C.-K.; Krische, M. J. Asymmetric Induction in Hydrogen-Mediated Reductive Aldol Additions to α-Amino Aldehydes Catalyzed by Rhodium: Selective Formation of *syn*-Stereotriads Directed by Intramolecular Hydrogen-Bonding. *J. Am. Chem. Soc.* **2006**, *128*, 17051–17056.

(18) Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. The direct catalytic asymmetric aldol reaction of α-substituted nitroacetates with aqueous formaldehyde under base-free neutral phase-transfer conditions. *Org. Biomol. Chem.* **2012**, *10*, 5753–5755.

(19) Trajkovic, J. M.; Milanovic, V.; Ferjancic, Z.; Saicic, R. N. On the Asymmetric Induction in Proline-Catalyzed Aldol Reactions: Reagent-Controlled Addition Reactions of 2,2-Dimethyl-1,3-dioxane-5-one to Acyclic Chiral α-Branched Aldehydes. *Eur. J. Org. Chem.*, **2017**, 6146–6153.

(20) Martin L. M.; Hu, B.-H. Thiazole and oxazole building blocks for combinatorial synthesis. *Tetrahedron Lett.* **1999**, *40*, 7951–7953.