Highly Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Imine s and an Application to a Formal Total Synthesis of Manzacidin C

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Formal Total Synthesis of Manzacidin C
Based on Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines

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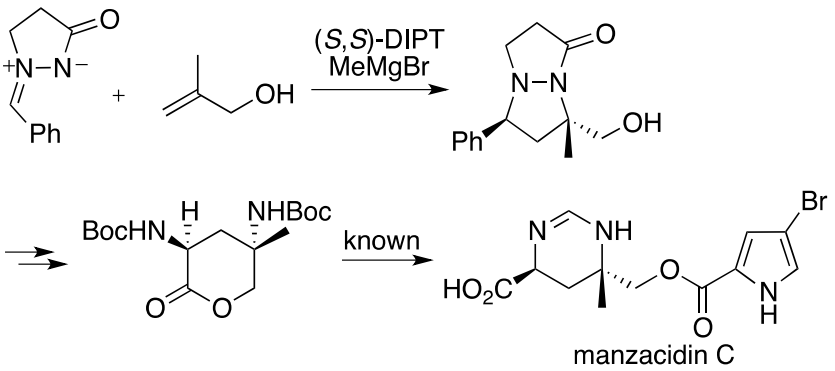


ABSTRACT: An enantioselective formal total synthesis of (+)-manzacidin C is described. A key feature of the synthesis is the construction of two chiral centers via the asymmetric 1,3-dipolar cycloaddition of an azomethine imine to methallyl alcohol by the use of (*S,S*)-DIPT as a chiral auxiliary.

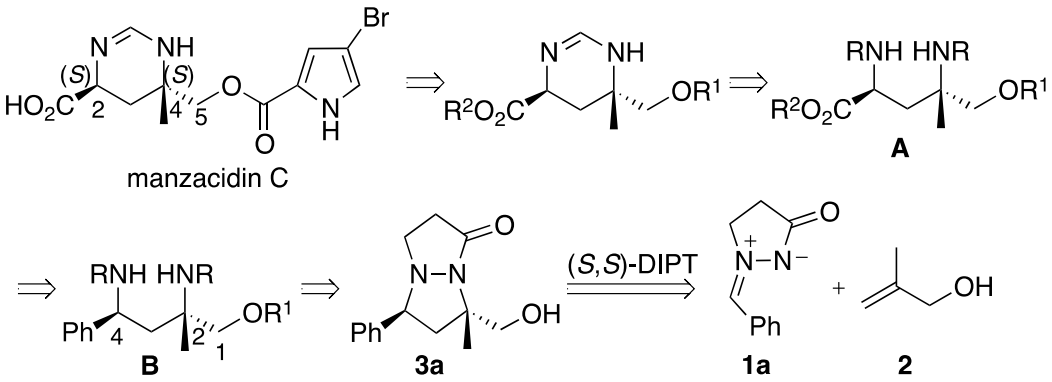
INTRODUCTION

Manzacidins A, B, and C are structurally unique bromopyrrole alkaloids isolated as bioactive constituents of the Okinawan sponge, *Hymeniacidon* sp., collected at the Manza beach of Okinawa island in Japan.[1] The significant amount of synthetic interest in the manzacidins stems from the intriguing structural features of their 1,3-diamine skeletons with a quaternary stereocenter and a desire to obtain significant amounts for more comprehensive pharmacological studies.[2,3] Manzacidins A and C have a 2,4-diamino-5-hydroxypentanoic acid skeleton that possesses a nitrogen-containing quaternary carbon center at the 4-position. In order to construct such a carbon skeleton, several

attempts have been made. Ofune and Shinada were the first to conquer the synthesis of manzacidins A and C via the Strecker reaction.[4] Ichikawa recently reported their synthesis via [3,3]-sigmatropic rearrangement of an allylic cyanate.[5] Asymmetric [3+2] cycloaddition is an efficient pathway to construct such a skeleton in an optically active form. Maruoka and Sibi independently employed asymmetric 1,3-dipolar cycloaddition of a diazoester, and Leighton reported the enantioselective establishment of two stereocenters via acylhydrazone-alkene [3+2] cycloaddition.[6–8]

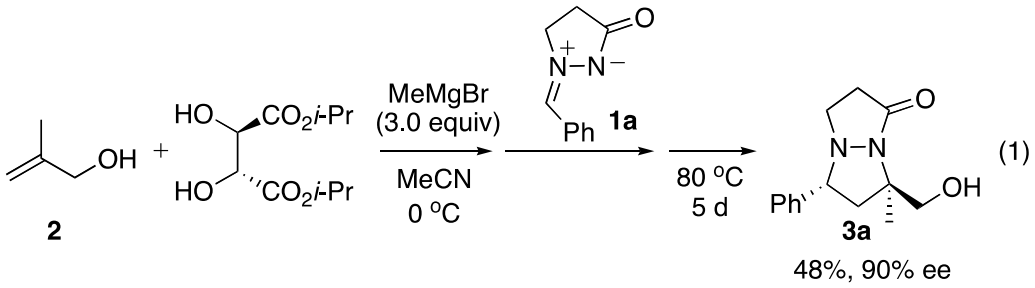
Stereoselective construction of 1,3-diamine skeletons is still a challenging task and asymmetric 1,3-dipolar cycloaddition of azomethine imines is generally a useful and effective tool to construct such a chiral backbone directly.[9] Recently, we developed the asymmetric 1,3-dipolar cycloaddition of azomethine imines to allylic and homoallylic alcohols, utilizing either stoichiometric or catalytic amounts of diisopropyl (*R*,*R*)-tartrate [(*R*,*R*)-DIPT] to furnish *trans*-pyrazolidines with excellent regio-, diastereo-, and enantioselectivities.[10] If our method could be applied to the cycloaddition of methallyl alcohol (2-methyl-2-propen-1-ol) (**2**), the (*S*,*S*)-2,4-diamino-2-methylbutan-1-ol unit **B** could be constructed by the use of (*S*,*S*)-DIPT through the cycloadduct **3a** as shown in Scheme 1. Furthermore, if phenyl-substituted azomethine imine **1a** could be used, the oxidation of the phenyl ring moiety might provide a ready route to the carboxylic acid functionality as shown in **A**. In this approach, the removal of the C3 unit on the pyrazolidine ring in **3a** is another challenge in synthesizing manzacidin C. Herein we report the formal total synthesis of manzacidin C based on asymmetric 1,3-dipolar cycloaddition of the azomethine imine utilizing (*S*,*S*)-DIPT as a chiral auxiliary. In addition, the C3 unit on nitrogens of the obtained cycloadduct could be removed through N–N bond cleavage followed by a retro-Michael addition reaction.

Scheme 1. Retrosynthetic Analysis of Manzacidin C



RESULTS AND DISCUSSION

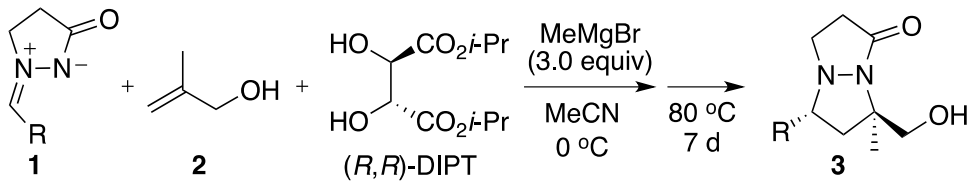
First, we examined the asymmetric 1,3-dipolar cycloaddition of phenyl-substituted azomethine imine possessing pyrazolidinone skeleton **1a** to methallyl alcohol (**2**) according to the previously reported procedure.[10] A mixture of methallyl alcohol (**2**) (1.0 equiv) and (*R*,*R*)-DIPT (1.0 equiv) in MeCN was treated with MeMgBr (3.0 equiv), followed by the addition of MeCN solution of azomethine imine **1a** (1.0 equiv) at 0 °C, and then the reaction mixture was heated at 80 °C (eq. 1). In the present case of sterically demanding methallyl alcohol (**2**), cycloaddition proceeded rather slowly. After 5 d, the corresponding pyrazolidine **3a** was obtained as a single diastereomer in 48% yield. The optical purity of the product was high at 90% ee. However, the chemical and optical yields fluctuated.



By the screening of conditions such as the halogen ion in Grignard reagents, solvents (MeCN or EtCN), and the addition order of the reagents, we determined the optimal procedure of adding the Grignard reagent last to the mixture of the azomethine imine **1a**, methallyl alcohol (**2**), and chiral DIPT in MeCN. The cycloaddition afforded the pyrazolidine **3a** in almost 60% yield with a constantly excellent enantioselectivity of 95% ee (Table 1, Entry 1).[11,12]

The 1,3-dipolar cycloaddition of several azomethine imines **1b**–**1e** to methallyl alcohol (**2**) was subsequently investigated by the improved procedure. Although the chemical yields were moderate, the aryl-substituted azomethine imines **1b** and **1c** afforded the corresponding cycloadducts **3b** and **3c** with high enantioselectivities and complete regio- and diastereoselectivities in each case (Entries 2 and 3). The cycloaddition of the cyclohexyl-substituted and *t*-butyl-substituted azomethine imines **2d** and **2e** also afforded the cycloadducts **3d** and **3e** with high enantioselectivities (Entries 4 and 5).

Table 1. Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Imines to Methallyl Alcohol



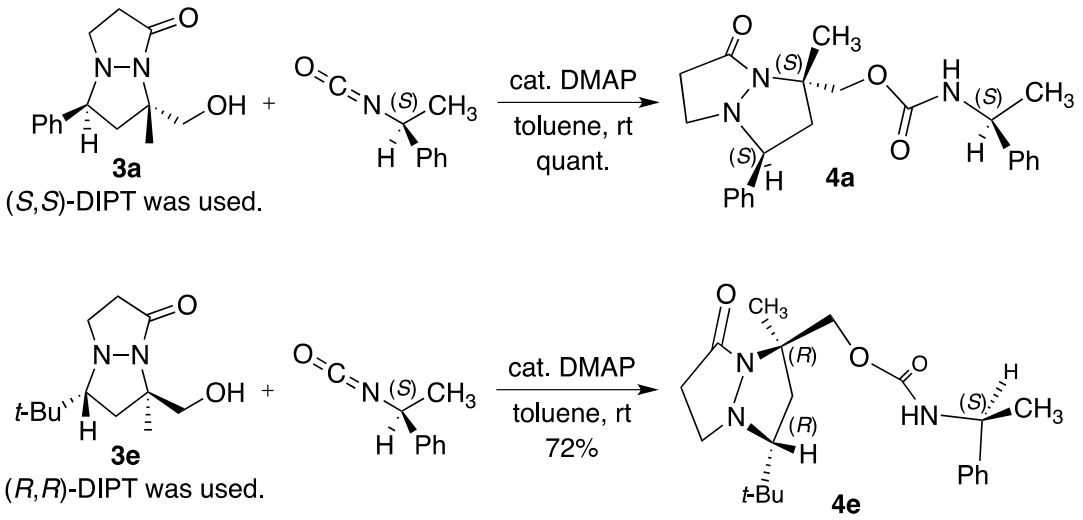
Entry	R		Yield/%	ee/%[a]
1[b]	Ph	**a**	59	95
2	*p*-MeC_6H_4	**b**	45	91
3	*p*-ClC_6H_4	**c**	51	91
4	*c*-Hex	**d**	64	85
5	*t*-Bu	**e**	56	88

[a]Enantioselectivities were determined by HPLC analysis (Daicel CHIRALPAK IA).
[b](*S*,*S*)-DIPT was used instead of (*R*,*R*)-DIPT and (*S*,*S*)-isomer of **3** was selectively obtained.

Recrystallization of the cycloadduct **3a** obtained by the use of (*S*,*S*)-DIPT enhanced the optical purity of the cycloadduct **3a** up to 99.4% ee.[11] The enantiomerically rich **3a** was treated with (*S*)-1-phenylethyl isocyanate in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give the corresponding carbamate **4a** (quant.) (Scheme 2). Recrystallization from AcOEt gave diastereomerically pure **4a**. The absolute stereochemistry of the pyrazolidine skeleton in **4a** was determined to be *S*,*S* by X-ray crystallographic analysis of its single crystal. Furthermore, the cycloadduct **3e** (83% ee) obtained by the use of (*R*,*R*)-DIPT was also converted to the corresponding carbamate **4e** (72%). The absolute configurations of the pyrazolidine skeleton in **4e** was unambiguously confirmed to be *R*,*R* by single-crystal X-ray diffraction analysis of the diastereomerically pure **4e** obtained by its recrystallization from AcOEt. The absolute configurations putatively assigned to the other products **3b**–**3d** by the use of (*R*,*R*)-DIPT were *R*,*R*.

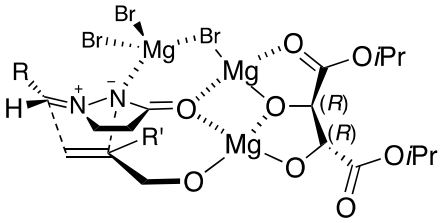
Scheme 2. Determination of Absolute Stereochemistry of 3a and 3e (ORTEPs of **4a** and **4e** were

shown in SI)



The precise mechanism of the present 1,3-dipolar cycloaddition is not yet clear. We have proposed the following transition state model, in which the carbonyl oxygen of azomethine imine **1** coordinates to the magnesium salt of (*R*,*R*)-DIPT as shown in Figure 1. The nitrogen connected with carbonyl group attacks to disubstituted C2-carbon of methallyl alcohol **2** (R' = CH_3) from *re*-face, which might be rather interrupted than the addition to monosubstituted C2-carbon of prop-2-en-1-ol (R' = H).

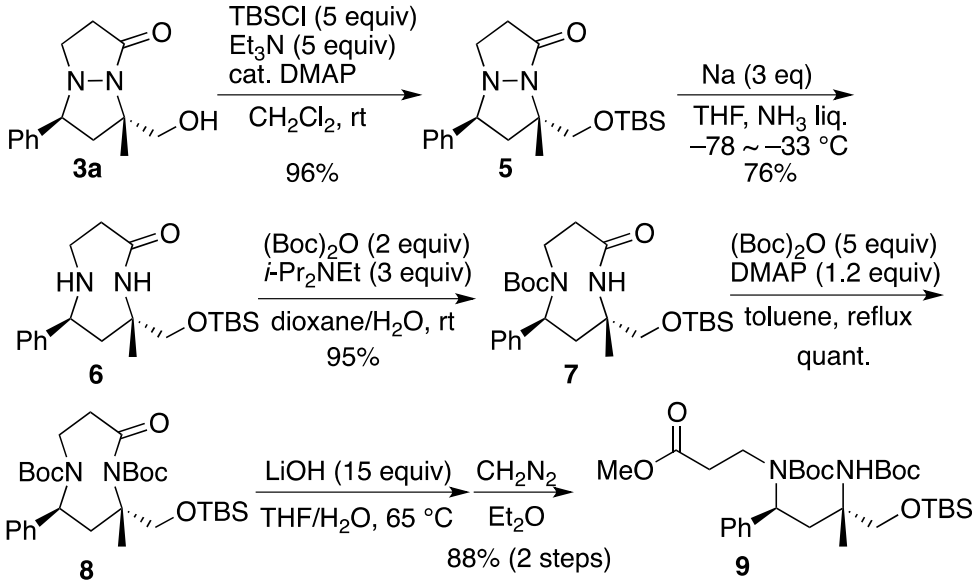
Figure 1. Proposed Transition State Model



With suitable conditions for the asymmetric 1,3-dipolar addition of azomethine imines to methallyl alcohol in hand, we turned our attention to the total synthesis of manzacidin C. One of the major challenges in synthesizing manzacidin C is the removal of the three-carbon bridge on the pyrazolidine ring. Although many asymmetric 1,3-dipolar cycloadditions of azomethine imines possessing pyrazolidinone moieties to olefins have been reported, the conversion of the produced fused pyrazolidines to acyclic 1,3-diamine derivatives has not yet been achieved to the best of our knowledge.[13] We envisaged that retro-Michael addition of the amino group from the propanamide moiety of the pyrazolidinone ring could proceed before or after cleavage of the N–N bond.

After intensive examination, we decided to cleave the N–N bond first. Thus, the pyrazolidine **3a** was converted to the corresponding *t*-butyldimethylsilyl (TBS) ether **5** (Scheme 3). Subsequent reduction with Na/NH_3 took place smoothly, cleaving the N–N bond to give **6** in 76% yield.[14] Stepwise Boc protection of the resulting amine and amide moieties was performed to afford the corresponding Boc-protected 8-membered azalactam derivative **8** in 95% yield. Although ring-opening of the *N*-Boc azalactam **8** by the treatment with phenyl- or ethyl Grignard reagents did not proceed,[15a] a selective nucleophilic attack on the ring carbonyl group by a small nucleophile, a hydroxy anion, was achieved by the use of LiOH to afford the *N*-substituted ω-amino acid.[15b] The produced carboxylic acid was converted to the corresponding methyl ester **9** by diazomethane in good yield.

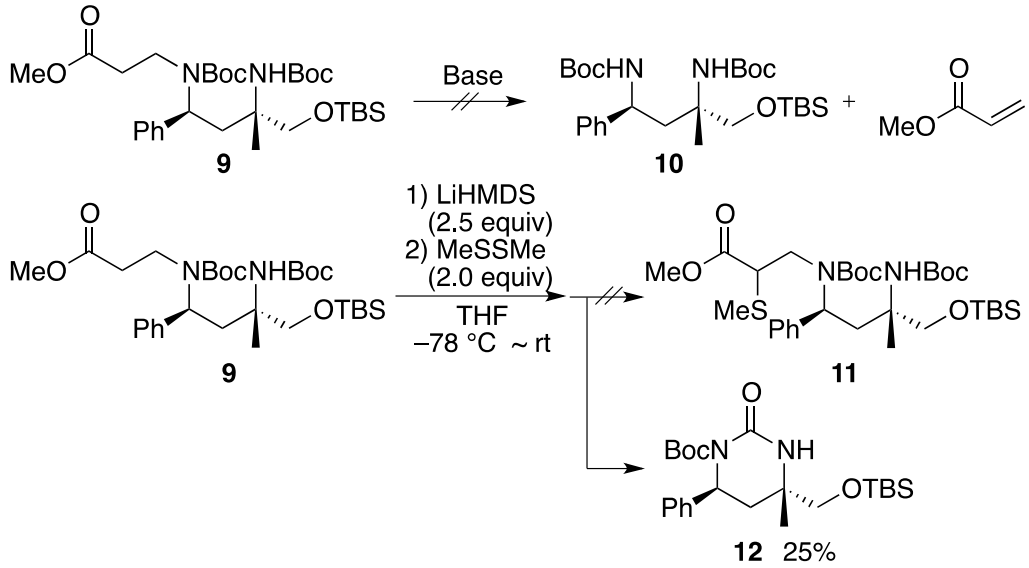
Scheme 3. N–N Cleavage and Ring Opening of Azalactam



Next, retro-Michael addition of the carbamate moiety in **9** was examined (Scheme 4). However, the desired elimination product **10** was not obtained by the use of several bases (NaH,[16a] *t*-BuOK,[16b] etc.). The failure of the retro-Michael reaction strategy led us to examine an alternative method for removal of the C3 unit. Thus, we planned to introduce a double bond at the α,β-position of the ester and execute an oxidative cleavage. The electrophilic introduction of sulfide moiety commenced by treatment with dimethyl disufide under basic conditions.[17] In this reaction, the desired α-sulfenated product **11** was again not obtained. To our surprise, an unpredicted urea product **12** without the propanoate moiety on nitrogen was instead isolated in 25% yield. From the ^{1}H NMR analyses of the byproducts whose structures were not determined yet, one of the byproducts contained the methyl

propanoate moiety, which might be produced via Michael addition of the generated urea anion **C** to the released methyl acrylate (Scheme 5). In addition, the production of **12** was not reproducible. Actually by monitoring the reaction by TLC, the urea, once formed, was consumed to form byproducts if the reaction was kept at 25 °C for a prolonged time. We hypothesized that addition of a thiolate anion could trap methyl acrylate as a Michael donor to avoid the undesired recombination of the anion **C** with methyl acrylate. The *β*-elimination reaction from **9** was again examined by the addition of *p*-MeC_6H_4SH. The urea **12** was obtained in improved yield (Table 2, Entry 1); however, the starting material **9** was still recovered. The production of *β*-thiopropanoate **13** (Ar = *p*-MeC_6H_4) was confirmed by the analyses of ^{1}H NMR spectra of the byproducts.[18] When LiHMDS was added to the reaction mixture on three occasions in the presence of 3 equiv of the thiol, the reaction was well-controlled to give the urea **12** in 65% yield (Entry 3).

Scheme 4. Examination of Retro-Michael Addition Reaction from 9



Scheme 5. Proposed Pathway from 9 to 12

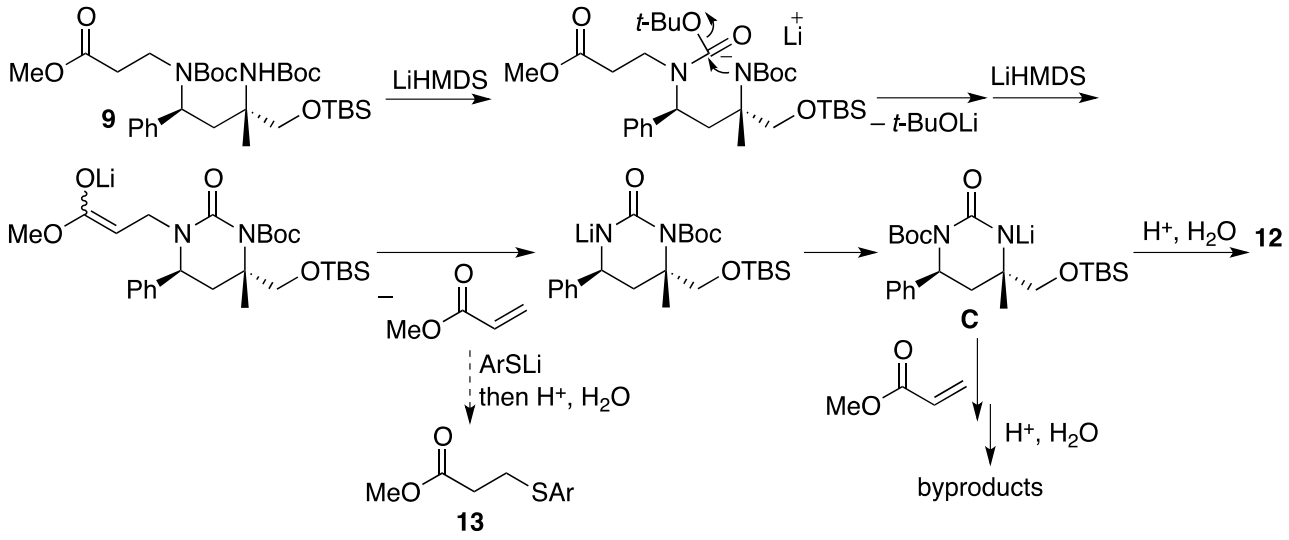
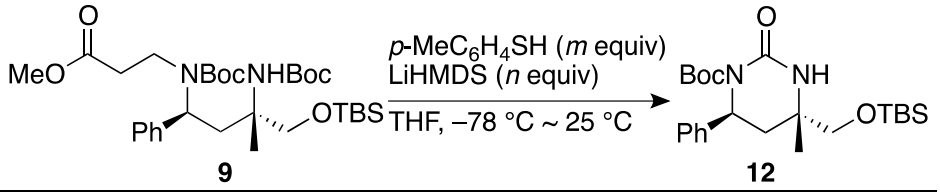


Table 2. Retro-Michael Addition Reaction from 9



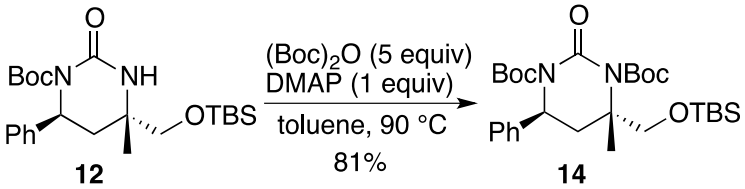
Entry	*m*	*n*	*t*/h	Yield/%
1	1.5	2.5	16	40[a]
2	1.5	3.0[b]	19	45
3	3.0	5.5[c]	24	65

[a]Starting compound **9** was recovered in 14% yield.

[b]LiHMDS was added in twice of 2.3 equiv and 0.7 equiv, respectively.

[c]LiHMDS was added in three parts of 3.0 equiv, 1.5 equiv, and 1.0 equiv, respectively: See experimental section.

The regiochemistry of the Boc group in **12** was confirmed by its transformation to **14** (eq. 2). The chemical shift of the benzylic proton in **14** was scarcely shifted from that of **12**, which suggests that the Boc group in **12** existed on the benzylic amine moiety.

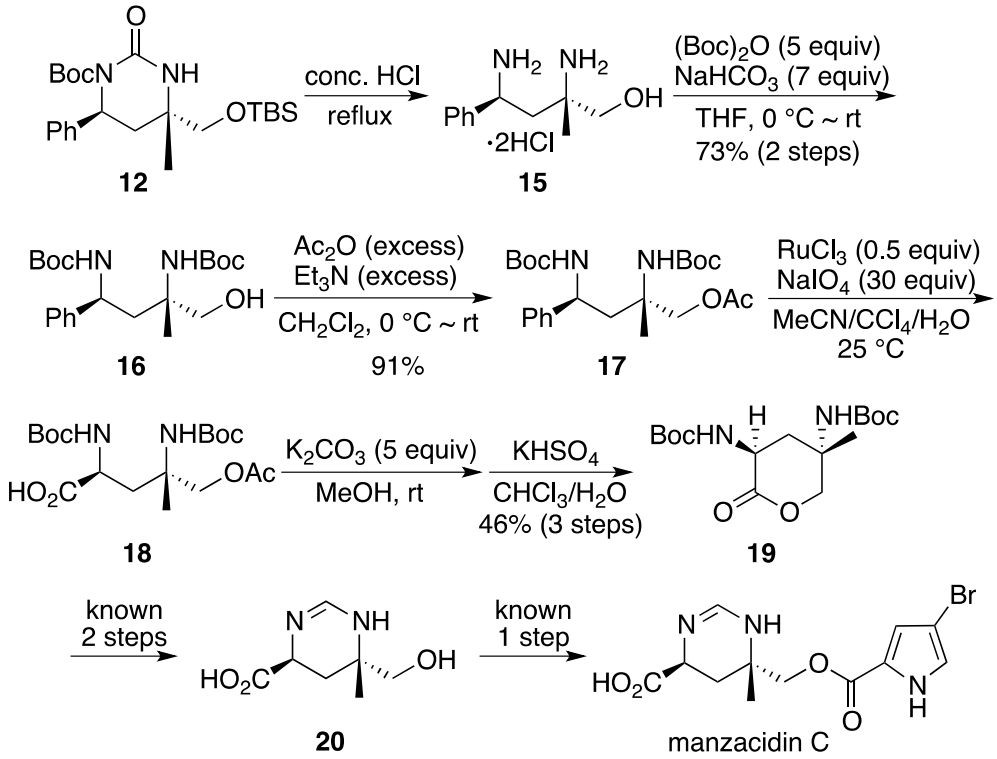


(2)

The remaining main task for the synthesis of manzacidin C was oxidation of the phenyl group into a carboxylic acid (Scheme 6). When the urea **12** was subjected to conc. HCl under reflux conditions,

the hydrolysis proceeded to give a 1,3-diamine hydrochloride **15**.[19] Boc protection of the resulting 1,3-diamine moiety gave **16** in 73% yield in 2 steps from **12**. Acetylation of the remaining hydroxyl group afforded **17**. $RuCl_3/NaIO_4$ oxidation of the phenyl group in **17** was performed to give the corresponding carboxylic acid **18**.[20] Finally, without further purification, **18** was subjected to saponification followed by acidic workup with an aqueous solution of $KHSO_4$ to afford lactone **19** in 46% yield. All spectroscopic data of synthetic **19** were identical to those reported in the literature.[4,5] The synthesis of manzacidin C in three steps from the lactone intermediate **19** through **20** has been reported by Ohfune and Shinada.[4] Thus, a formal total synthesis of manzacidin C has been accomplished.

Scheme 6. Oxidative Cleavage of Phenyl Ring and Transformation to Lactone 19



CONCLUSION

In conclusion, we accomplished the formal total synthesis of manzacidin C. Through the asymmetric 1,3-dipolar cycloaddition of the azomethine imine possessing a pyrazolidinone skeleton, the stereochemistry of two chiral centers could be built in a single step. Within the present synthesis, the C3 unit on the formed pyrazolidine ring could be removed through N–N bond cleavage followed by a retro-Michael addition reaction.

EXPERIMENTAL SECTION

General Method. ^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J) and integration. ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. The chemical shifts are reported relative to $CDCl_3$ (δ = 77.0 ppm). The wavenumbers of maximum absorption peaks in IR spectra are presented in cm^{-1}. All of the melting points were measured with a micro melting point apparatus. The specific optical rotations were recorded on a polarimeter. HRMS (EI, FAB, and DART) spectra were measured with quadrupole and TOF mass spectrometers. Dehydrated solvents were purchased for the reactions and used without further desiccation.

(5*S*,7*S*)-7-(Hydroxymethyl)-7-methyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3a): A MeCN (3.0 mL) solution of methallyl alcohol (**2**) (0.362 g, 5.0 mmol) and MeCN (57 mL) were consecutively added to a mixture of (*S*,*S*)-DIPT (1.175 g, 5.0 mmol) and azomethine imine **1a** (0.874 g, 5.0 mmol) under an argon atmosphere. Then the mixture was cooled to 0 °C, and methylmagnesium bromide (16.5 mL of 0.91 M solution in THF, 15.0 mmol) was slowly added. The reaction was stirred at 0 °C for 0.5 h, at rt for 1 h and then 7 d at 80 °C. The reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl and the mixture was subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1 to 0:1, then AcOEt/MeOH = 20/1 to 10/1) to give the corresponding pyrazolidine **3a** as a solid (0.727 g, 59%). R_f = 0.5 (AcOEt/MeOH = 5/1). Mp 111–112 °C. $[\alpha]^{25}_{D}$ –15 (*c* 0.31, EtOH). The ee was determined to be 95% by HPLC (Daicel CHIRALPAK IA, hexane/EtOH = 20/1, 0.75 mL/min, 254 nm, major 61 min and minor 49 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3H), 2.20 (dd, J = 12.8, 10.1 Hz, 1H), 2.50 (dd, J = 12.8, 7.3 Hz, 1H), 2.69–2.80 (m, 2H), 2.90–3.02 (m, 1H), 3.37–3.44 (m, 1H), 3.55 (dd, J = 10.1, 7.3 Hz, 1H), 3.71 (dd, 11.9, 8.6 Hz, 1H), 3.90 (d, J = 11.9 Hz, 1H), 5.30 (d, J = 8.6 Hz, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 36.6, 50.1, 51.0, 62.3, 68.8, 70.5, 127.0, 128.2, 128.7, 137.4, 164.3. IR (KBr): 3381, 3240, 2970, 2832, 1669, 1644, 1456, 1432, 1414, 1249, 1187, 1158, 1136, 1063, 1050, 774, 702 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.19; H, 7.49; N, 11.38.

In a similar manner, pyrazolidines **3b**–**3e** were obtained from azomethine imines **1b**–**1e**.

(5*R*,7*R*)-7-(Hydroxymethyl)-7-methyl-5-(*p*-tolyl)tetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3b): Starting from azomethine imine **1b** (391mg, 2.08 mmol) by the use of (*R*,*R*)-DIPT (487 mg, 2.08 mmol), **3b** (244 mg, 45%) was obtained as a solid. R_f = 0.6 (AcOEt/MeOH = 10/1). Mp 134–136 °C. $[\alpha]^{25}_D$ +21 (*c* 0.50, EtOH). The ee was determined to be 91% by HPLC (Daicel CHIRALPAK IA, hexane/isopropanol = 40/1, 1.0 mL/min, 254 nm, major 72 min and minor 90 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 3H), 2.18 (dd, *J* = 13.3, 10.1 Hz, 1H), 2.35 (s, 3H), 2.44 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.73 (dd, *J* = 15.6, 8.2 Hz, 1H), 2.76 (dd, *J* = 8.7, 5.0 Hz, 1H), 2.96 (m, 1H), 3.41 (dd, *J* = 8.7, 8.2 Hz, 1H), 3.48 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.65 (d, *J* = 11.9 Hz, 1H), 3.91 (d, *J* = 11.9 Hz, 1H), 5.31 (brs, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 22.5, 33.6, 50.2, 51.1, 62.5, 69.3, 70.5, 127.1, 129.5, 134.3, 138.1, 164.5. IR (KBr): 3264, 2975, 2910, 2850, 1663, 1518, 1413, 1151, 1086, 1051, 821 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.07; H, 7.80; N, 10.75.

(5*R*,7*R*)-5-(4-chlorophenyl)-7-(hydroxymethyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3c): Starting from azomethine imine **1c** (426 mg, 2.04 mmol) by the use of (*R*,*R*)-DIPT (479 mg, 2.04 mmol), **3c** (292 mg, 51%) was obtained as a solid. R_f = 0.4 (AcOEt/MeOH = 10/1). Mp 107–109 °C. $[\alpha]^{25}_D$ +29 (*c* 0.76, EtOH). The ee was determined to be 91% by HPLC (Daicel CHIRALPAK IA, hexane/EtOH = 20/1, 0.75 mL/min, 254 nm, major 78 min and minor 104 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (s, 3H), 2.13 (dd, *J* = 12.8, 10.0 Hz, 1H), 2.49 (dd, *J* = 12.8, 7.3 Hz, 1H), 2.69–2.78 (m, 2H), 2.91–3.02 (m, 1H), 3.41(dd, *J* = 9.2, 7.8 Hz, 1H), 3.52 (dd, *J* = 10.0, 7.3 Hz, 1H), 3.70 (d, *J* = 11.9 Hz, 1H), 3.88 (d, *J* = 11.9 Hz, 1H), 5.18 (brs, 1H), 7.29–7.35 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 36.6, 50.3, 51.0, 62.4, 68.8, 69.8, 128.4, 129.0, 134.0, 136.0, 164.4. IR (KBr): 3264, 2975, 2910, 2850, 1663, 1518, 1413, 1151, 1086, 1051, 821 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{17}N_2O_2Cl$ [M^+] 280.0979, found: 280.0976.

(5*R*,7*R*)-5-Cyclohexyl-7-(hydroxymethyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3d): Starting from azomethine imine **1d** (567 mg, 3.15 mmol) by the use of (*R*,*R*)-DIPT (737 mg, 3.15 mmol), **3d** (497 mg, 63%) was obtained as an oil. R_f = 0.4 (AcOEt/MeOH = 10/1). $[\alpha]^{25}_D$ –31 (*c* 0.47, EtOH). The ee was determined to be 85% by HPLC (Daicel CHIRALPAK IA, hexane/EtOH = 20/1, 0.75 mL/min, 254 nm, major 43 min and minor 49 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92–1.03 (m, 2H), 1.10–1.28 (m, 3H), 1.39–1.45 (m, 1H), 1.47 (s, 3H), 1.64–1.80 (m,

5H), 1.94 (dd, *J* = 12.8, 9.6 Hz, 1H), 2.12 (dd, *J* = 12.8, 7.8 Hz, 1H), 2.33 (m, 1H), 2.66 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.74 (td, *J* = 8.2, 12.8 Hz, 1H), 2.93 (ddd, *J* = 14.6, 12.8, 8.2 Hz, 1H), 3.57 (d, *J* = 11.9 Hz, 1H), 3.60 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 5.46 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 25.9, 26.0, 26.2, 28.6, 30.5, 36.6, 40.5, 44.0, 53.7, 61.3, 69.2, 71.6, 163.4. IR (neat): 3373, 2924, 2855, 1656, 1447, 1440, 1348, 1267, 1188, 1159, 1063, 892, 754 cm^{-1}. HRMS (DART) calcd for $C_{14}H_{25}N_2O_2$ $[(M+H)^+]$ 253.19160, found: 253.19150.

(5*R*,7*R*)-5-(*t*-Butyl)-7-(hydroxymethyl)-7-methyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (3e): Starting from azomethine imine **1e** (106 mg, 0.69 mmol) by the use of (*R*,*R*)-DIPT (161 mg, 0.69 mmol), **3e** (87 mg, 56%) was obtained as a solid. R_f = 0.6 (AcOEt/MeOH = 10/1). Mp 55–56 °C. $[\alpha]^{25}_D$ –52 (*c* 0.45, EtOH). The ee was determined to be 88% by HPLC (Daicel CHIRALPAK IA, hexane/EtOH = 30/1, 0.75 mL/min, 254 nm, major 42 min and minor 54 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 9H), 1.46 (s, 3H), 1.97 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.05 (dd, *J* = 13.3, 8.7 Hz, 1H), 2.35 (dd, *J* = 8.7, 8.2 Hz, 1H), 2.66 (dd, *J* = 15.1, 8.2 Hz, 1H), 2.77 (td, *J* = 8.2, 13.3 Hz, 1H), 2.93 (ddd, *J* = 15.1, 13.3, 8.7 Hz, 1H), 3.57 (d, *J* = 11.9 Hz, 1H), 3.61 (dd, *J* = 9.2, 8.7 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 5.58 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 26.8, 32.4, 36.9, 42.5, 55.2, 60.6, 69.0, 75.4, 163.1. IR (KBr): 3380, 2961, 2870, 1658, 1442, 1366, 1244, 1189, 1158, 1130, 1092, 1064, 964, 909, 822, 732 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{22}N_2O_2$ $[M^+]$ 226.1681, found: 226.1684.

((1*S*,3*S*)-1-Methyl-7-oxo-3-phenylhexahydropyrazolo[1,2-*a*]pyrazol-1-yl)methyl ((*S*)-1-phenylethyl)carbamate (4a): Recrystallization of **3a** (95% ee) from EtOH/hexane gave an enantiomerically enriched **3a** (99.4% ee). A mixture of the recrystallized **3a** (32 mg, 0.13 mmol), (*S*)-1-phenylethyl isocyanate (42 mg, 0.29 mmol), and a catalytic amount of *N*,*N*-dimethylpyridin-4-amine (DMAP) in toluene (1 mL) was stirred at rt for 5 d under an argon atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by TLC on SiO_2 (hexane/AcOEt = 1/1) to afford the carbamate **4a** (51 mg, quant.). R_f = 0.5 (AcOEt). Recrystallization from AcOEt gave the diastereomerically pure **4a**. Crystal data: $C_{23}H_{27}N_3O_3$, *FW* = 393.48, monoclinic, $P2_1$ (#4), *a* = 9.5902(2), *b* = 9.9373(3), *c* = 10.7178(3) Å, β = 95.5090(10)°, *V* = 1016.70(5) $Å^3$, *Z* = 2, D_{calcd} = 1.285 g cm^{-3}, *R* = 0.0250 (R_w = 0.0660) for 3643 reflections with I > 3.00σ(I) and 265 variable parameters. CCDC 1518209 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via

www.ccdc.cam.ac.uk/data_request/cif. Mp 172–173 °C. $[\alpha]^{25}_{D}$ –44 (*c* 0.26, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.58 (m, 3H), 1.53 (s, 3H), 2.17 (t, *J* = 11.9 Hz, 1H), 2.53–2.76 (m, 3H), 2.82–2.95 (m, 1H), 3.30–3.38 (m, 1H), 3.50–3.57 (m, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.82–4.91 (m, 1H), 5.18 (brs, 1H), 7.13–7.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.5, 37.2, 50.3, 50.7, 51.4, 59.0, 65.5, 69.4, 125.2, 126.0, 127.0, 127.4, 128.1, 128.6, 137.3, 143.1, 155.2, 163.2. IR (KBr): 3550, 3411, 3240, 2987, 2939, 1717, 1662, 1617, 1540, 1422, 1374, 1302, 1243, 1155, 1111, 1077, 1058, 762, 703 cm^{-1}. Anal. Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.06; H, 6.98; N, 10.55.

((1*R*,3*R*)-3-(tert-butyl)-1-methyl-7-oxohexahydropyrazolo[1,2-a]pyrazol-1-yl)methyl ((*S*)-1-phenylethyl)carbamate (4e): A mixture of the **3e** (83% ee, 78 mg, 0.34 mmol) obtained by another cycloaddition using (*R*,*R*)-DIPT, (*S*)-1-phenylethyl isocyanate (80 mg, 0.54 mmol), and a catalytic amount of DMAP in toluene (1 mL) was stirred at rt for 4 d under an argon atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by TLC on SiO_2 (AcOEt only) to afford the carbamate **4e** (93 mg, 72%). R_f = 0.7 (AcOEt). Recrystallization from AcOEt gave the diastereomerically pure **4e**. Crystal data: $C_{21}H_{31}N_3O_3$, *FW* = 373.49, orthorhombic, $P2_1\ 2_1\ 2_1$ (#19), *a* = 7.5338(2), *b* = 15.4969(4), *c* = 17.6570(5) Å, *V* = 2061.46(10) $Å^3$, *Z* = 4, D_{calcd} = 1.203 g cm^{-3}, *R* = 0.0301 (R_w = 0.0778) for 3901 reflections with I > 3.00σ(I) and 248 variable parameters. CCDC 1524360 (**4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Mp 183–184 °C. $[\alpha]^{25}_{D}$ –29 (*c* 0.31, EtOH). In ^{1}H and ^{13}C NMR spectra, two isomers of **4e**, which might be derived from restricted nitrogen–carbonyl carbon bond [N–C(=O)] rotation, were observed in the ratio of 3/1. Major isomer: δ = 0.85 (s, 9H), 1.36–1.39 (m, 3H), 1.49 (d, *J* = 6.4 Hz, 3H), 1.86–1.94 (m, 1H), 2.24–2.32 (m, 2H), 2.54 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.66–2.74 (m, 1H), 2.86 (dd, *J* = 14.7, 8.2 Hz, 1H), 3.51 (dd, *J* = 8.2, 7.8 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.80–4.87 (m, 1H), 5.27 (d, *J* = 7.8 Hz, 1H), 7.18–7.35 (m, 5H). Selected data of minor isomer; 1.36 (s, 3H), 5.22 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = Major isomer: δ = 22.3, 26.9, 31.8, 37.2, 42.8, 49.6, 50.6, 54.9, 57.7, 65.1, 74.2, 125.81, 127.2, 128.6, 144.6, 156.9, 162.8. Selected data of minor isomer; 23.2, 125.76, 126.8, 128.4, 143.5, 155.2. IR (KBr): 3276, 2961, 1716, 1673, 1627, 1533, 1442, 1366, 1240, 1077, 1063, 910, 766, 705 cm^{-1}. HRMS (TOF) calcd for $C_{21}H_{32}N_3O_3$ [$(M+H)^+$] 374.2444, found: 374.2447.

(5*S*,7*S*)-7-(((*t*-Butyldimethylsilyl)oxy)methyl)-7-methyl-5-phenyltetrahydropyrazolo[1,2-*a*]pyrazol-1(5*H*)-one (5): The recrystallized **3a** (3.0 g, 12 mmol) was dissolved in CH_2Cl_2 (23 mL) and DMAP (278 mg, 2.3 mmol), triethylamine (8.5 mL, 60 mmol), *t*-butyldimethylsilyl chloride (9.18 g, 60 mmol) were successively added and stirred at rt under a nitrogen atmosphere. After 24 h, cool water with ice was added and the mixture was allowed to stir for an additional 1 h. The reaction mixture was then extracted with $CHCl_3$, and the combined organic extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1 to 1/10) to give **5** as a solid (4.2 g, 96%). R_f = 0.6 (hexane/EtOAc = 1/1). Mp 129–130 °C. $[\alpha]^{25}_D$ –28 (*c* 0.33, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.117 (s, 3H), 0.120 (s, 3H), 0.96 (s, 9H), 1.46 (s, 3H), 2.15 (dd, *J* = 12.4, 11.0 Hz, 1H), 2.59 (dd, *J* = 15.2, 8.7 Hz, 1H), 2.66–2.71 (m, 1H), 2.74 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.93 (ddd, *J* = 15.2, 13.3, 8.7 Hz, 1H), 3.35 (t, *J* = 8.7 Hz, 1H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.77 (dd, *J* = 11.0, 6.0 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 7.27–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, –5.3, 18.2, 22.1, 25.9, 37.2, 50.8, 51.4, 60.8, 64.8, 69.7, 127.1, 128.0, 128.6, 138.1, 162.9. IR (KBr): 2950, 2928, 2857, 1676, 1494, 1463, 1430, 1414, 1254, 1103, 1003, 870, 853, 775, 727, 703 cm^{-1}. Anal. Calcd for $C_{20}H_{32}N_2O_2Si$: C, 66.62; H, 8.95; N, 7.77. Found: C, 66.41; H, 9.12; N, 7.79.

(6*S*,8*S*)-8-(((*t*-Butyldimethylsilyl)oxy)methyl)-8-methyl-6-phenyl-1,5-diazocan-2-one (6): To liquid ammonia (200 mL) under a nitrogen atmosphere was added a THF (5 mL) solution of **5** (3.0 g, 8.32 mmol) at –78 °C. Then sodium metal (0.57 g, 25.0 mmol) was slowly added in small species until the color of solution turned to dark blue.[14] After stirring 1 h at –78 °C, the reaction mixture was warmed to –33 °C and stirred for an additional 2 h. The reaction was quenched by the addition of solid NH_4Cl and liquid ammonia was distilled off. The residue was partitioned with $CHCl_3$ and H_2O and the mixture was subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1/10 to 1/20, then AcOEt/MeOH = 20/1 to 10/1) to give **6** as an oil (2.2 g, 76%). R_f = 0.6 (AcOEt/MeOH = 5/1). $[\alpha]^{25}_D$ + 19 (*c* 0.75, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 6H), 0.99 (s, 9H), 1.48 (s, 3H), 1.92 (s, 1H), 2.14 (dd, *J* = 15.6, 3.2 Hz, 1H), 2.42 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.59–2.68 (m, 1H), 2.97 (ddd, *J* = 13.3, 10.1, 4.6 Hz, 1H), 3.24 (ddd, *J* = 13.3, 10.1, 3.6 Hz, 1H), 3.37 (ddd, 13.3, 5.9, 4.6 1H), 3.40 (d, *J* = 9.6 Hz, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.98 (dd, *J* = 9.6, 3.2 Hz, 1H), 6.33 (s, 1H), 7.32–7.45 (m, 5H). ^{13}C NMR (100

MHz, $CDCl_3$): δ = –5.51, –5.46, 18.3, 25.8, 27.0, 37.8, 45.1, 45.5, 55.8, 58.6, 70.3, 126.2, 127.1, 128.8, 145.7, 175.3. IR (neat): 3368, 3062, 2960, 2928, 2857, 1652, 1471, 1255, 1200, 1103, 839, 778, 701 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{34}N_2O_2Si$ [M^+] 362.2390, found: 362.2378.

***t*-Butyl (2*S*,4*S*)- 4-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxo-2-phenyl-1,5-diazocane-1-carboxylate (7):** To a dioxane/water (4/1, 20 mL) solution of **6** (4.0 g, 11 mmol) and diisopropylethylamine (5.7 mL, 33 mmol), di-*t*-butyl dicarbonate (4.82 g, 22 mmol) was slowly added and the reaction mixture was at rt for 24 h under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure. The residue was partitioned with $CHCl_3$ and H_2O and subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 1/5 to 1/20) to give **7** as a solid (4.85 g, 95%). R_f = 0.6 (hexane/AcOEt = 1/2). Mp 107–109 °C. $[\alpha]^{25}_D$ +4 (*c* 0.32, EtOH). In ^1H and ^{13}C NMR spectra, two isomers of **7**, which might be derived from restricted nitrogen–carbonyl carbon bond [N–C(=O)] rotation, were observed in the ratio of 2/1. ^1H NMR (400 MHz, $CDCl_3$): Major isomer: δ = 0.10 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.34 (s, 3H), 1.47 (s, 9H), 1.99–2.08 (m, 1H), 2.48 (dd, *J* = 12.8, 7.8 Hz, 1H), 2.67 (dd, *J* = 16.0, 12.8 Hz, 1H), 2.74–2.88 (m, 1H), 2.88–3.01 (m, 1H), 3.40 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 4.03–4.16 (m, 1H), 5.74–5.83 (m, 1H), 6.02 (brs, 1H), 7.26–7.36 (m, 5H). Selected data of minor isomer; 0.13 (s, 6H), 0.94 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): Major isomer: δ = –5.57, –5.54, 18.2, 25.80, 28.0, 28.2, 36.5, 37.0, 51.6, 55.6, 55.8, 69.4, 80.6, 126.5, 127.3, 128.5, 140.7, 156.9, 171.8. Selected data of minor isomer; –5.46, –5.44, 18.3, 25.78, 37.5, 80.3. IR (KBr): 3440, 2955, 2930, 2857, 1689, 1666, 1473, 1414, 1473, 1414, 1365, 1249, 1218, 1162, 1118, 1048, 837, 779, 742, 698 cm^{-1}. Anal. Calcd for $C_{25}H_{42}N_2O_4Si$: C, 64.89; H, 9.15; N, 6.05. Found: C, 64.66; H, 9.39; N, 6.06.

Di-*t*-butyl(2*S*,4*R*)-2-(((*t*-butyldimethylsilyl)oxy)methyl)-2-methyl-8-oxo-4-phenyl-1,5-diazocane-1,5-dicarboxylate (8): To a toluene (30 mL) solution of **7** (3.88 g, 8.38 mmol), DMAP (1.23 g, 10 mmol) and di-*t*-butyl dicarbonate (9.14 g, 42 mmol) were added under an argon atmosphere and the reaction mixture was refluxed for 24 h. Solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 2/1) to give **8** as an oil (4.69 g, quant.). R_f = 0.4 (hexane/EtOAc = 5/1). $[\alpha]^{25}_D$ –128 (*c* 0.31, EtOH). ^1H NMR (400 MHz, $CDCl_3$): In ^1H and ^{13}C NMR spectra, two isomers of **8**, which might be derived

from restricted nitrogen–carbonyl carbon bond [N–C(=O)] rotation, were observed in the ratio of 2/1. Major isomer: δ = 0.112 (s, 3H), 0.12 (s, 3H), 0.826 (s, 9H), 1.43 (s, 3H), 1.47 (s, 9H), 1.52 (s, 9H), 1.85–1.96 (m, 1H), 2.30 (dd, J = 16.0, 3.7 Hz, 1H), 2.32–2.39 (m, 1H), 2.84–2.96 (m, 1H), 3.43 (td, J = 12.4, 5.0 Hz, 1H), 3.73–3.80 (m, 1H), 4.12 (d, J = 10.1 Hz, 1H), 4.64 (d, J = 10.1 Hz, 1H), 5.57 (d, J = 11.4 Hz, 1H), 7.20–7.32 (m, 5H). Selected data of minor isomer; 0.106 (s, 3H), 0.13 (s, 3H), 0.831 (s, 9H), 1.46 (s, 9H), 1.51 (s, 9H), 3.32 (ddd, J = 12.8, 11.4, 3.3 Hz, 1H), 3.43 (ddd, J = 14.6, 4.6, 2.8 Hz, 1H), 3.95 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 10.0 Hz, 1H), 5.76 (dd, J = 12.4, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = Major isomer: δ = –5.3, –5.0, 17.9, 25.1, 25.7, 27.9, 28.5, 35.4, 41.1, 53.5, 61.8, 66.2, 80.5, 80.9, 81.7, 126.2, 127.1, 128.4, 141.3, 151.6, 154.6, 183.6. Selected data of minor isomer; –5.6, –5.4, 18.0, 24.4, 25.8, 28.1, 28.4, 35.0, 42.1, 51.9, 61.6, 65.7, 79.8, 81.6, 126.6, 127.0, 128.3, 141.2, 152.1, 155.1, 183.7. IR (KBr): 2976, 2960, 2857, 1741, 1712, 1690, 1462, 1406, 1366, 1320, 1254, 1167, 1070, 975, 903, 839, 775, 699 cm^{-1}. HRMS (FAB) calcd for $C_{30}H_{51}N_2O_6Si$ [$(M+H)^+$] 563.3516, found: 563.3515.

Methyl3-((*t*-butoxycarbonyl)((1*S*,3*S*)-3-((*t*-butoxycarbonyl)amino)-4-((*t*-butyldimethylsilyl)oxy)-3-methyl-1-phenylbutyl)amino)propanoate (9): To a THF (10 mL) and H_2O (5 mL) solution of **8** (335 mg, 0.60 mmol), lithium hydroxide (214 mg, 8.93 mmol) was added and the reaction mixture was heated at 65 °C for 24 h.[15b] The reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl and the mixture was subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude carboxylic acid as an oil. The resulting carboxylic acid was dissolved in AcOEt and Et_2O. Subsequently, an Et_2O solution of diazomethane was added dropwise until the yellow color of the diazomethane solution persisted during several minutes. The solution was then kept under fume hood until solvent was completely evaporated. The residue was then purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 2/1) to give **9** as an oil (313 mg, 88%, 2 steps). R_f = 0.7 (hexane/AcOEt = 2/1). $[\alpha]^{25}_D$ –46 (*c* 0.41, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.29 (s, 3H), 1.38 (s, 9H), 1.48 (br s, 9H), 1.60–1.72 (m, 1H), 2.10–2.52 (m, 3H), 3.12–3.29 (m, 1H), 3.31–3.48 (m, 1H), 3.48–3.59 (m, 1H), 3.56 (s, 3H), 3.68–3.73 (m, 1H), 4.50–4.73 (m, 1H), 5.50 (brs, 1H), 7.17–7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, –5.4, 18.2, 22.3, 25.8, 28.4, 28.5, 33.9, 35.0, 39.4, 51.4, 53.9, 55.9, 67.3, 78.7, 80.0, 127.4, 127.7, 128.5, 141.5, 154.5, 155.2, 172.0. IR (neat): 3437, 2980, 2954, 2857, 1741 1720, 1691,

1497, 1462, 1408, 1366, 1253, 1168, 1105, 837, 777, 702 cm^{-1}. HRMS (FAB) calcd for $C_{31}H_{55}N_2O_7Si$ [$(M+H)^+$] 595.3779, found: 595.3773.

***t*-Butyl(4*S*,6*S*)-4-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyl-2-oxo-6-phenyltetrahydropyrimidine-1(2*H*)-carboxylate (12):** To a THF (3 mL) solution of hexamethyldisilazane (210 mg, 1.30 mmol) was added *n*-butyllithium (1.30 mmol, 0.81 mL of 1.6 M solution in *n*-hexane) at –78 °C under an argon atmosphere and the mixture was stirred at –78 °C for 1 h to give the first portion of LiHMDS (1.30 mmol). Then a THF (3 mL) solution of *p*-MeC_6H_4SH (162 mg, 1.30 mmol) was added and the mixture was stirred for 15 min. A THF (3 mL) solution of **9** (259 mg, 0.43 mmol) to the mixture and the reaction was stirred at –78 °C for 30 min and at 25 °C for 2 h. After that the reaction was cooled to –78 °C and stirred for 10 min, the second portion of LiHMDS (0.65 mmol), prepared from hexamethyldisilazane (106 mg, 0.65 mmol) and *n*-butyllithium (0.65 mmol, 0.41 mL of 1.6 M solution in *n*-hexane) in THF (3 mL), was added and stirred for additional 15 min at –78 °C. The reaction was stirred at 25 °C for 2 h. Next the reaction was again cooled to –78 °C and the third portion of LiHMDS (0.43 mmol), prepared from hexamethyldisilazane (70 mg, 0.43 mmol) and *n*-butyllithium (0.43 mmol, 0.27 mL of 1.6 M solution in *n*-hexane) in THF (3 mL), was added. Finally, the reaction was warmed to 25 °C and stirred for 20 h. The reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl and the mixture was concentrated under reduced pressure. The residue was partitioned with $CHCl_3$ and H_2O and subsequently extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 2/1) to give **12** as a solid (122 mg, 65%). R_f = 0.4 (hexane/AcOEt = 2/1). Mp 84–86 °C. $[\alpha]^{25}_D$ –32 (*c* 0.29, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 0.97 (s, 3H), 1.26 (s, 9 H), 1.90 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.26 (dd, *J* = 14.2, 5.5 Hz, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.51 (d, *J* = 9.6 Hz, 1H), 5.15 (s, 1H), 5.19 (dd, *J* = 8.7, 5.5 Hz, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.54, –5.48, 18.2, 25.2, 25.8, 27.6, 39.4, 53.8, 56.7, 69.8, 82.5, 125.4, 127.2, 128.6, 142.5, 151.6, 152.7. IR (KBr): 3480, 2929, 2857, 1756, 1638, 1458, 1409, 1367, 1309, 1252, 1146, 1093, 853, 779, 701 cm^{-1}. HRMS (FAB) calcd for $C_{23}H_{39}N_2O_4Si$ [$(M+H)^+$] 435.2679, found: 435.2680.

Di-*t*-butyl(4*S*,6*S*)-4-(((*t*-butyldimethylsilyl)oxy)methyl)-4-methyl-2-oxo-6-phenyldihydropyrimidine-1,3(2*H*,4*H*)-dicarboxylate (14): To a toluene (3 mL) solution of **12**

(10 mg, 0.023 mmol) was subsequently added DMAP (3 mg, 0.023 mmol) and di-*t*-butyl dicarbonate (25 mg, 0.12 mmol). The resulting mixture was heated at 90 °C for 1 h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 10/1 to 5/1) to give the corresponding product **14** as a solid (10 mg, 81%). R_f = 0.3 (AcOEt). Mp 96–97 °C. $[\alpha]^{25}_D$ –20 (*c* 0.09, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3H), δ = 0.12 (s, 3H), 0.93 (s, 9H), 1.16 (s, 12H), 1.53 (s, 9H), 1.93 (dd, *J* = 13.7, 10.5 Hz, 1H), 2.41 (dd, *J* = 13.7, 5.0 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 5.13 (dd, *J* = 10.5, 5.0 Hz, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.3, 22.7, 25.9, 27.4, 27.7, 41.8, 56.9, 58.4, 67.5, 82.7, 83.3, 125.7, 127.3, 128.6, 151.0, 151.2, 153.2. IR (KBr): 2928, 2855, 1765, 1734, 1673, 1386, 1367, 1247, 1136, 843, 784, 767 cm^{-1}. HRMS (FAB) calcd for $C_{28}H_{47}N_2O_6Si$ [$(M+H)^+$] 535.3203, found: 535.3195.

Di-*t*-butyl ((1*S*,3*S*)-4-hydroxy-3-methyl-1-phenylbutane-1,3-diyl)dicarbamate (16): A solution of **12** (257 mg, 0.59 mmol) in conc. HCl (3.0 mL) was stirred for 2 d at 120 °C (bath temp.).[19] The mixture was concentrated under reduce pressure to give a crude 1,3-diamine hydrochloride **15** as brown solid. The resulting ammonium salt was dissolved in THF (3 mL) and the solution was cooled to 0 °C. $NaHCO_3$ (348 mg, 4.14 mmol) was slowly added to the mixture at 0 °C. Subsequently, a THF (5 mL) solution of di-*t*-butyl dicarbonate (645 mg, 2.96 mmol) was added slowly during the time of 4 h at 0 °C. The reaction mixture was gradually warmed to rt and stirred for 20 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 2/1) to give **16** as a solid (170 mg, 73%, 2 steps). R_f = 0.3 (hexane/AcOEt = 2/1). Mp 117–119 °C. $[\alpha]^{25}_D$ –50 (*c* 0.47, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.32 (s, 18H), 2.03–2.07 (m, 1H), 2.17–2.24 (m, 1H), 3.53 (d, *J* = 11.9 Hz, 1H), 3.60 (d, *J* = 11.9 Hz, 1H), 4.60–4.63 (m, 1H), 4.86 (brs, 1H), 5.55 (brs, 1H), 7.11–7.29 (m, 5H). Signal of one OH or NH proton was not observed clearly. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0 28.3, 28.4, 42.3, 51.7, 56.4, 69.5, 79.5, 79.8, 126.1, 127.1, 128.7, 143.7, 155.3, 156.1. IR (KBr): 3411, 2979, 2932, 1686, 1510, 1455, 1391, 1366, 1252, 1170 1074, 700 cm^{-1}. HRMS (FAB) calcd for $C_{21}H_{35}N_2O_5$ [$(M+H)^+$] 395.2546, found: 395.2553.

(2*S*,4*S*)-2,4-Bis((*t*-butoxycarbonyl)amino)-2-methyl-4-phenylbutyl acetate (17): To a CH_2Cl_2 (3 mL) solution of **16** (150 mg, 0.38 mmol) were slowly added Ac_2O (0.4 mL) and Et_3N (0.5 mL)

during the time of 2 h at 0 °C under a nitrogen atmosphere and the reaction mixture was gradually warmed up to rt and stirred for 22 h. The mixture was concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 2/1) to give **17** as an oil (160 mg, 91%). R_f = 0.5 (hexane/AcOEt = 2/1). $[\alpha]^{25}_D$ –46 (*c* 0.33, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.33 (s, 9H), 1.34 (s, 9H), 1.82–2.10 (m, 1H), 1.97 (s, 3H), 2.17–2.22 (m, 1H), 4.04 (d, *J* = 11.0 Hz, 1H), 4.21 (d, *J* = 11.0 Hz, 1H), 4.72–4.76 (m, 2H), 4.98 (brs, 1H), 7.08–7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 22.9, 28.3, 42.5, 51.1, 54.2, 68.3, 79.3, 79.5, 125.9, 127.1, 128.6, 143.7, 154.4, 154.9, 170.6. IR (neat): 3420, 2979, 1742, 1718, 1700, 1521, 1366, 1247, 1169, 1042, 700 cm^{-1}. HRMS (FAB) calcd for $C_{23}H_{37}N_2O_6$ [$(M+H)^+$] 437.2652, found: 437.2649.

Di-*t*-butyl ((3*S*,5*S*)-5-methyl-2-oxotetrahydro-2*H*-pyran-3,5-diyl)dicarbamate (19): To a CCl_4 (2 mL) and MeCN (2 mL) solution of **17** (100 mg, 0.23 mmol) was added a H_2O (2 mL) solution of $RuCl_3$ hydrate (24 mg, 0.11 mmol) at rt and the reaction mixture was turned to be black after stirring. Subsequently, $NaIO_4$ (1.47 g, 6.9 mmol) was added and the black color of the mixture was turned to be yellow. The reaction was vigorously stirred at 25 °C for 24 h.[20] The reaction mixture was filtered and the filtrate was extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1 to 0/1, then AcOEt/MeOH = 10/1) to give the corresponding carboxylic acid **18**. To a dry MeOH (3 mL) solution of the resulting carboxylic acid **18** was added K_2CO_3 powder (158 mg, 1.15 mmol) at rt and the reaction mixture was stirred for 24 h.[20b] After the reaction mixture concentrated under reduced pressure, $CHCl_3$/H_2O (1/1, v/v, 4 mL) was added to the residue and the solution was acidified to pH 3–4 by the addition of 0.1 M $KHSO_4$ at 0 °C. The reaction mixture was warmed to rt and stirred for 24 h. The mixture was extracted with $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 10/1 to 2/1) to give **19** as a solid (36 mg, 46%, 3 steps). R_f = 0.3 (hexane/AcOEt = 2/1). Mp 183–184 °C. $[\alpha]^{25}_D$ +20 (*c* 0.30, $CHCl_3$); [lit.[5], $[\alpha]^{25}_D$ +19.1 (*c* 1.10, $CHCl_3$); lit.[4], $[\alpha]^{25}_D$ +21.5 (*c* 1.10, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3H), 1.44 (s, 9H), 1.45 (s, 9H) 1.60–1.68 (m, 1H), 2.68–2.77 (m, 1H), 4.18–4.26 (m, 1H), 4.51–4.62 (m, 2H), 4.75 (brs, 1H), 5.30 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 28.3, 39.7, 47.8, 50.7, 73.6, 80.4, 154.5, 155.1, 172.0; [lit.[5], δ = 25.8, 28.3, 39.7, 47.8, 50.7, 73.7, 80.3, 154.5,

155.1, 173.0; lit.[4], δ = 28.29, 29.66, 39.66, 47.78, 50.67, 73.65, 80.30, 154.52, 155.16, 172.05]. IR (KBr): 3444, 2978, 2927, 1718, 1696, 1636, 1519, 1247, 1164, 1045 cm^{-1}. HRMS (DART) calcd for $C_{16}H_{29}N_2O_6$ [$(M+H)^+$] 345.2026, found: 345.2033.

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SUPPORTING INFORMATION

Concise list of types of data or files found in the SI.

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(12) Catalytic method of the 1,3-dipolar cycloaddition of **1a** to **2** [(*S*,*S*)-DIPT (0.2 equiv), **1a** (1.0 equiv), **2** (1.0 equiv), $MgBr_2$ (1.0 equiv), *n*-BuMgCl (1.4 equiv), in EtCN at 80 °C, 7 d] (ref.10) gave the cycloadduct **3a** in 32% yield with 67% ee .

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学位論文審査報告書（甲）

１．学位論文題目（外国語の場合は和訳を付けること。）

Highly Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Imines and an Application to a Formal Total Synthesis of Manzacidin C （アゾメチンイミンの高エナンチオ選択的 1,3-双極子付加環化反応と Manzacidin C の形式全合成への応用）

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３．審査結果の要旨

提出学位論文について，各審査委員により個別に予備審査を実施するとともに，平成２９年２月６日に開催された口頭発表の結果を踏まえて，同日に論文審査委員会を開催して協議を行った。その結果，以下の様に判定した。

天然有機化合物の全合成研究は，天然から単離される化合物が極微量であり，その生理活性の探索には合成による化合物の供給が必要であることから，極めて重要である。沖縄の万座ビーチの海綿より単離された manzacidin C は，不斉４級炭素を含む *anti*-1,3-ジアミン部位を有する特徴的な構造を有するが，相対および絶対立体配置を制御して合成することは困難であった。本論文では，不斉合成を活用した manzacidin C の全合成研究について詳細に述べたものである。まず，アゾメチンイミンの不斉 1,3-双極子付加環化反応により，不斉４級炭素を含む *anti*-1,3-ジアミン部位の一挙構築を実現した。次に，得られた生成物からの官能基変換により，manzacidin C への変換が既知である光学活性ラクトンの合成に成功し，manzacidin C の不斉形式全合成を達成した。本論文の内容は，不斉合成手法を巧みに活用して有用な光学活性天然有機化合物合成への道筋をつけた研究として非常に意義深いことから，博士（理学）の学位に値するものと判断した。

４．審査結果　(1) 判　　定（いずれかに○印）（合　格）・

博士（理学）