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

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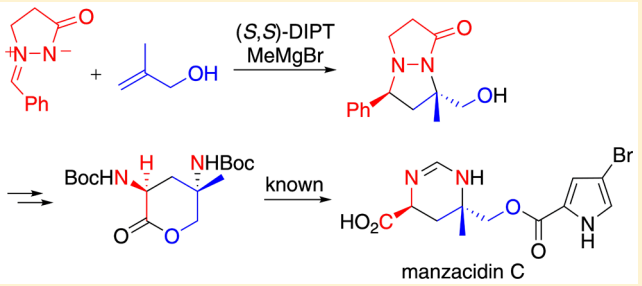
Supporting Information

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.



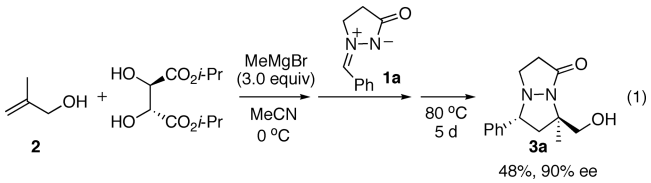
INTRODUCTION

Manzacidins A−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 diazo ester. Leighton reported the enantioselective establishment of two stereocenters via acyl hydrazone−alkene [3 + 2] cycloaddition.[6−8]

Stereoselective construction of 1,3-diamine skeletons is still a challenging task. 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**; 2-methylprop-2-en-1-ol), 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 the 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 was successfully removed through N−N bond cleavage followed by a retro-Michael addition reaction.

RESULTS AND DISCUSSION

First, we examined the asymmetric 1,3-dipolar cycloaddition of a phenyl-substituted azomethine imine possessing pyrazolidinone skeleton **1a** to methallyl alcohol (**2**) according to the previously reported procedure.[10a] 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 an 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 methallyl alcohol (**2**), cycloaddition proceeded rather



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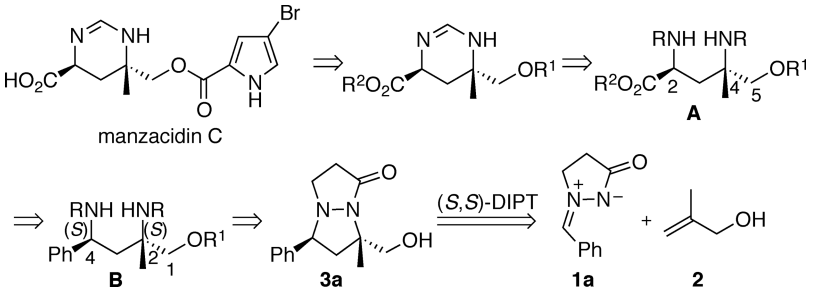
Scheme 1. Retrosynthetic Analysis of Manzacidin C

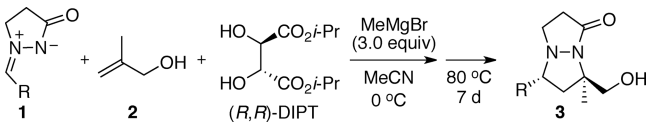


slowly in comparison with the cycloaddition to prop-2-en-1-ol.[11] After 5 days, the corresponding pyrazolidine **3a** was obtained as a single diastereomer in 48% yield.[12] The optical purity of the product was high at 90% ee. However, the chemical and optical yields fluctuated.

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 reproducibly excellent enantioselectivity of 95% ee (Table 1, entry 1).[13,14]

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

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



1 2 3

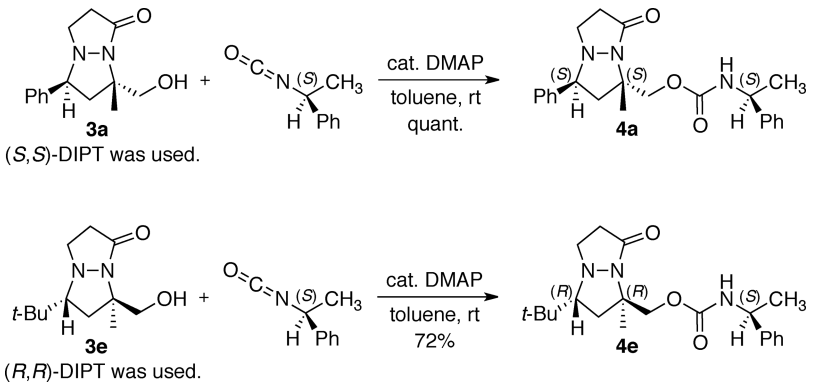
entry	R		yield/%	ee/%[a]
1[b]	Ph	**a**	59	95
2	*p*-MeC_6H_4	**b**	45	91
3	*p*-ClC_6H_4	**c**	51	91
4	*c*-Hex	**d**	63	85
5	*t*-Bu	**e**	56	88

[a]Enantioselectivities were determined by HPLC analysis (Daicel CHIRALPAK IA). [b](*S,S*)-DIPT was used instead of (*R,R*)-DIPT, and the *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.[13] 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** (quantitative) (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 configuration 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 putative absolute configuration of the other products **3b−d** by the use of (*R,R*)-DIPT was *R,R*.

The precise transition state of the present 1,3-dipolar cycloaddition is not yet clear. The transition state models as shown in Figure 1 could be proposed on the basis of the absolute configuration of **3a,e** and our previous results.[10] The carbonyl oxygen atom of azomethine imine **1** coordinates to the magnesium salt of (*R,R*)-DIPT as depicted in $\mathbf{T_1}$−$\mathbf{T_4}$. The nitrogen atom connected with the carbonyl group attacks the disubstituted internal olefinic carbon of methallyl alcohol (**2**; R′ = CH_3), which might be rather interrupted in comparison to the addition to the monosubstituted internal carbon of

Scheme 2. Determination of Absolute Stereochemistry of 3a,e[a]



[a]ORTEP drawings of **4a,e** are given in the Supporting Information.

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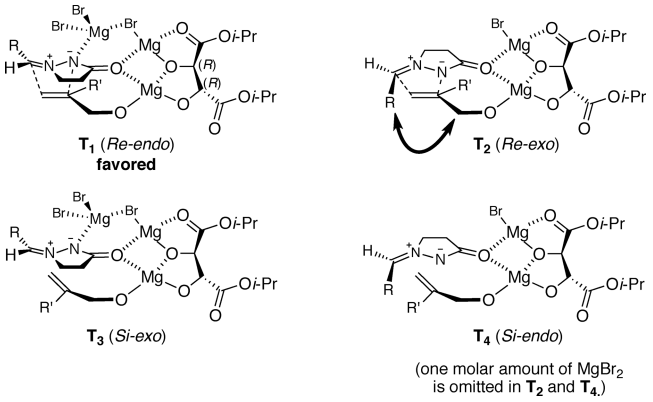


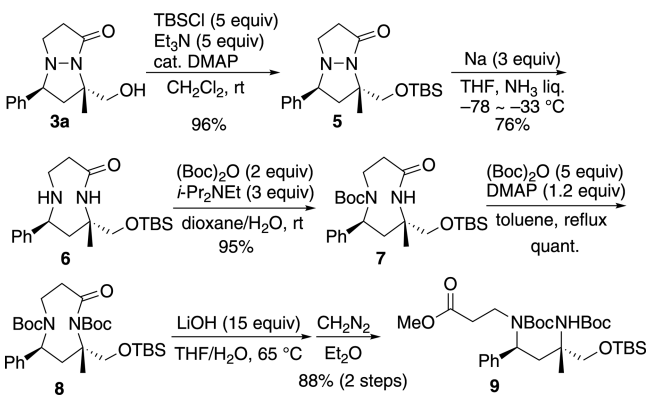
Figure 1. Proposed transition state models.

prop-2-en-1-ol (R′ = H). If the cycloaddition from the *Si* face of the internal olefinic carbon of methallyl alcohol in an exo or endo fashion is assumed, the azomethine imine unit and double bond in methallyl alcohol are located in a skew fashion with each other. Therefore, overlap between the azomethine imine unit and double bond would be rather difficult ($\mathbf{T}_3$ and $\mathbf{T}_4$). In the case of addition from the *Re* face, the exo transition state $\mathbf{T}_2$ might be disfavored due to the steric congestion between the substituent R in the azomethine imine and the methylene moiety in methallyl alcohol. As a result, the cycloaddition proceeds in an endo fashion from the *Re* face to afford *R*,*R* cycloadduct **3**.

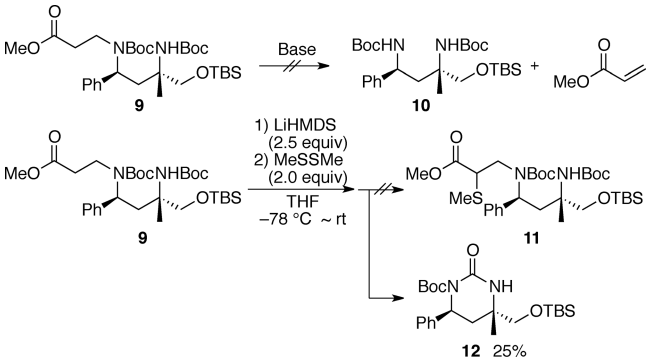
With optimized conditions for the asymmetric 1,3-dipolar addition of azomethine imines to methallyl alcohol in hand, we turned our attention to the total synthesis of manzacidin C. One of the major challenges in synthesizing manzacidin C is the removal of the three-carbon bridge on the pyrazolidine ring. 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.[15] 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 intense examinations, we decided to cleave the N−N bond first. Thus, the pyrazolidine **3a** was converted to the corresponding *tert*-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.[16] Stepwise Boc protection of the resulting amine and amide moieties was performed to afford the corresponding Boc-protected eight-membered azalactam derivative **8** in 95% yield. Although ring opening of the *N*-Boc azalactam **8** by treatment with phenyl or ethyl Grignard reagents did not proceed,[17a] a selective nucleophilic attack on the ring carbonyl group by a small nucleophile, a hydroxide ion, was achieved by the use of LiOH to afford the *N*-substituted *ω*-amino acid.[17b] 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



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



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,[18a] *t*-BuOK,[18b] 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*-positions of the ester and execute an oxidative cleavage. The electrophilic introduction of a sulfide moiety commenced by treatment with dimethyl disulfide and LiHMDS.[19] In this reaction, the desired *α*-sulfenated product **11** was not obtained. To our surprise, the unpredicted urea product **12** without the propanoate moiety on nitrogen was instead isolated in 25% yield. From ^{1}H NMR analyses of the byproducts whose structures were not yet determined, 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 of 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 analyses of the ^{1}H NMR spectra of the byproducts.[20] 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).

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**,

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Scheme 5. Proposed Pathway from 9 to 12

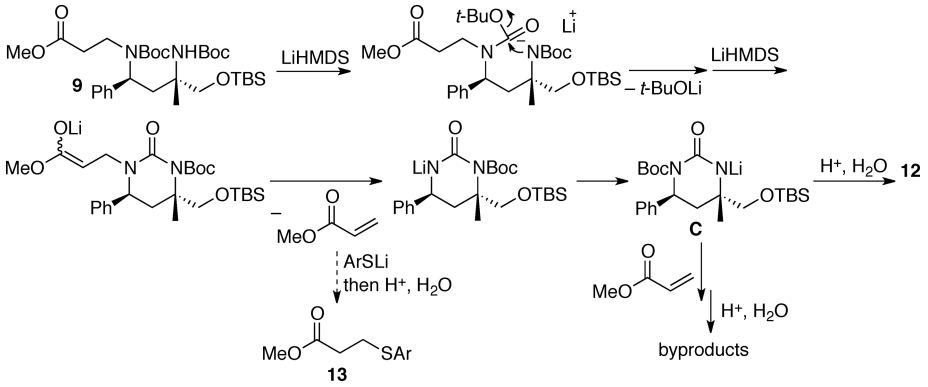
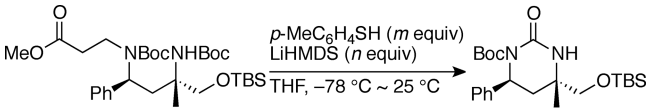


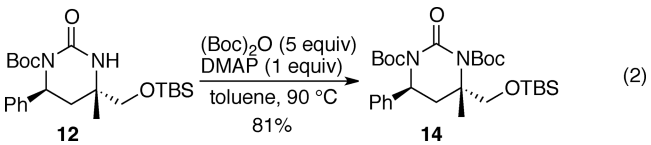
Table 2. Retro-Michael Addition Reaction from 9



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 twice in amounts of of 2.3 and 0.7 equiv, respectively. [c]LiHMDS was added in three parts of 3.0, 1.5, and 1.0 equiv, respectively: see the Experimental Section.

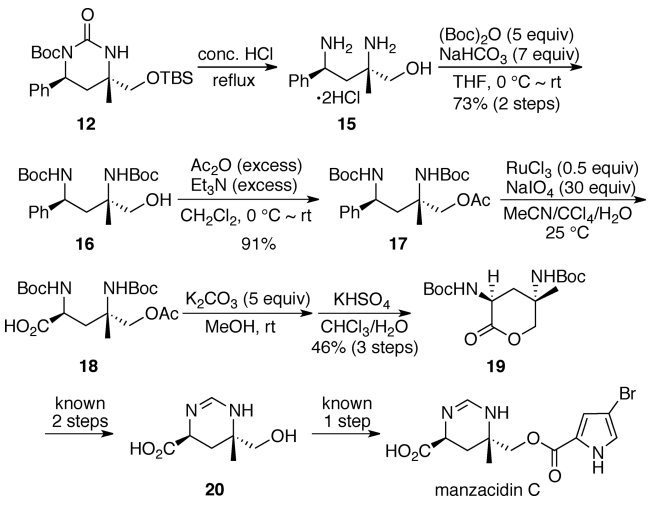
which suggests that the Boc group in **12** existed on the benzylic amine moiety.



(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 concentrated HCl under reflux conditions, the hydrolysis proceeded to give the 1,3-diamine hydrochloride **15**.[21] Boc protection of the resulting 1,3-diamine moiety gave **16** in 73% yield in two 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**.[22] Finally, after rough 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 with those reported in the literature.[4,5] The synthesis of manzacidin C in three steps from the lactone **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. ^1H 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). An 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 mixture was stirred at 0 °C for 0.5 h, at room temperature for 1 h, and then for 7 days at 80 °C. The reaction was quenched by the addition of a saturated 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

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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−e** 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** (391 mg, 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/isopropyl alcohol = 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 (br s, 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 (br s, 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), 2.30−2.36 (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)$^+$] 253.1916, found 253.1915.

(5*R*,7*R*)-5-(*tert*-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 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 room temperature for 5 days 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, quantitative). 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, $P2_1$ (No. 4), *a* = 9.5902(2) Å, *b* = 9.9373(3) Å, *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 $I > 3.00\sigma(I)$ and 265 variable parameters. CCDC 1518209 (**4a**) contains supplementary crystallographic data for this compound. 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 (br s, 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 **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 room temperature for 4 days 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, $P2_12_12_1$ (No. 19), *a* = 7.5338(2) Å, *b* = 15.4969(4) Å, *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 $I > 3.00\sigma(I)$ and 248 variable parameters. CCDC 1524360 (**4e**) contains supplementary crystallographic data for this compound. 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. ^{1}H NMR for the 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 ^{1}H NMR

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data of the minor isomer: 1.36 (s, 3H), 5.22 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 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-(((*tert*-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), and *tert*-butyldimethylsilyl chloride (9.18 g, 60 mmol) were successively added and stirred at room temperature under a nitrogen atmosphere. After 24 h, cold water with ice was added and the mixture was stirred 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/AcOEt = 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-(((*tert*-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 amounts until the solution turned dark blue.[16] After it was stirred for 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 between $CHCl_3$ 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 Hz, 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.

***tert*-Butyl (2*S*,4*S*)-4-(((*tert*-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) was slowly added di-*tert*-butyl dicarbonate (4.82 g, 22 mmol), and the reaction mixture was kept at room temperature for 24 h under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ 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 ^{1}H 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 a ratio of 2/1. ^{1}H 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 (br s, 1H), 7.26−7.36 (m, 5H); selected data of minor isomer, δ 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, δ −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-*tert*-Butyl (2*S*,4*R*)-2-(((*tert*-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) were added DMAP (1.23 g, 10 mmol) and di-*tert*-butyl dicarbonate (9.14 g, 42 mmol) 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, quantitative). R_f = 0.4 (hexane/AcOEt = 5/1). $[\alpha]^{25}_D$ = −128 (c 0.31, EtOH). In ^{1}H 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 a ratio of 2/1. ^{1}H NMR (400 MHz, $CDCl_3$): 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, δ 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, $CDCl_3$): 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.

Methyl 3-((*tert*-Butoxycarbonyl)((1*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-4-((*tert*-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) was added lithium hydroxide (214 mg, 8.93 mmol), and the reaction mixture was heated at 65 °C for 24 h.[17b] The reaction was quenched by the addition of a saturated 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 a fume hood until the 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 (br s, 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}.

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HRMS (FAB): calcd for $C_{31}H_{55}N_2O_7Si$ [(M + H)$^+$] 595.3779, found 595.3773.

***tert*-Butyl (4*S*,6*S*)-4-(((*tert*-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 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) was added to the mixture, and the reaction mixture was stirred at −78 °C for 30 min and at 25 °C for 2 h. After the reaction mixture 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 hexane) in THF (3 mL), was added and stirred for an additional 15 min at −78 °C. The reaction mixture was stirred at 25 °C for 2 h. Next the reaction mixture was again cooled to −78 °C and a 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 hexane) in THF (3 mL), was added. Finally, the reaction mixture was warmed to 25 °C and stirred for 20 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl, and the mixture was concentrated under reduced pressure. The residue was partitioned between $CHCl_3$ 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-*tert*-butyl (4*S*,6*S*)-4-(((*tert*-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) were subsequently added DMAP (3 mg, 0.023 mmol) and di-*tert*-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-*tert*-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 concentrated HCl (3.0 mL) was stirred for 2 days at 120 °C (bath temperature).[21] The mixture was concentrated under reduced pressure to give the crude 1,3-diamine hydrochloride **15** as a 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-*tert*-butyl dicarbonate (645 mg, 2.96 mmol) was added slowly over 4 h at 0 °C. The reaction mixture was gradually warmed to room temperature 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%, two 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 (br s, 1H), 5.55 (br s, 1H), 7.11−7.29 (m, 5H). The 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((*tert*-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) over 2 h at 0 °C under a nitrogen atmosphere, and the reaction mixture was gradually warmed to room temperature and stirred for 22 h. The mixture was concentrated under reduced 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 (br s, 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-*tert*-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 room temperature, and the reaction mixture turned black after stirring. Subsequently, $NaIO_4$ (1.47 g, 6.9 mmol) was added and the black mixture turned yellow. The reaction mixture was vigorously stirred at 25 °C for 24 h.[22] 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 room temperature, and the reaction mixture was stirred for 24 h.[22b] After the reaction mixture was 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 room temperature 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 (br s, 1H), 5.30 (br s, 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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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H NMR and ^{13}C NMR spectra of products, ORTEP drawings of **4a**,**e**, and HPLC data of cycloadducts **3** (PDF)

Crystallographic data of **4a** (CIF)

Crystallographic data of **4e** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) The cycloaddition reaction of **1a** to prop-2-en-2-ol gave the corresponding cycloadduct in 74% yield with 95% ee after 2 days and in 81% yield with 94% ee after 4 days.[10a]

(12) Even after 5 days, the starting azimethine imine **1a** still remained. We observed ca. 15% of benzaldehyde, which was generated from the unreacted **1a** by hydrolysis, in the crude reaction mixture after aqueous workup by ^{1}H NMR analysis.

(13) For the synthesis of manzacidin C, (*S*,*S*)-DIPT was used as a chiral auxiliary in the case of phenyl-substituted azomethine imine **1a**.

(14) 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 days)[10] gave the cycloadduct **3a** in 32% yield with 67% ee.

(15) Examples of cleavage of fused pyrazolidinone ring: (a) Turk, C.; Golič, L.; Selič, L.; Svete, J.; Stanovnik, B. *ARKIVOC* **2001**, 87−97. (b) Foroughifar, N.; Mobinikhaledi, A. *Asian J. Chem.* **2002**, *14*, 1441−1452. (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334−5335. (d) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324−6327. (e) Luo, N.; Zheng, Z.; Yu, Z. *Org. Lett.* **2011**, *13*, 3384−3387. (f) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337−13348. (g) Hori, M.; Sakakura, A.; Ishihara, K. *J. Am. Chem. Soc.* **2014**, *136*, 13198−13201. (h) Winterton, S. E.; Ready, J. M. *Org. Lett.* **2016**, *18*, 2608−2611.

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