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Complementary Stereocontrolled Approaches to 2-Pyrrolidinones Bearing a Vicinal Amino Diol Subunit with Three Continuous Chiral Centers: A Formal Asymmetric Synthesis of (−)-Detoxinine

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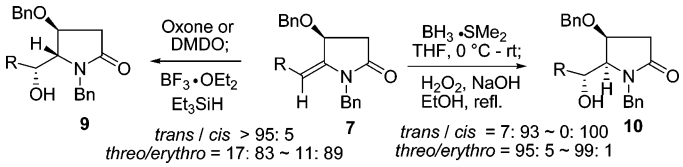
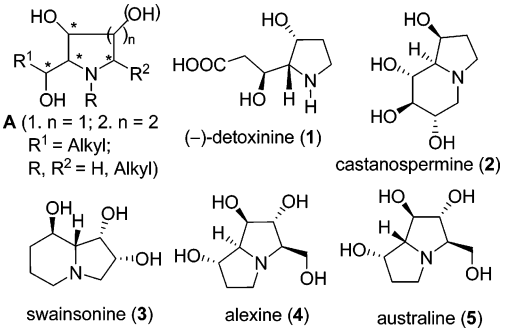


We report herein two stereocomplementary approaches to *erythro/trans* and *threo/cis* vicinal amino diol subunits containing 2-pyrrolidinones (**9** and **10**) starting from the known enamides **7**, easily available from malimides. The first approach consists of an epoxidation−reductive dehydroxylation procedure, and the second one is based on hydroboration−oxidation reactions. Using the second method, a formal asymmetric synthesis of (−)-detoxinine was achieved.

Introduction

Cyclic vicinal amino diols having three consecutive chiral centers as represented by the generic structure **A** are key substructures found in a number of polyhydroxylated bioactive alkaloids,[1] azasugars,[2] and amino acids.[3] Representative examples include the unusual amino acids (−)-detoxinine (**1**),[3−5] castanospermine[6] (**2**), swainsonine[7] (**3**), alexine[8] (**4**), and australine[9] (**5**) (Chart 1). The important bioactivities[1−4] exhibited by these molecules in association with their intriguing structural features make them attractive targets for the development of drugs and biological tools[2] as well as for testing synthetic strategies. Consequently, the asymmetric synthesis of these natural products and their stereoisomers has attracted considerable attention, and a number of ingenious approaches have been developed.[1,2,4,5,7,10,11]

CHART 1. Structure of Some Vicinal Amino Diol Subunits Containing Natural Products



As can be seen from Chart 1, both *cis* and *trans* stereochemical patterns around the pyrrolidine ring exist in these natural products. Except for some approaches using carbohydrates as the chiral starting materials, the stereoselective construction of the vicinal amino diol moiety with three continuous chiral centers remains a challenging problem, in particular, for the exocyclic chiral center.[11,5b,c] Among the known approaches to the compounds of type **A**, organometallic reagent addition to

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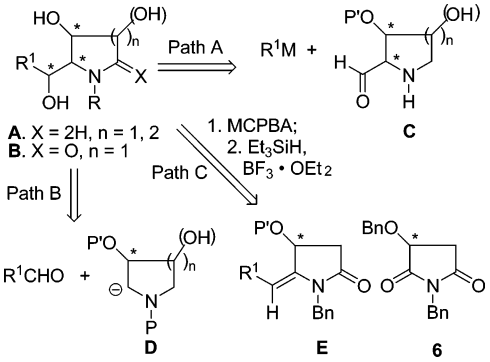
SCHEME 1. Typical Approaches to *N*-Containing Cyclic Compounds Having a Vicinal Amino Diol Substructure



2-formyl pyrrolidines[5b,c,12] **C** (Scheme 1, path A) and the reaction of pyrrolidine α-carbanions[13] of type **D** (Scheme 1, path B) with aldehydes represent two typical ones. Recently, we reported the third flexible approach to the building blocks with generic structure **B**, which relies on the epoxidation−reduction of the enamides[14] **E**. The major drawback of the reported approaches is two-fold, namely, poor stereoselectivity at the newly formed exocyclic chiral center[5b,c,12−14] and the limitation to only one, generally, *trans* diastereomer.[5b,c,12−14] In continuation of our work on the asymmetric synthesis of the scaffold **A**-containing alkaloids,[12,13] we now report two complementary and highly diastereoselective methods, which allow for control of the two newly formed stereocenters with either *trans* or *cis* stereoselectivity at the 2-pyrrolidinone ring (**B**). In addition, a formal asymmetric synthesis of (−)-detoxinine is disclosed.

Results and Discussion

Recently, we have reported an approach to scaffold **B** by epoxidation of enamides[14] **E** with *m*-chloroperbenzoic acid (MCPBA) followed by reductive dehydroxylation.[15] This method shows high *trans* diastereoselectivities at the pyrrolidine ring but only 1:1 to 1:4 *threo/erythro* diastereoselectivities at the exocyclic chiral center. Taking into account that the exo-diastereoselectivity in the transformation of **7** to **9** is determined in the epoxidation step, and to improve the stereoselectivity at the C1′ position, we investigated the use of oxidants other than MCPBA.[15] A search of literature revealed that a number of oxidation systems have been used to functionalize the enamides, which include dimethyldioxirane (DMDO),[15a,b,e,f,16] Oxone,[17] OsO_4/*N*-methylmorpholine-*N*-oxide,[18] microencapsulated OsO_4/NMO,[15c] $K_2OsO_4 \cdot 2H_2O/K_3Fe(CN)_6$,[15c] Jacobsen epoxidation,[19] Sharpless dihydroxylation,[15a,19] PhIO/MnO,[15a] (*S,S*)-(salen)Mn^{III}-Cl,[15a] and anodic oxidation conditions,[20] etc. Considering the environmental, economical, safety, and practice factors, Oxone ($2KHSO_5 + KHSO_4 + K_2SO_4$, potassium peroxomonosulphate), an oxidant that is stable and commercially available in large quantities, was selected for our investigation. Thus, treatment of a methanolic solution of **7d** (**7**, R = *i*-Pr) with Oxone resulted in, after reductive demethoxylation ($F_3B \cdot OEt_2$, Et_3SiH, CH_2-

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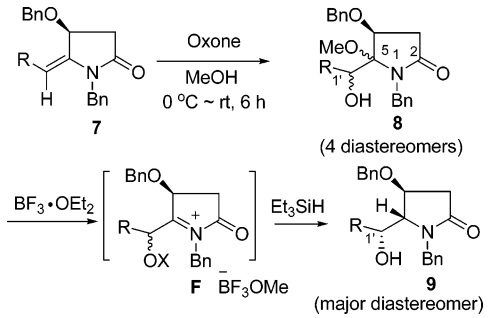
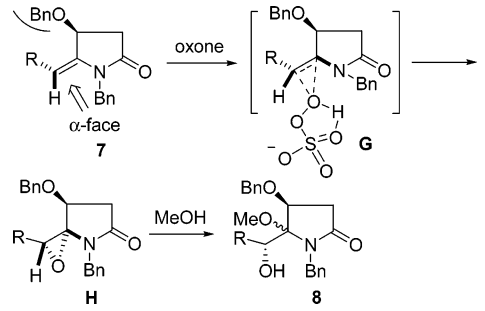
SCHEME 2



Cl_2, −78 °C to room temperature),[14,21] the formation of *erythro*/*trans*-**9d** (**9**, R = *i*-Pr) in an 8:1 diastereomeric ratio (Scheme 2). Encouraged by this result, the transformation of other enamides (**7**) to **9** was investigated, and as shown in Table 1, much better diastereoselectivities (from 1:3.8 to 1:8) than those using MCPBA (from 1:1 to 1:4)[14] were observed.

The stereoselectivity of the reaction can be rationalized by the approach of oxone from the less hindered α-face of the C═C bond in **7** to avoid the steric interaction with the benzyloxyl group at C4 (Scheme 3). The epoxide **H** thus formed was subjected to in situ solvolysis with methanol, which gave the epoxide ring opening product **8**.

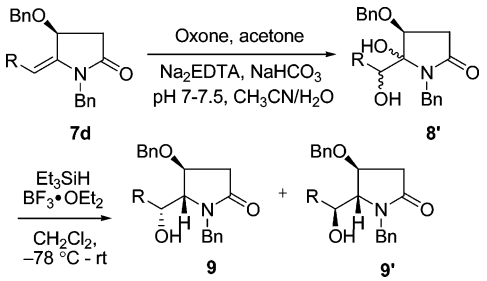
SCHEME 3. Possible Mechanism for Oxone Epoxidation of Enamide 7



In view of the high diastereoselectivities observed in the epoxidation of enamides[15a,b,e,16] or glycals[22] by DMDO, we also tested the epoxidation of **7** using DMDO, generated in situ from Oxone and acetone[23] (Scheme 4). However, as can be seen from Table 2, since there was no significant improvement over the diastereoselectivities, a systematic investigation of the DMDO oxidation was not pursued.

Given the stereodiversity of the cyclic vicinal amino diol systems as mentioned previously, we then turned our attention to explore other reaction conditions to establish other stereochemical patterns at the scaffold **B**. On the basis of the consideration that the observed *trans* stereochemistry in the BF_3•OEt_2-promoted Et_3SiH reduction[14,21] is a result of the *cis* attack of a hydride to the *N*-acyliminium intermediate **F** (Scheme

SCHEME 4



2),[14,24] the *trans* attack of a hydride to the enamide **7** would lead to *cis* diastereoselection at the 2-pyrrolidinone ring. The hydroboration−oxidation of enamines[25] has been known for a long time. Applications of this procedure to enamides have also been reported.[26] While the stereoselectivities of such a reaction at the rings are generally good,[26] to the best of our knowledge, those at the exocyclic stereocenters remain unknown. Considering the rigidity of our enamide system **7**, it was expected that the hydroboration−oxidation would provide good cyclic/exocyclic stereochemical control. Indeed, when enamide **7b** (**7**, R = Me) was treated successively with BH_3•SMe_2 in THF at room temperature and alkaline hydrogen peroxide (H_2O_2, NaOH) at reflux, compound **10b** (**10**, R = Me) was obtained as the only isolable diastereomer (Scheme 5), which means that the reaction proceeded with high cyclic and exocyclic stereoselectivities.

Encouraged by this result, the transformation of other enamides (**7**) to **10** was carried out, and as shown in Table 3, excellent cyclic and exocyclic diastereoselectivities were observed.

The *threo* (*syn*) stereochemistry of the product **10b** was confirmed by X-ray diffraction crystallographic analysis of the *O*-debenzylated product **11** (Figure 1). This allows us to speculate that the stereoselectivity of the hydroboration−oxidation is the result of, first, a *trans* attack of a borane to the α-face of the enamide C═C bond, namely, opposing the C-4 benzyloxyl group, and second, a retention of configuration during the migration of the alkyl group from *B* to *O* of the intermediate (Scheme 6).

To further demonstrate the flexibility of the method, we elected to synthesize polyhydroxylated pyrrolidinone **10i** and pyrrolidine **12** because such compounds have been used as the key intermediates for the asymmetric synthesis of (−)-retronecine,[27a] (+)-retronecine,[27] and (−)-detoxinine (**1**).[5g,h] (−)-

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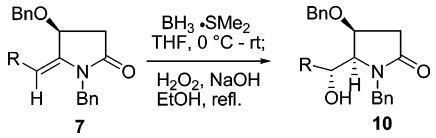
TABLE 1. Results of Oxone Epoxidation−Ring Opening of 7 and Subsequent Reductive Demethoxylation Reaction Leading to 9

entry	R	epoxidation (yield, %)[a]	reduction (yield, %)[b]	**9**: d.s. at C1′ *threo/erythro* ratio (using Oxone)	**9**: d.s. at C1′ *threo/erythro* ratio (using MCPBA)
1	Me	80 (**8a**)	84 (**9a**)	17:83[c]	38:62
2	Et	68 (**8b**)	84 (**9b**)	11:89[d]	33:67
3	*n*-Pr	74 (**8c**)	88 (**9c**)	21:79[d]	33:67
4	*i*-Pr	85 (**8d**)	82 (**9d**)	11:89[c]	20:80
5	*n*-Bu	87 (**8e**)	75 (**9e**)	16:84[d]	50:50
6	n-C_6H_{13}	88 (**8f**)	90 (**9f**)	18:82[d]	20:80
7	Ph	62 (**8g**)	64 (**9g**)	12.5:87.5[c]	28:72
8	$PhCH_2$	75 (**8h**)	73 (**9h**)	17:83[d]	40:60

[a] Combined yield of four diastereomers. [b] Combined yield of two diastereomers (only two diastereomers were obtained). [c] Ratio determined by ^{1}H NMR. [d] Diastereomeric ratio determined by chromatography separation.

Detoxinine is the parent structure of 10 components of the detoxin complex,[3,4] which have been isolated from the fermentation broth of *Streptomyces caespitosus* var. *detoxicus 7072 GC1*. As the first isolated natural product displaying detoxification as its bioactivity, the detoxin complex is applied as a selective antagonist against the cytotoxic activity of the nucleoside antibiotic blasticidin S (a fungicide used in the treatment of rice blast disease)[28] without impeding the antibiotic effect.[29] In vivo studies also showed that its administration decreased eye irritation caused by the antibiotic together with a remarkable decrease of conjunctivitis in rats.[28]

SCHEME 5



Treatment of (*R*)-malimide **6** with allyl magnesium bromide followed by TsOH catalyzed dehydration[22] gave enamide **7i** as an 8:1 *E/Z* geometric mixture in yields ranging from 59% to 63% over two steps (Scheme 7). Double hydroboration−oxidation of (*E*)-**7i** with a 1 M solution of a borane dimethyl sulfide complex provided lactam **10i** in 35% yield. Such a compound has served as a useful intermediate for the asymmetric synthesis of (−)-retronecine according to Nishimura et al.[27a] and Greene et al's procedures.[27b] Further reduction of the amide **10i** with the borane complex furnished pyrrolidine **12** in 83% yield. One-pot *N*,*O*-bisdebenzylation/*N*-protection provided pyrrolidinol **13** in 80% yield. The synthetic product **13** shows identical physical and spectral data to those reported (mp: 77 to 78 °C and lit.[5g] mp: 78 to 80 °C; $[\alpha]_D^{20}$ −63.5 (*c* 0.3, $CHCl_3$) and lit.[5g] $[\alpha]_D^{20}$ −61.3 (*c* 1.0, $CHCl_3$). Since compound **13** has been converted to detoxinine (**1**),[5g] our synthesis of **13** thus constitutes a formal asymmetric synthesis of detoxinine (**1**). It is noteworthy that the present synthesis of **13** also confirmed the *E*-stereoselection in the formation of **7** and *cis/threo* stereoselectivity in the hydroboration−oxidation of (*E*)-**7**.

Compound **15**, a higher homologue of **12**, was also synthesized from (*S*)-malimide **6** by the synthetic sequence depicted in Scheme 8, which consisted of 4-silyloxybutyl magnesium bromide addition, TsOH-mediated dehydration of the major diastereomer, hydroboration−oxidation, and amide reduction with borane.

In summary, using oxone as the oxidant, the epoxidation−reductive dehydroxylation of the known enamides **7** led to the substituted 2-pyrrolidinone **9** in 3.8:1 to 8:1 *erythro* selectivities and excellent *trans* diastereoselectivities; better *erythro* selectivities were observed with DMDO in cases where the *erythro* selectivities were modest using oxone. Alternatively, hydroboration−oxidation of enamides **7** afforded **10** in excellent *cis* diastereoselectivities (93:7 to 100:0) with *threo* selectivities ranging from 95:5 to 99:1. Using the hydroboration-based method, a formal asymmetric synthesis of (−)-detoxinine was achieved.

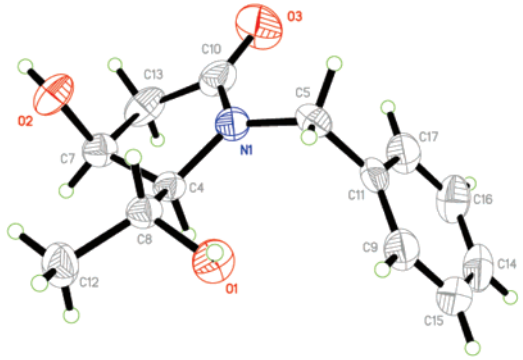
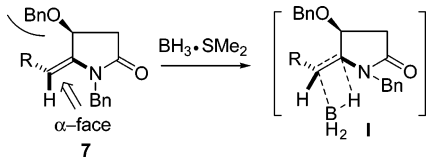


FIGURE 1. X-ray structure of **11**.

SCHEME 6



Experimental Section

General Procedure A: Preparation of 9 from 7 by Oxone Epoxidation−Reductive Dehydroxylation. To a suspension of Oxone (3.075 g, 5.0 mmol) and $NaHCO_3$ (504 mg, 6.0 mmol) in MeOH (5 mL) was added a methanolic solution (5 mL) of an enamide **7** (1.0 mmol), prepared as described previously.[14] After stirring for 6 h, the solid materials were removed by filtration. The filtrate was diluted with CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Filtration through a short pad of SiO_2 eluting with ethyl acetate-petroleum ether gave a diastereomeric

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(28) (a) Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem.* **1985**, *50*, 5210−5214. (b) Roche, C.; Kadlecikova, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 8352−8363.

(29) Kakinuma, K.; Otake, N; Yonehara, H. *Tetrahedron Lett.* **1972**, 2509−2512.

TABLE 2. Results of DMDO Epoxidation of 7 and Subsequent Reductive Dehydroxylation Reaction Leading to 9

entry	R	oxidation step (yield, %)[a]	reduction step (yield, %)[b]	**9**: d.s. at C1′ *threo/erythro* ratio (using DMDO)[c]	**9**: d.s. at C1′ *threo/erythro* ratio (using Oxone)[c]
1	Et	73 (**8b**)	73 (**9b**)	17:83	11:89
2	*n*-Pr	68 (**8c**)	79 (**9c**)	17:83	21:79
3	*n*-Bu	57 (**8e**)	81 (**9e**)	12.5:87.5	16:84
4	*n*-C_6H_{13}	69 (**8f**)	85 (**9f**)	12.5:87.5	18:82

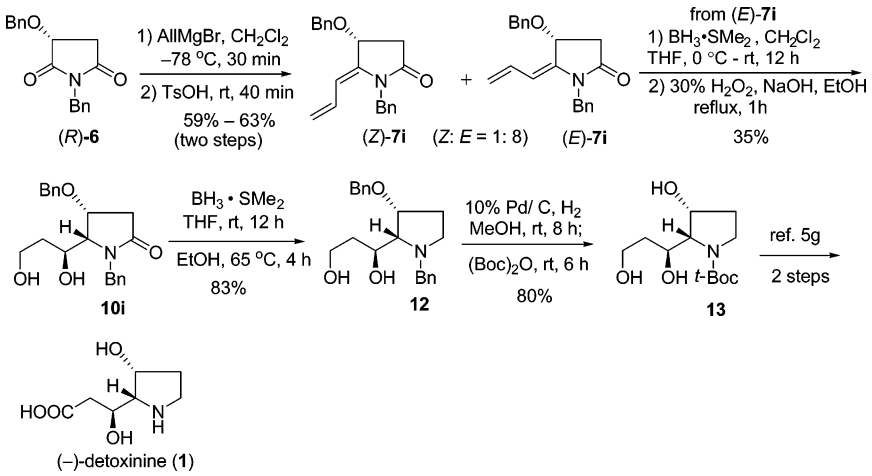
[a] Combined yield of four diastereomers. [b] Combined yield of two diastereomers (only two diastereomers were obtained). [c] Diastereomeric ratio determined by chromatography separation.

TABLE 3. Results of One-Pot Hydroboration (BH_3·SMe_2)−Oxidation (H_2O_2) of 7

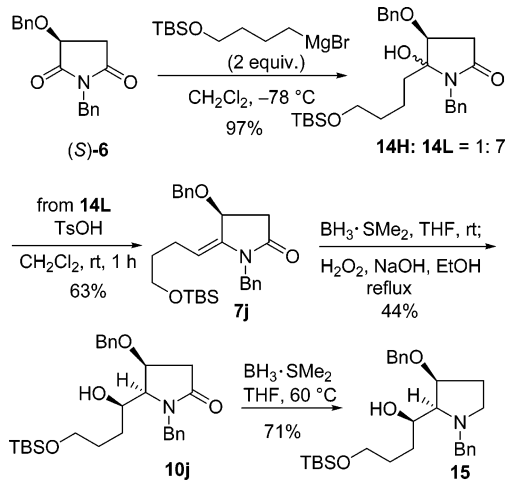
entry	R	yield (%) of **10**	d.s. at C5 *cis/trans*[a]	d.s. at C1′ *threo/erythro*[b]
1	H	62 (**10a**)	*ca.* 100:0	
2	Me	54 (**10b**)	*ca.* 100:0	99:1
3	Et	62 (**10c**)	96:4	99:1
4	*n*-Pr	78 (**10d**)	*ca.* 100:0	95:5
5	*i*-Pr	45 (71) (**10e**)	*ca.* 100:0	99:1
6	*n*-Bu	74 (**10f**)	*ca.* 100:0	99:1
7	*n*-C_6H_{13}	70 (**10g**)	93:7	96:4
8	$PhCH_2$	61(**10h**)	95:5	99:1
9	CH_2═CH	35 (**10i**)	*ca.* 100:0	99:1
10	$TBSOC_4H_8$	44 (**10j**)	*ca.* 100:0	99:1

[a] Diastereomeric ratio determined by chromatography separation. [b] Diastereomeric ratio determined by ^{1}H NMR.

SCHEME 7



SCHEME 8



mixture of **8** (yields: 62% to 88%), which without separation was used directly in the subsequent reductive dehydroxylation (Et_3SiH/F_3B·OEt_2) as described previously[14] to give the lactam **9** as a mixture of diastereomers. The diastereomeric ratios were determined either by flash chromatographic separation or by ^{1}H NMR analysis of the crude mixture. The characterization of lactams **9** was reported previously,[14] and the diastereomeric ratios were shown in Table 1.

General Procedure B: Preparation of 9 from 7 by DMDO Epoxidation−Reductive Dehydroxylation. To a CH_3CN solution (3.0 mL) of **7**[14] (0.28 mmol) and acetone (0.02 mL) at room temperature was added an aqueous Na_2EDTA solution (2 mL, 4×10^{-4} M). To this mixture was added portionwise a mixture of Oxone (676 mg, 1.1 mmol) and sodium bicarbonate (278 mg, 3.3 mmol). The reaction was complete in 8 h at room temperature as indicated by TLC monitoring. The reaction mixture was poured into water and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Filtration through a short pad of SiO_2 eluting with ethyl acetate-petroleum ether gave a mixture of diastereomers **8′**[14] (yield: 57% to 73%). Without separation, compound **8′** was used directly in the subsequent reductive dehydroxylation (Et_3SiH/F_3B·OEt_2) as described previously[14] to give the lactam **9** as a mixture of diastereomers. The diastereomeric ratios were determined either by flash chromatographic separation or by ^{1}H NMR spectra of the crude mixture. The characterization of lactams **9** has been reported previously,[14] and the diastereomeric ratios are shown in Table 2.

General Procedure C: Preparation of 10 from 7 by BH_3·SMe_2/H_2O_2. To a cooled (0 °C) solution of **7** (1.0 mmol) in THF (4 mL) was added dropwise borane dimethyl sulfide (0.1 mL, 1.03 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with ethanol (1.7 mL) and then treated with an aqueous solution of 3 N NaOH (0.37 mL, 1.13 mmol). To the resulting mixture was added dropwise 1 mL of H_2O_2 (30%) at 0 °C. The reaction mixture was refluxed for 1 to 2 h. After cooling, the reaction mixture was poured into ice water and then extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give **10**.

(*R*,*E*/*Z*)-1-Benzyl-4-benzyloxy-5-allylidenepyrrolidin-2-one (7i). Grignard addition of allyl magnesium bromide to **6** and the subsequent dehydration (1.971 g, 6.68 mmol) were performed under the conditions described previously,[14] which gave a separable mixture of (*Z*)-**7i** and (*E*)-**7**i in a 1:8 ratio (1.321 g) in a combined yield of 63% over two steps. (*Z*)-**7i**: colorless oil. $[\alpha]_D^{20}$ +122.0 (*c* 0.5, $CHCl_3$). IR (film): 3031, 2925, 2863, 1722, 1653, 1496, 1434, 1396, 1347, 1307, 1261, 1199, 1117, 1080, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.64 (dd, J = 3.4, 16.7 Hz, 1H), 3.04 (dd, J = 8.6, 16.7 Hz, 1H), 4.24 (dd, J = 3.4, 8.6 Hz, 1H), 4.56 (d, J = 15.5 Hz, 1H), 4.66 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 11.8 Hz, 1H), 4.84 (d, J = 10.2 Hz, 1H), 4.90 (d, J = 16.8 Hz, 1H), 4.94 (d, J = 11.8 Hz, 1H), 5.38 (d, J = 10.8 Hz, 1H), 6.10 to 6.24 (m, 1H), 7.10 to 7.40 (m, 10H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.3, 43.7, 72.3, 73.2, 104.8, 114.1, 127.0, 127.5, 127.9, 128.1, 128.5, 128.7, 131.1, 135.4, 137.4, 138.5, 173.6 ppm. MS (ESI, *m*/*z*): 342 (M + Na^+, 81), 320 (M + H^+, 100). (*E*)-**7i**: $[\alpha]_D^{20}$ −122.0 (*c* 0.6, $CHCl_3$). IR (film): 3030, 2927, 1719, 1652, 1496, 1433, 1393, 1344, 1199, 1070 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.70 (dd, J = 1.9, 18.0 Hz, 1H), 2.80 (dd, J = 7.1, 18.0 Hz, 1H), 4.44 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.72 (d, J = 15.7 Hz, 1H), 4.78 (d, J = 15.7 Hz, 1H), 4.86 (dd, J = 1.9, 7.1 Hz, 1H), 4.98 (d, J = 10.3 Hz, 1H), 5.04 (dd, J = 0.8, 16.8 Hz, 1H), 5.60 (d, J = 11.1 Hz, 1H), 6.40 to 6.54 (m, 1H, H), 7.20 to 7.40 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 43.5, 70.0, 70.1, 108.1, 115.6, 126.9, 127.4, 128.0, 128.1, 128.5, 128.7, 131.0, 135.4, 137.0, 141.3, 173.2 ppm. MS (ESI, *m*/*z*): 342 (M + Na^+, 50), 320 (M + H^+, 100). HRESIMS calcd for [$2C_{21}H_{21}NO_2$ + $Na]^+$: 661.3037; found: 661.3042.

(4*R*,5*R*,1′*S*)-1-Benzyl-4-benzyloxy-5-(1,3-dihydroxypropyl)-pyrrolidin-2-one (10i). To a cooled (0 °C) solution of (*E*)-**7i** (1.0 mmol, 319 mg) in THF (4 mL) was added dropwise a 1 M solution of borane dimethyl sulfide in CH_2Cl_2 (2.0 mL, 2.0 mmol). The reaction mixture was stirred for 12 h at room temperature. The reaction was quenched with ethanol (3.2 mL) and treated with an aqueous solution of 3 N NaOH (0.7 mL, 2.1 mmol). To the resulting mixture was added dropwise 2 mL of H_2O_2 (30%) at 0 °C. The reaction mixture was refluxed for 1 h. After cooling, the reaction mixture was poured into ice− water and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give **10i** (124 mg, 35%) as white crystals. Mp 98 to 99 °C (ethyl acetate/P.E.). R_f: 0.36 (EtOAc/PE = 3:1). $[\alpha]_D^{20}$ −23.9 (*c* 0.3, $CHCl_3$). IR (KBr pellet): 3406, 2925, 1670, 1594, 1416, 1259, 1116 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.60 to 1.64 (m, 1H, H-2′), 1.80 to 1.98 (m, 1H, H-2′), 2.60 to 2.78 (m, 3H, one proton is D_2O exchangeable), 3.30 (d, J = 5.5 Hz, 1H, D_2O exchangeable), 3.60 (dd, J = 3.7, 7.3 Hz, 1H), 3.62 to 3.80 (m, 2H), 4.16 (d, J = 15.2 Hz, 1H), 4.16 to 4.20 (m, 1H), 4.30 (q, J = 7.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 5.04 (d, J = 15.2 Hz, 1H), 7.20 to 7.40 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 37.0, 45.5, 61.2, 62.3, 70.3, 70.4, 72.1, 74.5, 127.6, 127.7, 127.9, 128.2, 128.6, 128.7, 136.3, 136.6, 172.8 ppm. MS (ESI, *m*/*z*): 356 (M + H^+, 49), 378 (M + Na^+, 100). Anal. calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.81; H, 7.13; N, 3.85.

(2*R*,3*R*,1′*S*)-1-Benzyl-3-benzyloxy-2-(1,3-dihydroxyprop-1-yl)-pyrrolidine (12). To a cooled solution (0 °C) of **10i** (120 mg, 0.34 mmol) in anhydrous THF (4 mL) was added BH_3·SMe_2 (0.2 mL, 2.03 mmol). After stirring at room temperature for 12 h, the reaction was quenched with EtOH (3 mL). The resulting mixture was stirred at 65 °C for 4 h and then extracted with EtOAc (3 × 10 mL). The combined extracts were successively washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give **12** (95 mg, yield, 83%) as a colorless oil. $[\alpha]_D^{20}$ −37.5 (*c* 0.3, $CHCl_3$). IR (film): 3394, 2952, 2853, 1453, 1312, 1068 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.70 to 1.80 (m, 1H), 1.85 to 2.07 (m, 3H), 2.61 (dt, J = 10.4, 7.2 Hz, 1H), 3.02 (dd, J = 5.7, 6.3 Hz, 1H), 3.08 (dt, J = 10.4, 6.5 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 3.70 to 3.81 (m, 2H), 4.10 to 4.15 (m, 1H), 4.22 (q, J = 5.7 Hz, 1H), 4.29 (d, J = 13.0 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 7.25 to 7.45 (m, 10H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 29.3, 29.4, 37.5, 50.3, 59.1, 61.2, 67.5, 71.2, 79.3, 127.3, 127.5, 128.0, 128.1, 129.2, 137.4, 138.2 ppm; MS (ESI, *m*/*z*): 342 (M + H^+, 100). HRESIMS calcd for [$C_{21}H_{27}NO_3$ + $H]^+$: 342.2064; found: 342.2067.

(2*S*,3*R*,1′*S*)-1-*t*-Butoxycarbonyl-2-(1,3-dihydroxyprop-1-yl)-3-hydroxy-pyrrolidine (13). A suspension of 10% Pd/C (167 mg) and compound **12** (84 mg, 0.25 mmol) in methanol (5 mL) was stirred at room temperature and under 1 atm hydrogen atmosphere for 8 h. To the resultant reaction mixture was added $(Boc)_2O$ (0.11 mL, 0.12 mol). After stirring at room temperature for 6 h, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give **13** (51 mg, yield, 80%) as white crystals. Mp: 77 to 78 °C (ethyl acetate/P.E.); $[\alpha]_D^{20}$ −63.5 (*c* 0.3, $CHCl_3$) {lit.[5g] mp 78 to 80 °C, $[\alpha]_D^{20}$ −61.3 (*c* 1.0, $CHCl_3$)}. IR (KBr, pellet): 3379, 2923, 1666, 1404, 1167 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.44 (s, 9H), 1.72 to 1.92 (m, 2H), 1.95 to 2.12 (m, 2H), 3.35 to 3.48 (m, 1H), 3.66 to 3.78 (m, 3H), 4.08 to 4.18 (m, 1H), 4.35 (dt, J = 7.7, 7.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 28.7, 33.3, 38.6, 45.3, 60.5, 64.8, 69.7, 72.4, 81.1, 157.4 ppm; MS (ESI, *m*/*z*): 262 (M + H^+, 7); 284 (M + Na^+, 100). HRESIMS calcd for [$C_{12}H_{23}NO_5$ + $Na]^+$: 284.1468; found: 284.1466.

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Supporting Information Available: Experimental procedures; spectral data for **7j**, **10a**−**h**, **10j**, **11**, and **15**; and ^1H NMR and ^{13}C NMR spectra of (***E***/***Z***)-**7i**, **7j**, **10a**−**j**, **11**−**13**, and **15**. X-ray crystallographic data (CIF) for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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