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Enantioselective Construction of a Polyhydroxylated Pyrrolidine Skeleton from 3-Vinylaziridine-2-carboxylates: Synthesis of (+)-DMDP and a Potential Common Intermediate for (+)-Hyacinthacine A_1 and (+)-1-*epi*-Australine

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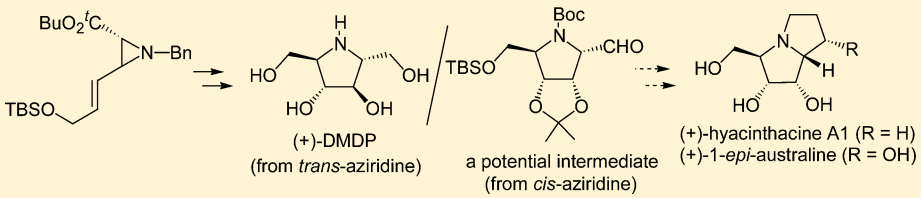
Supporting Information



ABSTRACT: We report an enantioselective synthesis of the polyhydroxylated pyrrolidine alkaloid (+)-DMDP. The key steps in the synthesis were guanidinium ylide mediated asymmetric aziridination, stereospecific ring opening of *trans*-3-vinylaziridine-2-carboxylate with an oxygen nucleophile, iodine-mediated 5-*endo*-*trig* amino cyclization, and Prévost displacement. In addition, a potential common intermediate for the polyhydroxylated pyrrolizidine alkaloids (+)-hyacinthacine A_1 and (+)-1-*epi*-australine was synthesized from a diastereoisomeric *cis*-aziridine coformed in the asymmetric aziridination using the same strategy. A rationale for the diastereoselectivity observed for the iodine-mediated amino cyclization reactions is proposed on the basis of the heats of formation of the products.

INTRODUCTION

Polyhydroxylated pyrrolidine and pyrrolizidine alkaloids, which contain a common 5-substituted 3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine core, have attracted much attention because of their interesting biological activity, such as the strong inhibition of a range of glucosidases.[1] These alkaloids have been the synthetic target of many studies, despite their relatively simple structures, owing to the presence of the 2,3,4,5-tetrasubstituted pyrrolidine skeleton with four stereogenic centers.[2] (+)-DMDP (**1**) was first isolated from *Derris elliptica* (Leguminosae; Papilionitae) in 1976,[3] and its structure was subsequently determined as C_2-symmetric (2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine by X-ray analysis.[4] (+)-Hyacinthacine A_1 (**2**) and (+)-1-*epi*-australine (**3**) were first isolated from *Muscari armeniacum* (Hyacinthaceae) in 2000[5] and *Castanospermum australe* (Leguminosae) in 1989,[6] respectively. They are classified as polyhydroxylated pyrrolizidine alkaloids, which contain a common 5-substituted (2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine core.

More than 20 groups[7] have achieved the asymmetric synthesis of DMDP. Although the majority of these syntheses used a sugar as a chiral source, Trost et al. used a dynamic kinetic asymmetric transformation in the asymmetric allylic alkylation of butadiene monoepoxide,[8] and an approach using an enzymatic resolution step has also been reported.[9] The asymmetric syntheses of (+)-hyacinthacine A_1 (**2**)[10] and (+)-1-*epi*-australine (**3**)[11] have been reported, although only three of the synthetic strategies did not use a sugar. The asymmetric induction step for the syntheses of (+)-hyacinthacine A_1 (**2**) has been achieved by the [2 + 2] cycloaddition of dichloroketene to an enol ether containing (*S*)-(−)-Stericol as a chiral auxiliary.[12] In the case of (+)-1-*epi*-australine (**3**), sequential intramolecular [4 + 2] and intermolecular [3 + 2] nitroalkene cycloadditions[13] and Sharpless dihydroxylation of pyrrolo[1,2-*c*]oxazol-3-one[11] were used as the asymmetric induction step, respectively.

We have developed a unique method for forming aziridines by the reaction of guanidinium ylide with an aromatic or unsaturated aldehyde, which can be used in asymmetric synthesis.[14] We have also examined the ring-opening reaction of unactivated 3-aryl or unsaturated aziridine-2-carboxylates formed by using various nucleophiles.[14c,e,15] In this paper we report the enantioselective synthesis of (+)-DMDP (**1**) and a potential common intermediate for (+)-hyacinthacine A_1 (**2**) and (+)-1-*epi*-australine (**3**). The key steps in the synthesis were guanidinium ylide mediated asymmetric aziridination,

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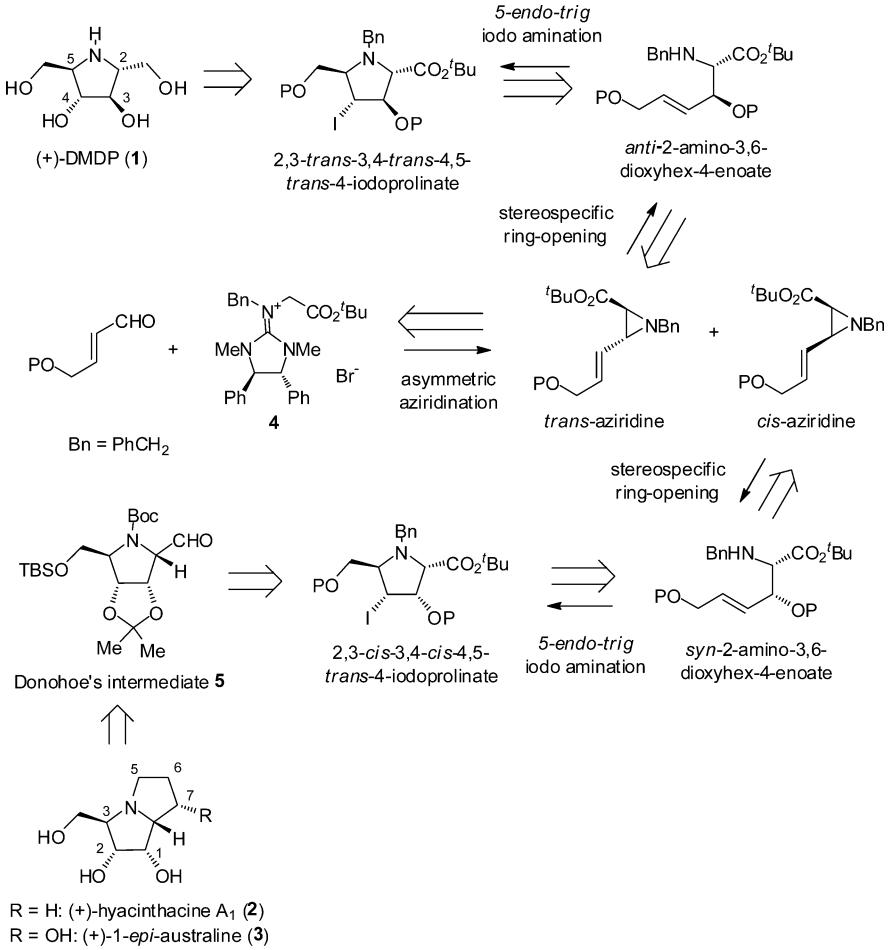
Scheme 1. Retrosynthetic Analysis



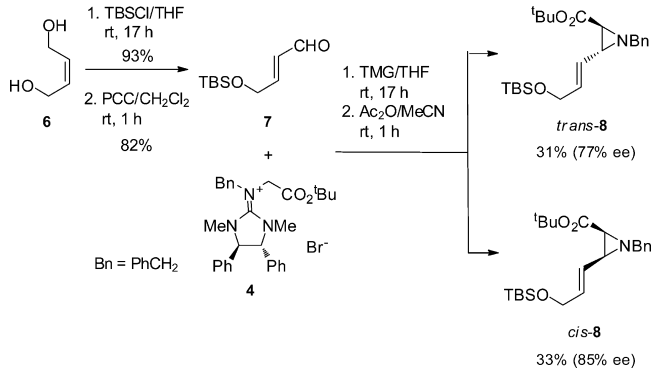
stereospecific ring opening of diastereoisomeric 3-vinylaziridine-2-carboxylates with an oxygen (*O*-) nucleophile, iodine-mediated *5-endo-trig* amino cyclization, and Prévost displacement.

RESULTS AND DISCUSSION

Our retrosynthetic analysis is shown in Scheme 1. The (2*S*,3*R*)-*trans*- and (2*S*,3*S*)-*cis*-3-vinylaziridine-2-carboxylates can be obtained by aziridination of 4-oxybut-2-enal with (*R*,*R*)-guanidinium bromide (**4**) and would produce the *anti*- and *syn*-2-amino-3,6-dioxyhex-4-enoates, respectively, through the regioselective and stereospecific ring-opening reaction with an *O*-nucleophile.[14c,e] The iodine-catalyzed 5-*endo*-*trig* cyclization of these amino esters should afford 4-iodoprolinates,[16] and the 2,3-*trans*-3,4-*trans*-4,5-*trans* derivative could be used to access (+)-DMDP (**1**) after chemical manipulation of the iodine atom and the ester functional group. The corresponding 2,3-*cis*-3,4-*cis*-4,5-*trans*-4-iodoprolinate could function in a way similar to that for the prolinal (**5**) reported by Donohoe et al., which has been converted into (±)-hyacinthacine A_1 ((±)-**2**) and (±)-1-*epi*-australine ((±)-**3**).[17]

The (*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-enal (**7**) starting material for the aziridination was prepared by partial protection of commercially available (*Z*)-1,4-dihydroxybut-2-ene (**6**) with *tert*-butyldimethylsilyl chloride (TBSCl; 93%) and then by oxidative isomerization with pyridinium chlorochromate (PCC; 82%).[18] Treatment of butenal **7** with (*R*,*R*)-guanidinium bromide **4** in the presence of tetramethylguanidine (TMG) as a base followed by treatment with acetic anhydride according to our protocol[14] provided *trans*-3-vinylaziridine-2-carboxylate (*trans*-**8**) in 31% yield (77% ee as the 2*S*,3*R* configuration) and the *cis* isomer (*cis*-**8**) in 33% yield (85% ee as the 2*S*,3*S* configuration) (Scheme 2).

Scheme 2. Asymmetric Aziridination



Invertomers at the aziridine nitrogen were observed for the *trans*-aziridine (*trans*-**8**) at a ratio of 1.2:1 by ^{1}H NMR spectroscopy (Figure 1).

Synthesis of (+)-DMDP (1). Initially, the synthesis of (+)-DMDP (**1**) was attempted. The *trans*-aziridine (*trans*-**8**) underwent a ring-opening reaction upon treatment with an *O*-nucleophile, providing a 4,5-unsaturated 2-amino ester

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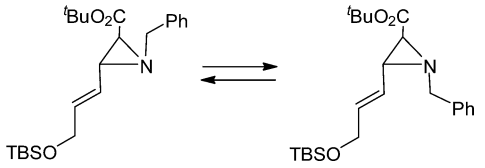


Figure 1. Invertomers of *trans*-aziridine (*trans*-**8**).

substrate for intramolecular cyclization. The treatment of *trans*-**8** with acetic acid exclusively provided *anti-tert*-butyl 3-acetoxy-2-benzylamino-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate (*anti*-**9**) in 91% yield. The coupling constant between the C2 and C3 protons (J = 5.5 Hz) indicated that the 2,3-stereochemistry was *anti*.[14c] When *trans*-**8** was treated with water in the presence of *p*-toluenesulfonic acid hydrate ($TsOH{\cdot}H_2O$), the same *anti*-amino ester (*anti*-**10**) was obtained in 84% yield as a single product, even though desilylation occurred.

Treatment of *anti*-**9** in ethyl acetate with iodine in the presence of potassium carbonate (K_2CO_3) at −40 °C for 1 h provided the 5-*endo-trig* cyclization products in 83% yield. The reaction produced a diastereoisomeric mixture of 2,3-*trans*-3,4-*trans*-4,5-*trans*-3-acetoxy-4-iodoprolinate **11** and the 2,3-*trans*-3,4-*cis*-4,5-*trans* one **12** in a 9:1 ratio, as determined by ^1H NMR. In the reaction of *anti*-**10**, the cyclized products were chromatographically separable, which allowed the isolation of 3,4-*trans*-3-hydroxy-4-iodoprolinate **13** and its 3,4-*cis* diastereoisomer **14** in 62% and 13% yields, respectively (Scheme 3).

The stereochemistry of the diastereoisomers derived from *anti*-**10** was deduced from NOE enhancements between the C3 and C4 protons in the minor diastereoisomer **14** (Figure 2a). The selectivity of the iodoamination reaction was not improved when dichloromethane (CH_2Cl_2) or tetrahydrofuran (THF) was used instead of ethyl acetate.

The heat of formation of the *N*-benzyl-3-hydroxy-4-iodoprolinates derived from *anti*-**10** was calculated by MOPAC, a semiempirical molecular orbital program. This showed that the major diastereoisomer **13** (−153.0 kcal/mol) was slightly less stable than the minor isomer **14** (−154.0 kcal/mol), and the predicted stability of *all-trans*-**13a** was compared

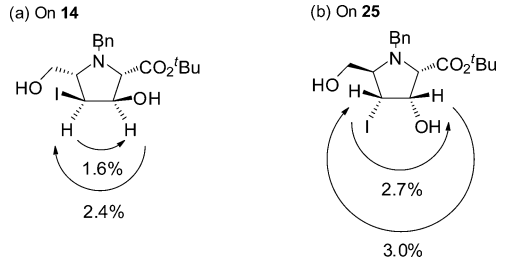


Figure 2. NOE enhancements in 3,4-*cis*-3-hydroxy-4-iodoprolinates: (a) the minor diastereoisomer **14** derived from *anti*-**10**; (b) the major diastereoisomer **25** derived from *syn*-**10**.

with those of the corresponding *N*-deprotected derivatives (**13a**, −184.4 kcal/mol; **14a**, −180.7 kcal/mol) (Figure 3a). Therefore, each transition state (TS) was examined to explain the observed diastereoselectivity.

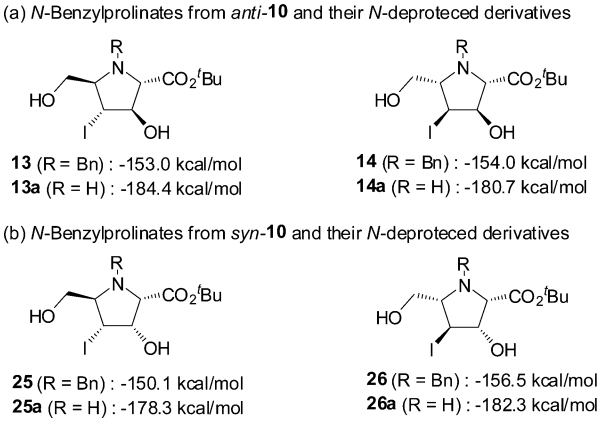
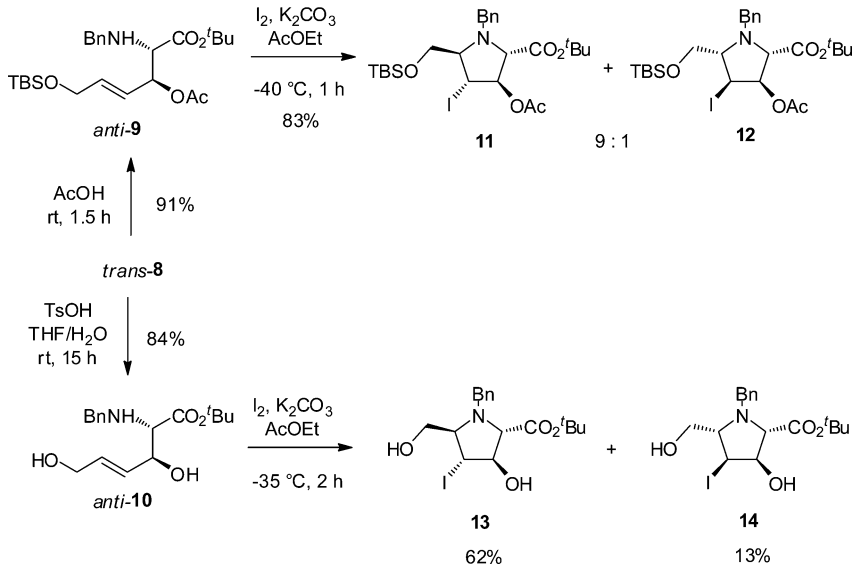


Figure 3. Heat of formation of *tert*-butyl 1-benzyl-3-hydroxy-5-hydroxymethyl-4-iodoprolinates and their *N*-deprotected derivatives: (a) derivatives from *anti*-**10**; (b) derivatives from *syn*-**10**.

TS-1 produces the 3,4-*trans* derivatives (**11**, **13**), whereas **TS-2** produces the 3,4-*cis* derivatives (**12**, **14**). In **TS-2**, two bulky substituents at the C2 ($CO_2{}^tBu$) and C5 (CH_2OR^1)

Scheme 3. Ring-Opening Reaction



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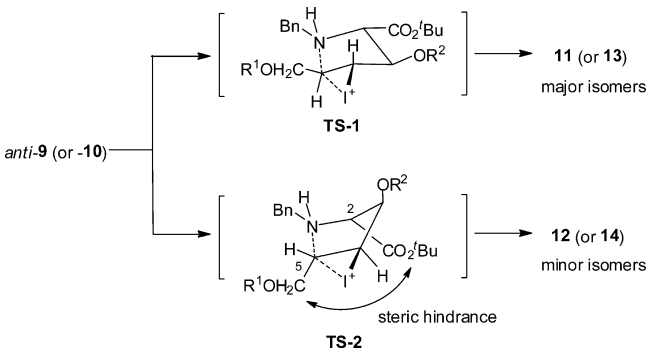
positions (pyrrolidine system numbering) are close to each other. This could explain the preferred formation of *all-trans* pyrrolidines **11** and **13** during the intramolecular iodoamination of *anti*-**9** and -**10** (Scheme 4). The product distribution

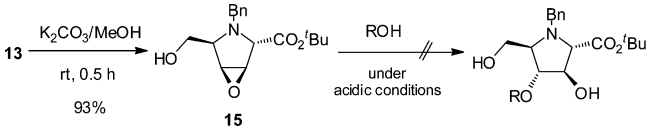
Scheme 4. Rationale for Diastereoselectivity in Iodination



from the transition states has been discussed by Knight et al. in relation to the iodoamination of homoallylic sulfonamides[16d,e] and in the synthesis of anisomycin by Park et al.[16b]

The conversion of the iodoprolinate to the corresponding hydroxy derivative through epoxide formation was examined first. Treatment of 3,4-*trans*-3-hydroxy-4-iodoprolinate (**13**) with K_2CO_3 in methanol (MeOH) smoothly afforded epoxide **15**. However, the acid-catalyzed ring-opening reaction with *O*-nucleophiles failed (Scheme 5).

Scheme 5. Attempts to Incorporate O Functionality



Therefore, we used a Prévost displacement with neighboring group participation.[16b,c] The treatment of 3-acetoxy-4-iodoprolinate **11** (92% de) with silver acetate (AcOAg) in acetic acid (AcOH) at 40 °C for 15 h gave the desired 3,4-*trans*-3,4-diacetoxyprolinate **16** in 57% yield as a single diastereoisomer. The coformation of aromatized pyrrole derivative **17** as a byproduct (26%) was observed. A double S_N2 substitution through the neighboring group participation of the 3-acetoxy function in **11**, followed by the nucleophilic attack of an alternative acetoxy function at the less hindered C4 position, gave 3,4-*trans*-3,4-diacetoxyprolinate **16** with retention of the substituent at the C4 position (Scheme 6).

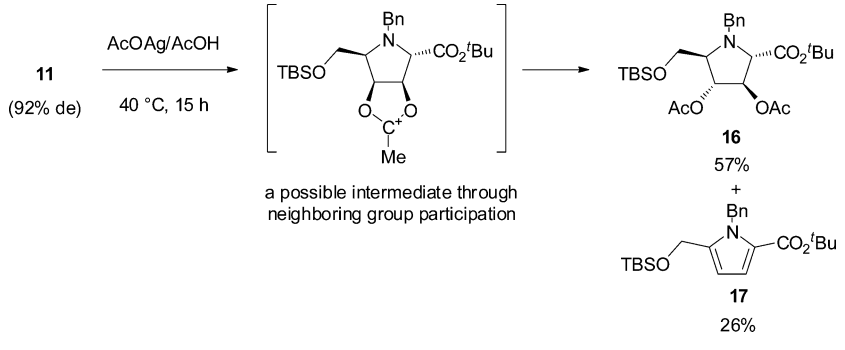
The reduction of diacetoxyprolinate **16** with lithium borohydride, followed by the deprotection of the TBS group, provided C_2-symmetric (−)-*N*-benzyl (Bn)-DMDP **19** as a crystalline product ($[\alpha]_D$ = −14.2°). An optically pure (+)-enantiomer (*ent*-**19**) ($[\alpha]_D$ = +20°) has been synthesized by Colobert et al.[19] The recrystallization of **19** from chloroform/acetone/hexane (5/1/0.1) afforded an optically pure (−)-product ($[\alpha]_D$ = −20.8°). However, a discrepancy was found in the assignment of the coupling constant of the double doublet for the C3 and C4 protons in the ^{1}H NMR spectrum. In the literature[19] the coupling constants were reported as $J_{3,4}$ = 8.6 and 2.7 Hz, whereas we measured coupling constants of $J_{3,4}$ = 2.4 and 1.1 Hz. Therefore, we examined the X-ray crystallographic structure of **19** and unambiguously established its stereochemistry to be 2*R*,3*R*,4*R*,5*R* (see the ORTEP drawing in Scheme 7).[20] Finally, the *N*-Bn group on **19** was removed by catalytic hydrogenation and the product was purified using an ion-exchange resin to afford (+)-DMDP (**1**) in 71% yield.

This synthetic approach can be applied to the synthesis of (+)-casuarine (**21**) because 3,4-*trans*-3,4-dibenzyloxy-5-[(*tert*-butyldimethylsilyloxy)methyl]prolinate **20**, which was reported as a key synthetic precursor by Izquierdo et al.,[21] may be derived from diacetoxyprolinate **16** by applying our reaction conditions of basic hydrolysis (see **29** → **30** in Scheme 12) and deprotection of the *N*-benzyl group by catalytic hydrogenation (see **19** → **1** in Scheme 7) (Scheme 8).

Synthesis of a Potential Common Intermediate for (+)-Hyacinthacine A_1 (2) and (+)-1-*epi*-Australine (3). Donohoe et al. reported the syntheses of (±)-hyacinthacine A_1 ((±)-**2**) and (±)-1-*epi*-australine ((±)-**3**) starting from *N*-*tert*-butoxycarbonyl (Boc)-2,5-bis(methoxycarbonyl)pyrrole via *N*-Boc-5-[(*tert*-butyldimethylsilyloxy)methyl]-3,4-dihydroxyprolinal dimethylacetal ((±)-**5**) as a common synthetic intermediate.[17] Thus, we attempted the preparation of the optically active prolinal (**5**) reported by Donohoe et al. as a potential common intermediate for (+)-hyacinthacine A_1 (**2**) and (+)-1-*epi*-australine (**3**). Prolinal **5** was obtained from *cis*-aziridine-2-carboxylate (*cis*-**8**), which was produced by the diastereoisomeric asymmetric aziridination as shown in Scheme 2, using the same strategy as for the synthesis of (+)-DMDP (**1**).

The stereospecific ring-opening reaction of the *cis*-aziridine *cis*-**8** with *O*-nucleophiles afforded the *syn* products *syn*-**9** and -**10**. Product *syn*-**10**, which was more easily crystallized than *syn*-**9**, was optically purified up to 99% ee from 85% ee by recrystallization from hexane/ethyl acetate (10/1) (Scheme 9).

Scheme 6. Prévost Displacement



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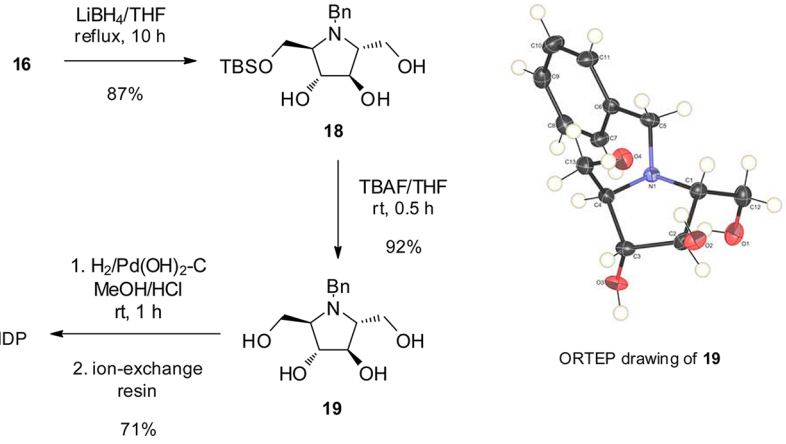
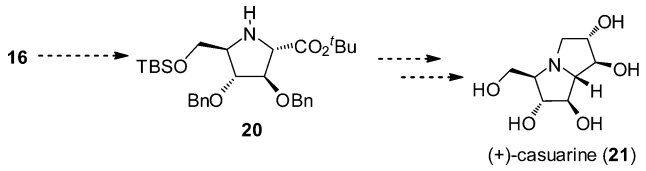
Scheme 7. Synthesis of (+)-DMDP (1)



Scheme 8. Possible Conversion to (+)-Casuarine (21)



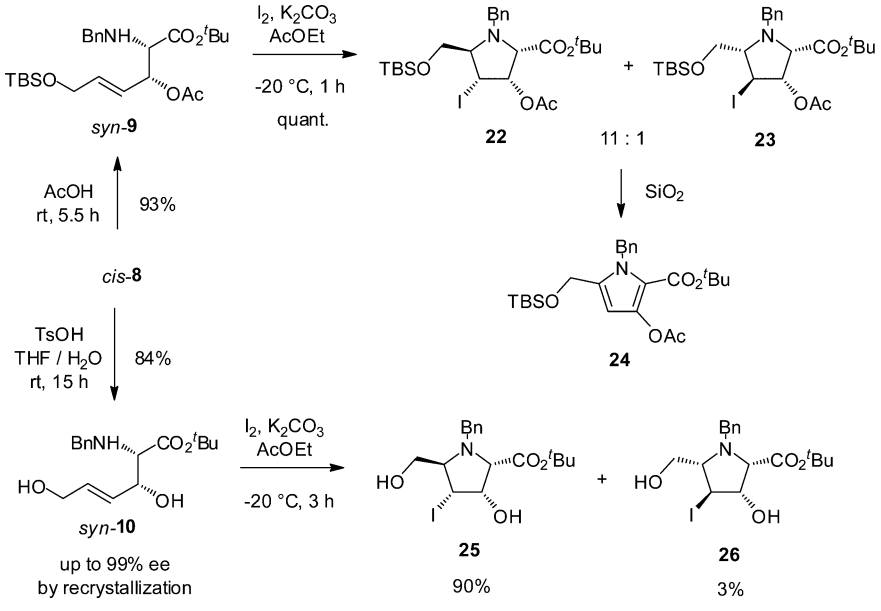
In the subsequent iodoamination, the 5-*endo*-*trig* cyclization provided the 2,3-*cis*-3,4-*cis*-3-acetoxy-4-iodoprolinate **22** from *syn*-**9** and the corresponding 3-hydroxy derivative **25** from *syn*-**10** as major products, respectively. Interestingly, better diastereoselectivity than for the *anti* derivatives was obtained in these cyclizations (see Scheme 3). Partial aromatization was observed during the trial purification of 2,3-*cis*-3-acetoxy-4-iodoprolinates **22** and **23** by silica gel column chromatography, which produced pyrrole derivative **24**. However, 2,3-*cis*-3,4-*cis*-3-hydroxy-4-iodoprolinate **25** was successfully isolated in 90% yield when *syn*-**10** was cyclized.

The stereochemistry of the ring-opened products *syn*-**9** and -**10** was assigned based on the coupling constant between the C2 and C3 protons (J = 4.4 Hz in *syn*-**9**),[14c] and the 3,4-*cis* configuration of the major diastereoisomers **22** and **25** in the iodoamination was assigned from the NOE enhancement between the C3 and C4 protons on **25** derived from *syn*-**10** (Figure 2b).

The calculation of the heat of formation of 3-hydroxy-4-iodoprolinates **25** (−150.1 kcal/mol) and **26** (−156.5 kcal/mol) derived from *syn*-**10** (Figure 3b) predicted diastereoselectivity opposite to that observed in the iodoamination of *syn*-**9** and -**10**. The same rationale for the transition states in Scheme 4 could be applied to the preferential formation of the 3,4-*cis*-pyrrolidines **22** and **25** to the 3,4-*trans*-pyrrolidines **23** and **26** (Scheme 10). In **TS-4**, which produces the 3,4-*trans* derivatives **23** and **26**, steric hindrance could arise between the 2-$CO_2{}^t$Bu and the 5-CH_2OR^1 groups, whereas there is no steric hindrance in **TS-3**. This results in the major 3,4-*cis* diastereoisomers **22** and **25**.

Here it is worthwhile to discuss the relative stability of the iodoamination products from *anti*- and *syn*-alcohols **10** on the basis of their heats of formation (Figure 3). As expected, *all-trans* **13a** was calculated to be the most stable prolinate in the

Scheme 9. Ring-Opening Reaction and Iodoamination



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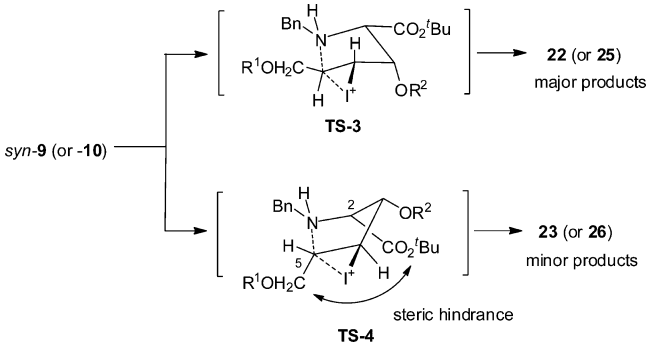
Scheme 10. Rationale for Diastereoselectivity in Iodoamination



N-deprotected prolinate series. Furthermore, the order of stability was **13a** > **26a** > **14a** > **25a**, which suggests that the *cis* relationship between the 3-hydroxy group and the 4-iodine atom in **14a** and **25a** ($\Delta H_{13a\text{-}14a}$ = 3.7 kcal/mol and $\Delta H_{26a\text{-}25a}$ = 5.0 kcal/mol) caused more severe steric repulsion than the *cis* relationship between the 2-ester and 3-hydroxy groups in **25a** and **26a** ($\Delta H_{14a\text{-}25a}$ = 2.4 kcal/mol and $\Delta H_{13a\text{-}26a}$ = 2.1 kcal/mol). In contrast, the stability order of the *N*-benzyl prolinates was **26** > **14** > **13** > **25**. In particular, the lower stability of *all-trans* derivative **13** could be attributed to the steric repulsion introduced between the benzyl substituent on the ring nitrogen atom and either the 2-ester or the 5-hydroxymethyl groups (Figure 4). This destabilization effect caused by the *N*-substitution may also be supported by comparing the energy difference between the 2,5-*cis* and 2,5-*trans* derivatives. Larger differences were calculated in the *N*-benzyl prolinates than in the corresponding *N*-deprotected ones: $\Delta H_{26\text{-}13}$ = 3.5 kcal/mol vs $\Delta H_{13a\text{-}26a}$ = 2.1 kcal/mol in the 3,4-*trans* series and $\Delta H_{14\text{-}25}$ = 3.9 kcal/mol vs $\Delta H_{14a\text{-}25a}$ = 2.4 kcal/mol in the 3,4-*cis* series.

To displace the iodine atom in 4-iodoprolinates **22** and **25** with an oxygen functional group and retain the stereochemistry, we intended to exploit Prévost neighboring group participation of the primary acetoxy group on the 5-substituent. In cyclic intermediate **27**, two electrophilic carbons (4-CH and 5′-CH_2) are present. We predicted that the 4-methine carbon should be more easily attacked by an acetoxy anion than the 5′-methylene carbon, because of the potential carbocationic character, even though it is more sterically crowded (Scheme 11).

Following the selective acetylation of the primary alcoholic function in 3-hydroxy-5-hydroxymethyl-4-iodoprolinate (**25**), monoacetate **28** was treated with AcOAg in a mixture of AcOH and CH_2Cl_2 to provide diacetate **29** in 59% yield. Diacetate **29** was obtained as an inseparable regioisomeric mixture of the 3- and 4-acetoxy derivatives and was chemically identified after conversion into a single triol (**30**) by methanolysis. Displacement of the iodine atom in 3-hydroxy-4-iodoprolinate **28** with an *O*-functional group with stereochemical retention was confirmed by X-ray crystallographic analysis of triol **30** (see the ORTEP drawing in Scheme 12).[20] After the selective protection of the primary hydroxyl group in triol **30** with TBSCl, the 3,4-dihydroxy functions were acetalized with 2,2-dimethoxypropane. The nitrogen substituent in acetal **32** was changed from a Bn to a Boc group by catalytic hydrogenation in the presence of $(Boc)_2O$, which afforded the *N*-Boc acetal **33.** Treatment of **33** with lithium borohydride provided alcohol **34** in 79% yield, which was then oxidized with Dess−Martin periodinane (DMP) without further purification to afford aldehyde **5** as a crystalline (−)-derivative (mp 65−69 °C; $[\alpha]_D^{24}$ = −145.3°) in an overall yield of 26% from triol **30** (Scheme 12). The data for prolinal **5** were identical with those reported by Donohoe et al. for the intermediate of (±)-hyacinthacine A_1 ((±)-**2**) and (±)-1-*epi*-australine ((±)-**3**)[17] except for the optical rotation. Trials for the direct conversion of the *tert*-butyl ester in *N*-Boc acetal **33** to an aldehyde group using diisobutylaluminum hydride as a reductant resulted in a poor yield of prolinal **5** (18%; 22% based on recovered starting material) and the coproduction of an over-reduced **34**.

CONCLUSION

We have successfully achieved the enantioselective synthesis of (+)-DMDP, a typical polyhydroxylated pyrrolidine alkaloid. The key steps in the synthesis were guanidinium ylide mediated asymmetric aziridination, stereospecific ring opening of *trans*-3-vinylaziridine-2-carboxylate with an *O*-nucleophile, iodine-mediated *5-endo-trig* amino cyclization, and Prévost displacement. Using the same strategy, we also synthesized a potential common intermediate for polyhydroxylated pyrrolizidine alkaloids (+)-hyacinthacine A_1 and (+)-1-*epi*-australine from a diastereoisomeric *cis*-aziridine coformed during the asymmetric aziridination. It was suggested that product distribution in the iodine-mediated amino cyclization reaction was controlled by both the C_2 stereogenic center and the configuration of the double bond in the *tert*-butyl 2-benzylamino-3,6-dioxyhexa-4-enoate starting material.

EXPERIMENTAL SECTION

Melting points were determined with a melting point hot-stage instrument and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with 400 and 600 MHz spectrometers in $CDCl_3$ unless otherwise stated. FAB and ESI mass spectra were obtained using a double-focusing magnetic sector mass spectrometer and time-of-flight mass spectrometer, respectively. For column and flash chromatography silica gel 60 (63−210 and 40−100 μm, respectively) was used. The organic extracts were dried over $MgSO_4$, and evaporations were done under reduced pressure.

Preparation of Guanidinium Bromide 4. *(4R,5R)-2-[(tert-Butoxycarbonyl)methyl]imino-1,3-dimethyl-4,5-diphenylimidazolidine.*[14a] A mixture of (4*R*,5*R*)-1,3-dimethyl-4,5-(diphenyl)-imidazolidin-2-one[22] (3.93 g, 14.8 mmol) and oxalyl chloride (6.5 mL, 74.5 mmol) in dry benzene (40 mL) was stirred at 80 °C for 9 h under Ar and evaporated to give 2-chloroimidazolium chloride (4.64 g, 88% purity by ^1H NMR) as colorless solids. After the whole crude chloride was dissolved in dry CH_2Cl_2 (30 mL), triethylamine (6.5 mL, 47.2 mmol) and a mixture of *tert*-butyl glycinate hydrochloride (1.59 g,

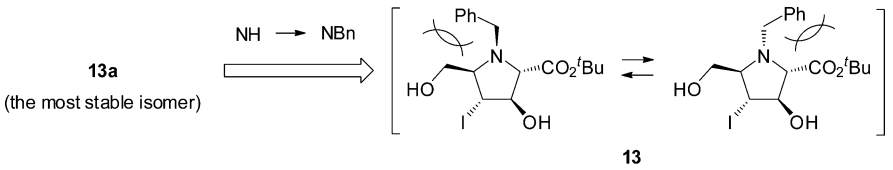


Figure 4. Effect of the introduction of an *N*-benzyl protecting group on the stability of *all-trans*-3-hydroxy-5-hydroxymethyl-4-iodoprolinate (**13a**).

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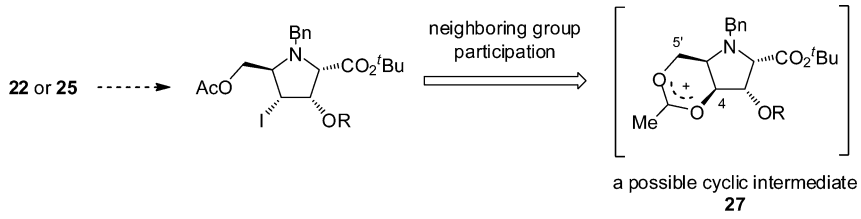
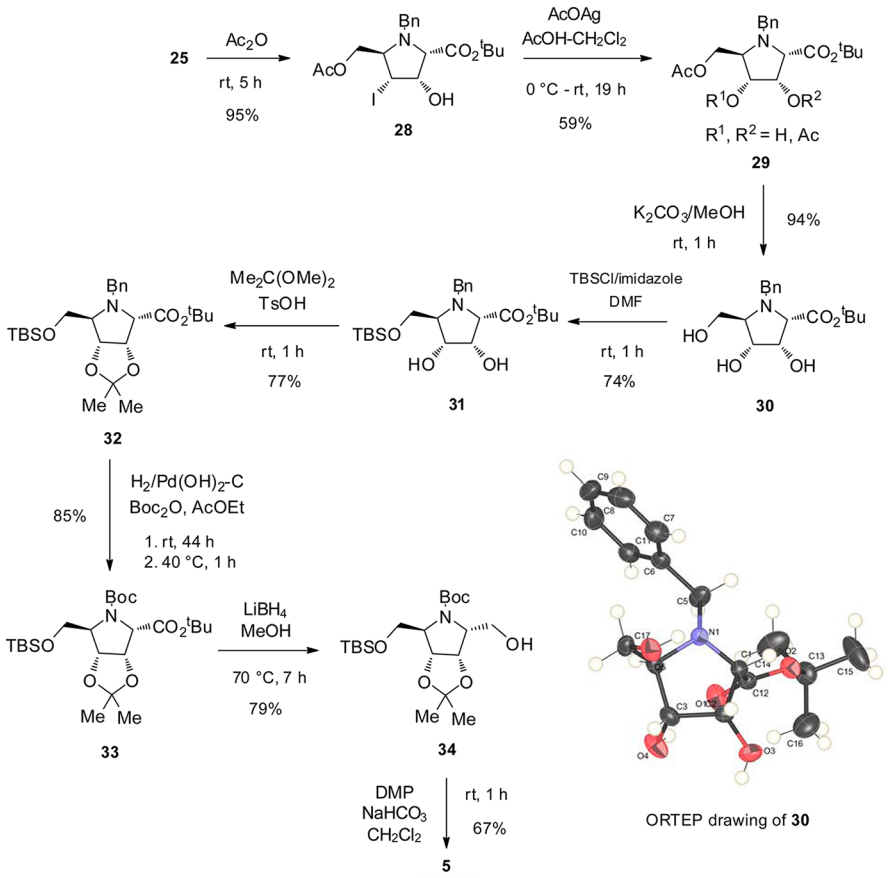
Scheme 11. Possible Cyclic Intermediate



Scheme 12. Asymmetric Synthesis of Prolinal 5



9.51 mmol) in dry CH_2Cl_2 (9 mL) were successively added with ice cooling under an Ar atomsphere. The resulting mixture was stirred at room temperature (rt) for 3 h and evaporated. The brownish oily residue was dissolved in toluene (100 mL) and extracted with 10% aqueous citric acid solution (50 mL). The aqueous solution was basified (pH >12) with 20% aqueous NaOH solution and extracted with toluene (50 mL × 4). The combined organic solutions were washed with H_2O (20 mL × 5) and brine (20 mL × 5), dried, and evaporated to give a guanidine (3.54 g, 98%) as colorless solids, mp 97−100 °C: $[\alpha]_D^{24.5}$ = −85.0° (*c* 1.04, $CHCl_3$); IR (ATR) 1738, 1651 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (s, 9H), 2.75 (br s, 6H), 3.90 (s, 2H), 4.26 and 4.34 (each d, *J* = 18.0 Hz), 7.13−7.16 (m, 4H), 7.27−7.35 (m, 6H); HRMS (ESI) calcd for $C_{23}H_{30}N_3O_2$ 380.233 80, found 380.232 41.

(4R,5R)-2-[(tert-Butoxycarbonyl)methyl]imino-1,3-dimethyl-4,5-diphenylimidazolidinium Bromide (4).[14a] The guanidine (1.53 g, 4.0 mmol) and benzyl bromide (0.65 mL, 5.47 mmol) were dissolved in dry MeCN (17.5 mL), and the resulting solution was stirred at rt for 12 h under Ar and evaporated. Washing the residual solid with 1/1 hexane/Et_2O (15 mL) gave **4** (2.10 g, 95%) as colorless solids, mp 171−173 °C: $[\alpha]_D^{25}$ = −95.0° (*c* 1.01, $CHCl_3$); IR (ATR) 1742 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (s, 9H), 3.17 (s, 6H), 4.28 (d, *J* = 19.0 Hz, 1H), 4.47 (d, *J* = 19.0 Hz, 1H), 4.68 (s, 2H), 4.73 (d, *J* = 14.6 Hz, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 7.18−7.20 (m, 4H), 7.31−7.36 (m, 6H), 7.44−7.52 (m, 3H), 7.70−7.72 (m, 2H); HRMS (ESI) calcd for $C_{30}H_{36}N_3O_2$ 470.280 75, found 470.279 63. Anal. Calcd for $C_{30}H_{36}BrN_3O_2$: C, 65.45; H, 6.59; N, 7.63. Found: C, 65.22; H, 6.61; N, 7.60.

Preparation of (*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]but-2-enal (7). *(Z)-4-[(tert-Butyldimethylsilyl)oxy]but-2-en-1-ol.*[18] To a suspension of NaH (1.10 g, 60% oil suspension, 27.6 mmol) in THF (40 mL) was added **6** (2.28 mL, 27.7 mmol) under Ar, and the resulting mixture was stirred at rt for 1 h. After addition of a solution of TBSCl (4.16 g, 27.6 mmol) in THF (40 mL) at rt the mixture was stirred at rt for 5 h and quenched with saturated NH_4Cl aolution (20 mL). After evaporation of the THF the residue was partitioned using H_2O (50 mL) and Et_2O (100 mL × 3). The combined organic solutions were washed with brine (30 mL × 2), dried, and evaporated. The residue was purified by column chromatopgrahy (hexane/AcOEt 10/1) to afford the *tert*-butyldimethylsilyloxy alcohol (5.19 g, 93%) as a colorless oil: IR (ATR) 3359 cm^{-1}; ^1H NMR (400 MHz) δ 0.10 (s, 6H), 0.91 (s, 9H), 2.18 (s, 1H), 4.20 (dif d, *J* = 5.7 Hz, 2H), 4.27 (dif d, *J* = 5.7 Hz, 2H), 5.65−5.73 (m, 2H).

(E)-4-[(tert-Butyldimethylsilyl)oxy]but-2-enal (7).[18] A solution of the alcohol (5.08 g, 25.1 mmol) in dry CH_2Cl_2 (30 mL) was added to a stirred mixture of PCC (8.11 g, 37.7 mmol) and sodium acetate

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(3.12 g, 38.1 mmol) in dry CH_2Cl_2 (100 mL) under Ar. The resulting mixture was stirred at rt for 3.5 h and evaporated. The residual black solid was suspended in Et_2O (500 mL) and filtered through Celite. After evaporation of the filtrate the residue was purified by column chromatography (hexane/AcOEt 10/1) to give **7** (4.11 g, 82%) as a colorless oil: IR (ATR) 1693 cm^{-1}; ^1H NMR (400 MHz) δ 0.07 (s, 6H), 0.90 (s, 9H), 4.43 (dd, J = 3.0, 2.2 Hz, 2H), 6.38 (ddt, J = 15.4, 8.2, 2.2 Hz, 1H), 6.88 (dt, J = 15.4, 3.0 Hz, 1H), 9.58 (d, J = 8.2 Hz, 1H).

Asymmetric Aziridination. Freshly distilled TMG (0.69 mL, 5.50 mmol) was added to a solution of **4** (2.01 g, 3.64 mmol) in dry THF (8 mL) at rt under Ar. To the above solution was slowly added a solution of **7** (0.929 g, 4.64 mmol) in dry THF (4 mL), and the resulting mixture was stirred at rt for 16.5 h and then dropped to a solution of Ac_2O (2 mL, 21.2 mmol) in MeCN (300 mL). The whole was stirred at rt for 1 h and evaporated. The residue was purified by flash chromatography (hexane/AcOEt 20/1) to give *trans*-**8** (0.474 g, 31%, 77% ee) and *cis*-**8** (0.445 g, 33%, 85% ee) as yellow oils, respectively, between which *trans*-**8** existed as a mixture of invertomers in a ratio of 1.2:1.

***trans*-(2*S*,3*R*)-*tert*-Butyl 1-Benzyl-3-[(*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]aziridine-2-carboxylate (*trans*-8):** $[\alpha]_D^{21}$ = +7.2° (*c* 1.09, $CHCl_3$); IR (ATR) 1735 cm^{-1}; ^1H NMR (400 MHz) for major invertomer δ 0.06 (s, 6H), 0.90 (s, 9H), 1.39 (s, 9H), 2.58 (d, J = 2.6 Hz, 1H), 2.77 (dd, J = 7.8, 2.6 Hz, 1H), 3.95 (d, J = 14.0 Hz, 1H), 4.13 (d, J = 14.0 Hz, 1H), 4.16 (d, J = 4.8 Hz, 2H), 5.47 (dd, J = 15.5, 7.8 Hz, 1H), 5.91 (dt, J = 15.5, 4.8 Hz, 1H), 7.21−7.36 (m, 5H); ^1H NMR (400 MHz) for minor invertomer δ 0.06 (s, 6H), 0.90 (s, 9H), 1.46 (s, 9H), 2.27 (d, J = 2.4 Hz, 1H), 3.06 (dd, J = 8.8, 2.4 Hz, 1H), 3.68 (d, J = 14.0 Hz, 1H), 3.87 (d, J = 14.0 Hz, 1H), 4.20 (d, J = 4.8 Hz, 2H), 5.70 (dd, J = 15.5, 8.2 Hz, 1H), 6.03 (dt, J = 15.5, 4.8 Hz, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR (100 MHz) for major invertomer δ −5.3, 18.3, 25.9, 43.0, 47.3, 54.4, 63.1, 81.5, 126.7, 127.9, 128.1, 128.2, 132.8, 139.2, 167.9; ^{13}C NMR (100 MHz) for minor invertomer δ −5.3, 18.3, 27.9, 45.1, 47.7, 55.7, 62.9, 81.3, 122.0, 126.8, 127.5, 128.1, 137.1, 138.8, 169.4; HRMS (FAB) calcd for $C_{23}H_{38}NO_3Si$ 404.2621, found 404.2600; HPLC (CHIRALCEL OD-H, λ 254 nm, hexane/^{i}PrOH 400/1, flow rate 0.5 mL/min at 40 °C) t_R for minor isomer 23.1 min, t_R for major isomer 66.5 min.

***cis*-(2*S*,3*S*)-*tert*-Butyl 1-Benzyl-3-[(*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl]aziridine-2-carboxylate (*cis*-8).** $[\alpha]_D^{21.5}$ = +2.7° (*c* 1.09, $CHCl_3$); IR (ATR) 1717 cm^{-1}; ^1H NMR (400 MHz) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.45 (s, 9H), 2.32 (d, J = 6.8 Hz, 1H), 2.41 (t-like, J = 7.2 Hz, 1H), 3.59 (d, J = 14.0 Hz, 1H), 3.71 (d, J = 14.0 Hz, 1H), 4.16 (d, J = 5.9 Hz, 2H), 5.71 (dd, J = 15.5, 8.0 Hz, 1H), 5.91 (dt, J = 15.5, 5.1 Hz, 1H), 7.22−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ −5.2, 18.4, 25.9, 28.1, 45.0, 46.8, 63.1, 63.4, 81.3, 125.4, 126.9, 127.6, 128.2, 134.4, 137.9, 168.0; HRMS (FAB) calcd for $C_{23}H_{37}NO_3NaSi$ 426.2440, found 426.2425; HPLC (CHIRALCEL OD-H, λ 254 nm, hexane/^{i}PrOH 400/1, flow rate 0.5 mL/min at 40 °C) t_R for minor isomer 30.8 min, t_R for major isomer 34.9 min.

(2*S*,3*S*,4*E*)-*tert*-Butyl 3-Acetoxy-2-benzylamino-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate (*anti*-9). A solution of *trans*-**8** (0.505 g, 1.25 mmol) in AcOH (1.6 mL, 28 mmol) was stirred at rt for 1.5 h and evaporated. Column chromatography of the residue (hexane/AcOEt 6/1) afforded *anti*-**9** (0.529 mg, 91%) as a yellow oil: $[\alpha]_D^{24}$ = +3.5° (*c* 0.96, $CHCl_3$); IR (ATR) 1731 cm^{-1}; ^1H NMR (400 MHz) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.46 (s, 9H), 2.04 (s, 3H), 3.37 (d, J = 5.5 Hz, 1H), 3.70 (d, J = 13.2 Hz, 1H), 3.87 (d, J = 13.2 Hz, 1H), 4.17 (d, J = 4.0 Hz, 2H), 5.48 (dd, J = 6.7, 5.5 Hz, 1H), 5.74 (ddt, J = 15.5, 6.7, 1.6 Hz, 1H), 5.83 (dt, J = 15.5, 4.0 Hz, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ −5.3, 18.3, 21.1, 25.9, 28.0, 52.1, 62.7, 64.0, 74.6, 81.7, 124.0, 127.0, 128.2, 128.3, 134.2, 139.6, 169.7, 171.0; HRMS (ESI) calcd for $C_{25}H_{41}NO_5NaSi$ 486.265 17, found 486.265 18.

(2*S*,3*S*,4*E*)-*tert*-Butyl 2-Benzylamino-3,6-dihydroxyhex-4-enoate (*anti*-10). A solution of *trans*-**8** (0.084 g, 0.209 mmol) in THF (1 mL) was stirred with a solution of TsOH + H_2O (0.049 g, 0.255 mmol) in H_2O (1 mL) at rt for 15 h. After addition of 20% aqueous NaOH solution (1 mL) and H_2O (4 mL) with ice cooling, the mixture was extracted with AcOEt (20 mL × 3). The combined organic solutions were washed with H_2O (20 mL × 2) and brine (20 mL × 2), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 2/3) afforded *anti*-**10** (0.054 g, 84%) as a colorless oil: IR (ATR) 3400 (br), 1725 cm^{-1}; ^1H NMR (400 MHz) δ 1.46 (s, 9H), 2.60 (br s, 3H), 3.39 (d, J = 4.8 Hz, 1H), 3.63 (d, J = 12.8 Hz, 1H), 3.88 (d, J = 12.8 Hz, 1H), 4.08 (d, J = 5.2 Hz, 2H), 4.37 (ddd, J = 6.0, 4.8, 1.2 Hz, 1H), 5.58 (ddt, J = 15.2, 6.0, 1.6 Hz, 1H), 5.88 (dtd, J = 15.2, 5.2, 1.6 Hz, 1H), 7.24−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ 28.0, 52.6, 62.6, 65.2, 70.9, 82.1, 127.3, 128.41, 128.43, 128.6, 131.9, 139.2, 171.5; HRMS (ESI) calcd for $C_{17}H_{25}NO_4Na$ 330.168 13, found 330.168 55.

Iodoamination of *anti*-9. To a stirred solution of *anti*-**9** (0.153 g, 0.330 mmol) in AcOEt (4 mL) was successively added K_2CO_3 (0.156 g, 1.13 mmol) and iodine (0.250 g, 0.984 mmol) at −40 °C. The mixture was stirred at the same temperature for 1 h, diluted with AcOEt (20 mL), and extracted with 20% aqueous $Na_2S_2O_3$ solution (20 mL × 3). The organic solution was washed with H_2O (20 mL × 3) and brine (20 mL × 3), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 5/1) afforded a 9/1 diastereoisomeric mixture of **11** and **12** as a yellow oil (0.161 g, 83%): IR (ATR) 1747 cm^{-1}; ^1H NMR (400 MHz) for major **11** δ 0.06 (s, 6H), 0.92 (s, 9H), 1.48 (s, 9H), 2.07 (s, 3H), 3.47 (d, J = 2.8 Hz, 1H), 3.69 (ddd, J = 7.8, 3.6, 2.8 Hz, 1H) 3.71 (dd, J = 11.7, 3.6 Hz, 1H), 3.78 (d, J = 14.4 Hz, 1H), 3.80 (dd, J = 11.7, 2.8 Hz, 1H), 4.13 (dd, J = 7.8, 5.2 Hz, 1H), 4.16 (d, J = 14.4 Hz, 1H), 5.46 (dd, J = 5.2, 2.8 Hz, 1H), 7.22−7.37 (m, 5H); ^1H NMR (400 MHz) for minor **12** δ −0.01 (d, J = 4.8 Hz, 6H), 0.86 (s, 9H), 1.37 (s, 9H), 2.08 (s, 3H), 3.42−3.55 (m, 1H), 3.64 (d, J = 5.2 Hz, 1H), 3.73 (d, J = 13.7 Hz, 1H), 3.82 (d, J = 13.7 Hz, 1H), 4.06 (d, J = 3.2 Hz, 2H), 4.52 (dd, J = 5.2, 5.2 Hz, 1H), 4.91 (dd, J = 5.2, 5.2 Hz, 1H), 7.22−7.37 (m, 5H); ^{13}C NMR (100 MHz) for major **11** δ −5.5, −5.4, 18.2, 20.7, 22.9, 25.8, 28.0, 51.2, 60.3, 69.2, 71.1, 81.9, 83.3, 127.0, 128.2, 128.3, 138.7, 169.9, 170.4; ^{13}C NMR (100 MHz) for minor **12** δ −5.5, −5.4, 14.5, 21.0, 23.1, 26.6, 27.8, 59.4, 65.0, 69.9, 73.0, 74.8, 81.3, 127.2, 129.1, 138.5, 169.4, 169.6; HRMS (ESI) calcd for $C_{25}H_{40}NO_5NaSiI$ 612.161 81, found 612.161 74.

Iodoamination of *anti*-10. To a stirred solution of *anti*-**10** (0.061 g, 0.198 mmol) in THF (2 mL) was successively added K_2CO_3 (0.087 g, 0.631 mmol) and iodine (0.154 g, 0.606 mmol) at −35 °C. The mixture was stirred at the same temperature for 2 h and evaporated. After dilution with CH_2Cl_2 (20 mL), the solution was successively washed with 20% aqueous $Na_2S_2O_3$ solution (20 mL × 3), H_2O (20 mL × 3), and brine (20 mL × 3), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 5/1) afforded **13** (0.054 g, 62%) and **14** (0.011 g, 13%) as yellow oils, respectively.

(2S,3R,4R,5R)-tert-Butyl 1-Benzyl-3-hydroxy-5-hydroxymethyl-4-iodopyrrolidine-2-carboxylate (13): IR (ATR) 3409, 1722 cm^{-1}; ^1H NMR (400 MHz) δ 1.50 (s, 9H), 3.33 (bs, 1H), 3.60 (dd, J = 12.0, 0.8 Hz, 1H), 3.63 (s, 1H) 3.67 (dd, J = 12.0, 2.4 Hz, 1H), 3.83 (dt, J = 5.7, 2.4 Hz, 1H), 3.98 (d, J = 14.0 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 4.13 (dd, J = 5.7, 2.4 Hz, 1H), 4.57 (s, 1H), 7.27−7.32 (m, 5H); ^{13}C NMR (100 MHz) δ 26.3, 28.1, 51.6, 58.2, 71.9, 73.0, 82.1, 82.6, 127.4, 128.3, 128.6, 138.5, 170.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_4NaI$ 456.064 77, found 456.064 88.

(2S,3R,4S,5S)-tert-Butyl 1-Benzyl-3-hydroxy-5-hydroxymethyl-4-iodopyrrolidine-2-carboxylate (14): IR (ATR) 3395, 1718 cm^{-1}; ^1H NMR (400 MHz) δ 1.31 (s, 9H), 2.23 (d, J = 2.8 Hz, 1H), 3.48 (t, J = 5.5 Hz, 1H), 3.56 (d, J = 9.2 Hz, 1H), 3.66−3.68 (m, 3H), 3.84 (d, J = 13.2 Hz, 1H), 4.07 (d, J = 13.2 Hz, 1H), 4.08 (br, 1H), 4.49 (dd, J = 9.2, 3.6 Hz, 1H), 7.24−7.31 (m, 5H); ^{13}C NMR (100 MHz) δ 27.8, 30.8, 58.1, 59.1, 71.0, 72.4, 76.6, 82.0, 127.5, 128.5, 128.9, 138.1, 172.1; HRMS (FAB) calcd for $C_{17}H_{24}NO_4NaI$ 456.0648, found 456.0656.

(1*R*,2*S*,4*R*,5*S*)-*tert*-Butyl 3-Benzyl-4-(hydroxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-2-carboxylate (15). A mixture of **13** (0.179 g, 0.414 mmol) and K_2CO_3 (0.148 g, 1.07 mmol) in MeOH (3 mL) was stirred at rt for 0.5 h, quenched with saturated aqueous NH_4Cl solution (3 mL), and extracted with AcOEt (20 mL × 4). The combined organic solutions were washed with H_2O (20 mL × 3) and

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brine (20 mL × 2), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 2/1) gave **15** (0.117 g, 93%) as a yellow oil: IR (ATR) 3450, 1726 cm^{-1}; ^1H NMR (400 MHz) δ 1.47 (s, 9H), 2.44 (br s, 1H), 3.41 (s, 1H), 3.58 (d, J = 2.8 Hz, 1H), 3.74 (s, 1H), 3.77 (d, J = 14.0 Hz, 1H), 3.95 (d, J = 14.0 Hz, 1H), 3.80 (d, J = 2.8 Hz, 1H), 3.90 (dd, J = 11.2, 4.0 Hz, 1H), 3.94 (d, J = 11.2 Hz, 1H), 7.25−7.30 (m, 5H); ^{13}C NMR (100 MHz) δ 28.2, 50.8, 55.0, 57.5, 59.8, 61.7, 64.0, 82.1, 127.4, 128.4, 128.6, 139.5, 170.0; HRMS (ESI) calcd for $C_{17}H_{23}NO_4Na$ 328.152 48, found 328.155 47.

Prévost-Type Displacement of a 9/1 Mixture of 11 and 12. A solution of a 9/1 mixture of **11** and **12** (0.161 g, 0.273 mmol) in AcOH (1 mL) was added to AcOAg (0.122 g, 0.733 mmol) under Ar, and the resulting mixture was stirred at 40 °C for 15 h and filtered through Celite. After evaporation of the filtrate column chromatography of the residue (hexane/AcOEt 10/1) afforded **16** (0.073 g, 57%) and **17** (0.026 g, 26%) as colorless oils, respectively.

(2S,3R,4R,5S)-tert-Butyl 1-Benzyl-3,4-diacetoxy-5-[(tert-butyldimethylsilyloxy)methyl]prolinate (16): $[\alpha]_D^{23.4}$ = −20.8° (*c* 2.00, $CHCl_3$); IR (ATR) 1744 cm^{-1}; ^1H NMR (400 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.48 (s, 9H), 2.06 (s, 3H), 2.07 (s, 3H), 3.31 (dd, J = 4.0, 4.0 Hz, 1H), 3.63 (d, J = 3.2 Hz, 1H), 3.75 (dd, J = 10.8, 4.0 Hz, 1H), 3.81 (dd, J = 10.8, 4.0 Hz, 1H), 3.85 (d, J = 14.4 Hz, 1H), 4.09 (d, J = 14.4 Hz, 1H), 5.18 (dd, J = 4.0, 3.2 Hz, 1H), 5.27 (dd, J = 3.2, 3.2 Hz, 1H), 7.24 (dd, J = 7.2, 7.2 Hz, 1H), 7.31 (dd, J = 7.2, 7.2 Hz, 2H), 7.37 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz) δ −5.6, −5.5, 18.1, 20.8, 20.9, 25.8, 28.0, 51.5, 62.3, 66.4, 69.1, 79.0, 79.3, 81.5, 127.0, 128.25, 128.27, 138.8, 170.0, 170.3, 170.4; HRMS (ESI) calcd for $C_{27}H_{43}NO_7NaSi$ 544.270 65, found 544.274 06.

tert-Butyl 1-Benzyl-5-[(tert-butyldimethylsilyloxy)methyl]-1H-pyrrole-2-carboxylate (17): IR (ATR) 1698 cm^{-1}; ^1H NMR (400 MHz) δ −0.01 (s, 6H), 0.85 (s, 9H), 1.45 (s, 9H), 4.51 (s, 2H), 5.70 (s, 2H), 6.10 (d, J = 4.0 Hz, 1H), 6.91 (d, J = 4.0 Hz, 1H), 6.92 (d, J = 7.2 Hz, 2H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.25 (dd, J = 7.6, 7.6 Hz, 2H); ^{13}C NMR (100 MHz) δ −5.4, 18.2, 25.8, 28.3, 48.3, 57.6, 80.3, 108.5, 117.0, 124.9, 125.7, 126.7, 128.4, 138.6, 138.9, 160.6; HRMS (ESI) calcd for $C_{23}H_{35}NO_3NaSi$ 424.228 39, found 424.226 39.

(2R,3R,4R,5S)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)-methyl]-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine (18). A mixture of **16** (0.101 g, 0.194 mmol) and $LiBH_4$ (0.091 g, 4.17 mmol) in dry THF (1.5 mL) was refluxed for 10 h under Ar. To the mixture were successively added THF (5 mL), MeOH (4 mL), and saturated aqueous NH_4Cl solution (1 mL), and then the whole mixture was stirred at rt for 10 min. After addition of H_2O (20 mL), the mixture was extracted with AcOEt (30 mL × 3). The combined organic solutions were washed with H_2O (30 mL × 2) and brine (30 mL × 2), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 1/2) afforded **18** (0.062 g, 87%) as a colorless oil: $[\alpha]_D^{23}$ = −21.2° (*c* 2.01, $CHCl_3$); IR (ATR) 3342 cm^{-1}; ^1H NMR (400 MHz) δ 0.14 (s, 3H), 0.16 (s, 3H), 0.95 (s, 9H), 1.75−2.30 (br, 2H), 3.15 (s, 1H), 3.20 (s, 1H), 3.62 (dd, J = 10.8, 1.5 Hz, 1H), 3.64 (dd, J = 11.2, 1.3 Hz, 1H), 3.70 (dd, J = 11.2, 3.1 Hz, 1H), 3.86 (dd, J = 10.8, 2.9 Hz, 1H), 3.94 (s, 1H), 3.95 (s, 2H) 4.01 (s, 1H), 4.35−4.55 (br, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR (100 MHz) δ −5.7, −5.4, 18.2, 25.9, 51.2, 60.9, 62.4, 70.0, 71.8, 80.3, 80.4, 127.0, 127.7, 128.5, 139.5; HRMS (ESI) calcd for $C_{19}H_{34}NO_4Si$ 368.225 71, found 368.228 48.

(2R,3R,4R,5R)-1-Benzyl-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (19). To a stirred solution of **18** (0.101 g, 0.272 mmol) in dry THF (0.5 mL) was added a 1.0 M solution of TBAF in THF (0.54 mL, 0.54 mmol) at rt under Ar. The whole mixture was stirred at rt for 0.5 h and evaporated. Column chromatography of the residue (AcOEt/MeOH 5/1) afforded **19** (0.064 g, 92%) as colorless needles: mp 132−133 °C; $[\alpha]_D^{19}$ = −20.8° (*c* 0.31, MeOH); IR (ATR) 3294 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.03 (m, 2H), 3.60 (dd, J = 11.2, 2.8 Hz, 2H), 3.71 (dd, J = 11.4, 4.8 Hz, 2H), 3.96 (dd, J = 2.4, 1.3 Hz, 2H), 3.96 (d, J = 14.3 Hz, 1H), 4.03 (d, J = 14.3 Hz, 1H), 7.19 (dd, J = 7.5, 7.5 Hz, 1H), 7.28 (dd, J = 7.5, 7.5 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 52.6, 61.6, 71.0, 80.7, 127.8, 129.2, 129.3, 141.2; HRMS (ESI) calcd for $C_{13}H_{19}NO_4Na$ 276.121 18, found 276.120 01.

(+)-DMDP [(2R,3R,4R,5R)-3,4-Dihydroxy-2,5-bis-(hydroxymethyl)pyrrolidine] (1). A mixture of **19** (0.064 g, 0.251 mmol) and 20% $Pd(OH)_2$ on C (0.021 g) in a solution of HCl in MeOH (1.3 mL), which was prepared by passing HCl gas (NaCl (50 g) and concentrated H_2SO_4 (10 mL)) into MeOH (100 mL), was stirred at rt and at atmospheric pressure for 1 h under hydrogen. The catalyst was filtered off through Celite, and the filtrate was evaporated. Column chromatography of the residue (DOWEX 50WX8 100−200 H FORM, EtOH → H_2O → 2 M aqueous NH_3 solution) afforded **1** (0.035 g, 71%) as brownish solids: mp 112−114 °C (lit.[8] mp 112−115 °C); $[\alpha]_D^{24}$ = +58.8° (*c* 0.10, H_2O) (lit.[8] $[\alpha]_D^{28}$ = +55.4° (*c* 1.25, H_2O)); IR (ATR) 3293 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.00−3.06 (m, 2H), 3.61 (dd, J = 11.5, 6.4 Hz, 2H), 3.68 (ddd, J = 11.5, 4.1 Hz, 2H), 3.81 (d, J = 7.8 Hz, 1H), 3.84 (dd, J = 10.1, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 61.8, 62.3, 78.1; HRMS (FAB) calcd for $C_6H_{14}NO_4$ 164.0923, found 164.0921.

(2S,3R,4E)-*tert*-Butyl 3-Acetoxy-2-benzylamino-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate (*syn*-9). A solution of *cis*-**8** (0.023 g, 0.057 mmol) in AcOH (0.07 mL, 1.26 mmol) was stirred at rt for 5.5 h and evaporated. Column chromatography of the residue (hexane/AcOEt 10/1) afforded *syn*-**9** (0.025 g, 93%) as a yellow oil: IR (ATR) 1733 cm^{-1}; ^1H NMR (400 MHz) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.45 (s, 9H), 2.03 (s, 3H), 3.30 (d, J = 4.4 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H), 4.18 (d, J = 1.6 Hz, 2H), 5.57 (dd, J = 5.2, 4.4 Hz, 1H), 5.84−5.88 (m, 2H), 7.21−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ −5.31, −5.28, 18.4, 21.0, 25.9, 28.0, 52.2, 62.7, 63.9, 74.6, 81.7, 124.5, 127.0, 128.27, 128.29, 134.7, 139.8, 169.8, 171.3; HRMS (ESI) calcd for $C_{25}H_{41}NO_5NaSi$ 486.265 17, found 486.261 15.

(2S,3R,4E)-*tert*-Butyl 2-Benzylamino-3,6-dihydroxyhex-4-enoate (*syn*-10). A solution of *cis*-**8** (0.538 g, 1.33 mmol) in dry THF (5 mL) was stirred with a solution of TsOH + H_2O (0.441 g, 2.32 mmol) in H_2O (6 mL) at rt for 4.5 h. After addition of 20% aqueous NaOH solution (6 mL) and H_2O (16 mL) with ice cooling, the mixture was extracted with AcOEt (50 mL × 3). The combined organic solutions were washed with H_2O (100 mL × 2) and brine (100 mL × 2), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 1/2) afforded *syn*-**10** (0.341 g, 83%) as colorless needles: mp 73−75 °C; $[\alpha]_D^{19}$ = −21.4° (*c* 1.03, $CHCl_3$); IR (ATR) 3400, 1721 cm^{-1}; ^1H NMR (400 MHz) δ 1.44 (s, 9H), 3.06 (d, J = 7.5 Hz, 1H), 3.71 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 13.2 Hz, 1H), 4.03 (t-like, J = 7.0 Hz, 1H), 4.13 (br d, J = 5.0 Hz, 2H), 5.70 (ddt, J = 15.2, 6.8, 1.6 Hz, 1H), 5.91 (dt, J = 15.2, 5.0 Hz, 1H), 7.25−7.36 (m, 5 H); ^{13}C NMR (100 MHz) δ 28.1, 52.6, 62.8, 66.5, 72.5, 82.1, 127.4, 128.3, 128.5, 129.7, 132.6, 139.1, 172.1; HRMS (ESI) calcd for $C_{17}H_{26}NO_4$ 308.1862, found 308.1876; HPLC (CHIRALCEL OD-H, λ 254 nm, hexane/^{i}PrOH 20/1, flow rate, 0.5 mL/min at 40 °C) t_R for minor isomer 33.6 min, t_R for major isomer 35.8 min.

Iodoamination of *syn*-9. To a stirred solution of *syn*-**9** (0.020 g, 0.043 mmol) in CH_2Cl_2 (0.5 mL) was successively added K_2CO_3 (0.018 g, 0.13 mmol) and iodine (0.033 g, 0.13 mmol) at −20 °C. The mixture was stirred at the same temperature for 1 h, diluted with CH_2Cl_2 (20 mL), and extracted with 20% aqueous $Na_2S_2O_3$ solution (10 mL × 3). The organic solution was washed with H_2O (10 mL × 3) and brine (10 mL × 3), dried, and evaporated to give a 11/1 diastereoisomeric mixture of **22** and **23** (0.027 g, quantitative) as a yellow oil, which was used for the next step without any purification: IR (ATR) 1751, 1733 cm^{-1}; ^1H NMR (400 MHz) for major **22** δ 0.07 (s, 6H), 0.92 (s, 9H), 1.46 (s, 9H), 2.13 (s, 3H), 3.59 (dd, J = 11.5, 2.8 Hz, 1H), 3.73 (dd, J = 11.5, 2.8 Hz, 1H), 3.79 (dt, J = 6.8, 2.8 Hz, 1H), 3.89 (d, J = 6.8 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 4.07 (d, J = 14.0 Hz, 1H), 4.53 (dd, J = 6.8, 6.8 Hz, 1H), 5.32 (dd, J = 6.8, 6.8 Hz, 1H), 7.23−7.38 (m, 5H); ^1H NMR (400 MHz) for minor **23** δ −0.01 (s, 6H), 0.82 (s, 9H), 1.37 (s, 9H), 2.04 (s, 3H), 3.34 (dt, J = 10.0, 5.2 Hz, 1H), 3.47−3.56 (m, 2H), 3.89 (d, J = 14.9 Hz, 1H), 4.07 (d, J = 14.9 Hz, 1H), 4.08 (d, J = 2.4 Hz, 1H), 4.19 (dd, J = 4.0, 4.0 Hz, 1H), 5.50 (dd, J = 6.0, 3.6 Hz, 1H), 7.23−7.38 (m, 5H); ^{13}C NMR (100 MHz) for major **22** δ −5.6, −5.4, 18.2, 21.3, 25.9, 26.7, 28.1, 52.0, 60.7, 66.6, 70.5, 71.2, 81.4, 127.0, 128.27, 128.30, 138.9, 168.9, 169.5; HRMS (ESI) calcd for $C_{25}H_{40}NO_5NaSiI$ 612.161 81, found 612.158 90.

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Iodoamination of *syn*-10. To a stirred solution of *syn*-**10** (0.116 g, 0.377 mmol) in CH_2Cl_2 (5 mL) was successively added K_2CO_3 (0.154 g, 1.11 mmol) and iodine (0.287 g, 1.13 mmol) at −20 °C. The mixture was stirred at the same temperature for 3 h and evaporated. After dilution with CH_2Cl_2 (40 mL), the mixture was successively washed with 20% aqueous $Na_2S_2O_3$ solution (20 mL × 3), H_2O (20 mL × 3), and brine (20 mL × 3), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 2/1) afforded **25** (0.147 g, 91%) and **26** (0.006 g, 3%) as yellow oils, respectively.

*(2S,3S,4R,5R)-tert-Butyl 1-Benzyl-3-hydroxy-5-hydroxymethyl-4-iodopyrrolidine-2-carboxylate (**25**):* IR (ATR) 3400, 1725 cm^{-1}; ^1H NMR (400 MHz) δ 1.51 (s, 9H), 2.70 (d, J = 7.2 Hz, 1H), 3.63 (d, J = 12.0 Hz, 1H), 3.73 (dd, J = 12.0, 2.5 Hz, 1H), 3.89 (d, J = 7.0 Hz, 1H), 3.90 (s, 1H), 3.94 (s, 2H), 4.01 (dd, J = 13.4, 7.0 Hz, 1H), 4.63 (t-like, J = 7.0 Hz, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ 28.2, 33.3, 52.1, 58.4, 67.6, 69.6, 71.5, 82.5, 127.5, 128.4, 128.6, 138.3, 169.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_4NaI$: 456.064 77, found 456.065 67.

*(2S,3S,4S,5S)-tert-Butyl 1-Benzyl-3-hydroxy-5-hydroxymethyl-4-iodopyrrolidine-2-carboxylate (**26**):* IR (ATR) 3357, 1723 cm^{-1}; ^1H NMR (400 MHz) δ 1.41 (s, 9H), 3.17 (dd, J = 11.4, 3.7 Hz, 1H), 3.46 (d, J = 11.4 Hz, 1H), 3.70 (t-like, J = 3.7 Hz, 1H), 3.95 (d, J = 12.8 Hz, 1H), 3.99 (d, J = 12.8 Hz, 1H), 4.12 (d, J = 6.4 Hz, 1H), 4.13 (dd, J = 6.4, 4.1 Hz, 1H), 4.56 (dd, J = 6.4, 3.7 Hz, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 28.0, 28.3, 59.2, 62.2, 69.3, 74.1, 80.5, 82.5, 127.9, 128.5, 129.2, 137.4, 170.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_4NaI$ 456.064 77, found 456.062 04.

(2S,3S,4R,5R)-tert-Butyl 5-Acetoxymethyl-1-benzyl-3-hydroxy-4-iodoprolinate (28). A solution of **25** (0.383 g, 0.884 mmol) in Ac_2O (2 mL, 21.2 mmol) was stirred at rt for 5 h and evaporated. Column chromatography of the residue (hexane/AcOEt 3/1) afforded **28** (0.399 g, 95%) as a yellow oil: $[\alpha]_D^{14.5}$ = +2.4° (*c* 3.22, $CHCl_3$); IR (ATR) 3440, 1739 cm^{-1}; ^1H NMR (400 MHz) δ 1.48 (s, 9H), 2.08 (s, 3H), 2.85 (br, 1H), 3.82 (d, J = 6.2 Hz, 1H), 3.83 (d, J = 14.0 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 3.91 (dt, J = 6.8, 3.2 Hz, 1H), 4.03−4.12 (m, 1H) 4.07 (dd, J = 12.5, 3.2 Hz, 1H), 4.31 (dd, J = 12.5, 3.2 Hz, 1H), 4.43 (dd, J = 6.8, 6.8 Hz, 1H), 7.21−7.30 (m, 5H); ^{13}C NMR (100 MHz) δ 20.9, 28.1, 32.9, 51.7, 61.8, 66.9, 67.5, 70.1, 82.3, 127.2, 128.25, 128.31, 138.1, 169.7, 170.5; HRMS (ESI) calcd for $C_{19}H_{26}NO_5NaI$ 498.075 33, found 498.077 13.

Prévost-Type Displacement of 28. A mixture of **28** (0.120 g, 0.253 mmol) and AcOAg (0.114 g, 0.684 mmol) in AcOH (3 mL) and CH_2Cl_2 (1 mL) was stirred at rt for 19 h under Ar and filtered through Celite. After evaporation of the filtrate column chromatography of the residue (hexane/AcOEt 2/1) afforded **29** (0.061 g, 59%) as a colorless oil, which was estimated to be a ca. 2/1 mixture: IR (ATR) 3500, 1740 cm^{-1}; ^1H NMR (400 MHz) for a major isomer δ 1.46 (s, 9H), 2.07 (s, 3H), 2.09 (s, 3H), 3.48−3.55 (m, 1H), 3.75 (d, J = 7.6 Hz, 1H), 3.75 (d, J = 13.6 Hz, 1H), 3.83 (d, J = 12.4 Hz, 1H, exchangeable), 4.00 (d, J = 13.6 Hz, 1H), 4.07 (dd, J = 11.6, 3.6 Hz, 1H), 4.25 (dd, J = 12.0, 6.0 Hz, 1H), 4.38 (dd, J = 11.6, 5.2 Hz, 1H), 5.05 (t-like, J = 6.8 Hz, 1H), 7.21−7.31 (m, 5H); ^1H NMR (400 MHz) for a minor isomer δ 1.51 (s, 9H), 2.08 (s, 3H) 2.10 (s, 3H), 3.48−3.55 (m, 1H), 3.63 (d, J = 7.2 Hz, 1H), 3.96 (d, J = 13.6 Hz, 1H), 4.01 (d, J = 13.6 Hz, 1H), 4.07 (dd, J = 12.0, 4.0 Hz, 1H), 4.38 (dd, J = 12.0, 4.0 Hz, 1H), 4.41 (t-like, J = 6.4 Hz, 1H), 5.11 (dd, J = 6.4, 2.8 Hz, 1H), 7.21−7.31 (m, 5H); ^{13}C NMR (100 MHz) for a major isomer δ 20.8, 28.0, 53.3, 63.6, 65.0, 69.9, 72.1, 72.9, 82.8, 127.4, 128.3, 137.8, 169.5, 170.8, 173.2; ^{13}C NMR (100 MHz) for a minor isomer δ 20.5, 28.2, 51.7, 62.4, 65.0, 65.1, 70.4, 75.0, 81.9, 127.2, 128.3, 128.4, 138.4, 170.4, 170.7, 170.8; HRMS (FAB) calcd for $C_{21}H_{30}NO_7$ 408.2022, found 408.2019.

(2S,3S,4R,5R)-tert-Butyl 1-Benzyl-3,4-dihydroxy-5-(hydroxymethyl)prolinate (30). A mixture of **29** (0.125 g, 0.307 mmol) and K_2CO_3 (0.129 g, 0.932 mmol) in MeOH (10 mL) was stirred at rt for 1 h and extracted with $CHCl_3$ (30 mL × 3) after addition of H_2O (10 mL). The combined organic solutions were washed with H_2O (20 mL × 2) and brine (20 mL × 2), dried, and evaporated. Column chromatography of the residue (AcOEt) afforded **30** (0.093 g, 94%) as colorless needles: mp 106−108 °C; $[\alpha]_D^{17}$ = −57.1° (*c* 1.86, $CHCl_3$); IR (ATR) 3440 (br), 1700 cm^{-1}; ^1H NMR (400 MHz) δ 1.50 (s, 9H), 2.20 (d, J = 9.6 Hz, 1H, exchangeable), 3.03 (d, J = 6.9 Hz, 1H, exchangeable), 3.39 (br s, 1H), 3.58 (dd, J = 11.4, 3.2 Hz, 1H), 3.66 (dd, J = 11.4, 1.4 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.84 (d, J = 13.3 Hz, 1H), 3.80 (d, J = 6.8 Hz, 1H), 4.09 (dd, J = 6.4, 2.0 Hz, 1H), 4.14 (t-like, J = 6.8 Hz, 1H), 7.23−7.33 (m, 5H); ^{13}C NMR (100 MHz) δ 28.1, 53.3, 60.6, 68.3, 71.2, 72.7, 74.9, 83.2, 127.6, 128.5, 128.6, 138.0, 174.4; HRMS (ESI) calcd for $C_{17}H_{25}NO_5Na$ 346.163 04, found 346.165 87.

(2S,3S,4R,5S)-tert-Butyl 1-Benzyl-3,4-dihydroxy-5-[(*tert*-butyldimethylsilyloxy)methyl]prolinate (31). A mixture of **30** (0.057 g, 0.18 mmol), TBSCl (0.035 g, 0.23 mmol), and imidazole (0.026 g, 0.38 mmol) in DMF (3 mL) was stirred at rt for 1 h and extracted with AcOEt (20 mL × 3) after addition of saturated aqueous NH_4Cl solution (6 mL). The combined organic solutions were washed with H_2O (20 mL × 2) and brine (20 mL × 2), dried, and evaporated. Column chromatography of the residue (hexane/AcOEt 6/1) afforded **31** (0.057 g, 74%) as colorless needles: mp 79−81 °C; $[\alpha]_D^{16}$ = −33.5° (*c* 1.15, $CHCl_3$); IR (ATR) 3410, 1700 cm^{-1}; ^1H NMR (400 MHz) δ −0.06 (s, 3H), −0.05 (s, 3H), 0.91 (s, 9H), 1.43 (s, 9H), 3.00 (d, J = 8.7 Hz, 1H, exchangeable), 3.31 (t-like, J = 3.5 Hz, 1H), 3.56 (dd, J = 11.0, 4.4 Hz, 1H), 3.59 (dd, J = 11.0, 3.6 Hz, 1H), 3.72 (d, J = 7.6 Hz, 1H), 3.79 (d, J = 13.7 Hz, 1H), 3.92 (d, J = 13.7 Hz, 1H), 3.99 (dd, J = 5.7, 1.0 Hz, 1H), 4.36 (dd, J = 7.6, 5.7 Hz, 1H), 7.24−7.30 (m, 5H); ^{13}C NMR (100 MHz) δ −5.5, 18.2, 25.9, 28.0, 53.7, 62.9, 68.5, 71.0, 71.4, 75.0, 82.5, 127.1, 128.2, 128.5, 138.8, 174.6; HRMS (ESI) calcd for $C_{23}H_{39}NO_5NaSi$ 460.249 52, found 460.248 82.

(3aS,4S,6S,6aR)-tert-Butyl 5-Benzyl-6-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyltetrahydro[1,3]-dioxolo[4,5-*c*]pyrrole-4-carboxylate (32). A mixture of **31** (0.0103 g, 0.0235 mmol) and TsOH + H_2O (0.0065 g, 0.0342 mmol) in 2,2-dimethoxypropane (0.3 mL) was stirred at rt for 1 h and evaporated after addition of triethylamine (0.1 mL). Column chromatography of the residue (hexane/AcOEt 4/1) afforded **32** (0.0086 g, 77%) as a colorless oil: $[\alpha]_D^{21}$ = −67.7° (*c* 0.66, $CHCl_3$); IR (ATR) 1740 cm^{-1}; ^1H NMR (400 MHz) δ 0.05 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.33 (s, 3H), 1.56 (s, 3H), 1.49 (s, 9H), 3.19 (s, 1H), 3.42 (dd, J = 11.0, 2.6 Hz, 1H), 3.61 (d, J = 13.5 Hz, 1H), 3.87 (dd, J = 11.0, 2.2 Hz, 1H), 3.95 (d, J = 6.6 Hz, 1H), 4.07 (d, J = 13.5 Hz, 1H), 4.59 (d, J = 6.2 Hz, 1H), 4.91 (dd, J = 6.4, 6.2 Hz, 1H), 7.22 (dd, J = 7.3, 7.3 Hz, 1H), 7.30 (dd, J = 7.3, 7.3 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz) δ −5.7, −5.5, 18.0, 25.8, 25.9, 26.6, 28.2, 51.8, 61.6, 64.6, 70.9, 80.6, 81.3, 83.0, 112.0, 126.8, 128.2, 128.3, 139.1, 169.5; HRMS (ESI) calcd for $C_{26}H_{43}NO_5NaSi$ 500.280 82, found 500.277 02.

(3aS,4S,6S,6aR)-Di-tert-butyl 6-[(*tert*-Butyldimethylsilyloxy)-methyl]-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-4,5-dicarboxylate (33). A mixture of **32** (0.0395 g, 0.0827 mmol), $(Boc)_2O$ (0.0345 g, 0.158 mmol), and 20% $Pd(OH)_2$ on C (0.0123 g) in AcOEt (2 mL) was stirred at rt for 44 h and then at 40 °C for 1 h and filtered through Celite. After evaporation of the filtrate, column chromatography of the residue (hexane/AcOEt 10/1) afforded **33** (0.0344 g, 85%) as a colorless oil, which exists as rotational isomers in a ratio of 7/3: $[\alpha]_D^{21.5}$ = −89.2° (*c* 0.688, $CHCl_3$); IR (ATR) 1756, 1700 cm^{-1}; ^1H NMR (400 MHz) for a major rotamer δ 0.01 (s, 3H), 0.02 (s, 3H), 0.88 (s, 9H), 1.30 (s, 3H), 1.44 (s, 3H), 1.42 (s, 9H), 1.49 (s, 9H), 3.56 (dd, J = 10.1, 1.8 Hz, 1H), 4.14 (dd, J = 10.1, 1.8 Hz, 1H), 4.26 (s, 1H), 4.28 (d, J = 7.8 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.88 (t-like, J = 7.2 Hz, 1H); ^1H NMR (400 MHz) for a minor rotamer δ 0.02 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.30 (s, 3H), 1.48 (s, 3H), 1.45 (s, 9H), 1.48 (s, 9H), 3.63 (dd, J = 10.1, 1.8 Hz, 1H), 3.87 (dd, J = 10.1, 2.7 Hz, 1H), 4.13 (s, 1H), 4.37 (d, J = 7.8 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.86 (t-like, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz) for a major rotamer δ −5.7, −5.3, 18.1, 24.6, 25.5, 25.9, 28.27, 28.32, 62.0, 64.0, 65.8, 79.9, 80.2, 80.9, 82.2, 112.2, 153.6, 167.8; ^{13}C NMR (100 MHz) for a minor rotamer δ −5.7, −5.5, 18.1, 24.6, 25.5, 25.9, 28.1, 28.4, 63.5, 63.9, 77.2, 78.6, 80.0, 80.9, 83.3, 112.2, 153.6, 167.2; HRMS (ESI) calcd for $C_{24}H_{45}NO_7NaSi$ 510.286 30, found 510.284 04.

(3aR,4S,6R,6aR)-tert-Butyl 4-[(*tert*-Butyldimethylsilyloxy)-methyl]-6-hydroxymethyl-2,2-dimethyltetrahydro[1,3]-dioxolo[4,5-*c*]pyrrole-5-carboxylate (34). A mixture of **33** (0.0116 g, 0.0238 mmol) and $LiBH_4$ (0.0026 g, 0.1194 mmol)) in MeOH (1.2

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mL) was stirred with heating at 70 °C for 7 h under Ar, quenched with saturated aqueous NH_4Cl solution (0.6 mL), and extracted with AcOEt (20 mL × 2). The combined organic solutions were washed with H_2O (1 mL × 2) and brine (1 mL × 2), dried, and evaporated to give **34** (0.0078 g, 76%) as a yellow oil, which exists as rotational isomers in a ratio of 6/1: IR (ATR) 3430, 1680 cm^{-1}; ^1H NMR (600 MHz) for a major rotamer δ 0.047 (s, 3H), 0.052 (s, 3H), 0.89 (s, 9H), 1.32 (s, 3H), 1.45 (s, 3H), 1.47 (s, 9H), 3.67 (dd, J = 10.4, 2.2 Hz, 1H), 3.76 (ddd, J = 13.2, 7.4, 2.5 Hz, 1H) 3.84 (dd, J = 10.4, 3.6 Hz, 1H), 3.87−3.92 (m, 2H), 3.98 (t-like, J = 2.8 Hz, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.75 (t-like, J = 6.0 Hz, 1H), 5.27 (dd, J = 11.0, 2.7 Hz, 1H, exchangeable); ^1H NMR (600 MHz) for a minor rotamer δ 0.025 (s, 3H), 0.033 (s, 3H), 0.88 (s, 9H), 1.26 (s, 3H), 1.37 (s, 3H), 1.47 (s, 9H), 2.88 (dd, J = 11.0, 6.6 Hz, 1H, exchangeable), 3.57 (d, J = 10.4 Hz, 1H), 3.66−3.68 (m, 1H), 3.92−3.96 (m, 2H), 4.09 (dd, J = 11.0, 6.0 Hz, 1H), 4.17 (dd, J = 11.0, 2.5 Hz, 1H), 4.65 (d, J = 6.0 Hz, 1H), 4.85 (t-like, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz) for a major rotamer δ −5.6, −5.5, 18.1, 24.7, 25.9, 26.0, 28.4, 63.1, 63.4, 65.0, 66.1, 80.4, 80.8, 81.1, 110.9, 155.9; HRMS (ESI) calcd for $C_{20}H_{39}NO_6NaSi$ 440.244 43, found 440.240 66.

(3a*R*,4*S*,6*S*,6a*S*)-*tert*-Butyl 4-[(*tert*-Butyldimethylsilyloxy)-methyl]-6-formyl-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]-pyrrole-5-carboxylate (5). A mixture of **34** (0.0078 g, 0.0187 mmol), DMP (0.0119 g, 0.0281 mmol), and $NaHCO_3$ (0.0047 g, 0.0559 mmol) in dry CH_2Cl_2 (0.4 mL) was stirred at rt for 1 h, quenched with saturated aqueous $NaHCO_3$ solution (0.2 mL), and extracted with AcOEt (20 mL × 2). The combined organic solutions were washed with H_2O (1 mL × 2) and brine (1 mL × 2), dried, and evaporated. Purification of the residue by column chromatography (hexane/AcOEt 10/1) afforded **5** (0.0052 g, 67%) as colorless prisms, which exists as rotational isomers in a ratio of 2/1: mp 65−69 °C; $[\alpha]_D^{24}$ = −145.3° (c = 0.06, $CHCl_3$); IR (ATR) 1742, 1706 cm^{-1}; ^1H NMR (600 MHz) for a major rotamer δ 0.03 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 1.30 (s, 3H), 1.41 (s, 9H), 1.46 (s, 3H), 3.64 (dd, J = 10.6, 1.8 Hz, 1H), 4.12 (d, J = 10.8 Hz, 1H), 4.15 (dd, J = 10.7, 2.2 Hz, 1H), 4.26 (t-like, J = 1.8 Hz, 1H), 4.72 (d, J = 5.9 Hz, 1H), 4.95 (t-like, J = 6.0 Hz, 1H), 9.29 (d, J = 4.0 Hz, 1H); ^1H NMR (600 MHz) for a minor rotamer δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.31 (s, 3H), 1.41 (s, 9H), 1.48 (s, 3H), 3.69 (dd, J = 10.5, 1.8 Hz, 1H), 3.90 (dd, J = 10.5, 2.0 Hz, 1H), 4.12 (dd, J = 8.4, 5.2 Hz, 1H), 4.20 (dd, J = 7.0, 3.7 Hz, 1H), 4.73 (d, J = 5.1, 1H), 4.92 (t-like, J = 6.0 Hz, 1H), 9.34 (d, J = 3.7 Hz, 1H); ^{13}C NMR (150 MHz) for a major rotamer δ −5.7, 18.1, 24.0, 25.8, 28.1, 62.3, 64.8, 69.0, 81.4, 81.7, 82.3, 112.0, 153.4, 198.9; ^{13}C NMR (150 MHz) for a minor rotamer δ −5.6, 18.1, 24.0, 25.7, 28.4, 63.5, 64.5, 69.0, 80.3, 81.1, 83.2, 112.0, 154.4, 198.4; HRMS (ESI) calcd for $C_{20}H_{37}NO_6NaSi$ 438.228 78, found 438.230 20.

Direct Reduction of the *N*-Boc Acetal 33. A 1 M solution of DIBAL in toluene (0.15 mL, 0.15 mmol) was added to a solution of the *N*-Boc acetal **33** (0.0237 g, 0.0486 mmol) in dry CH_2Cl_2 (0.2 mL) at −50 °C, and the whole mixture was stirred at the same temperature for 8 h. After further addition of a 1 M solution of DIBAL in toluene (0.25 mL, 0.25 mmol) at −50 °C, the whole mixture was stirred at rt for 5.5 h and at 40 °C for 0.5 h and quenched with MeOH (0.5 mL) and saturated aqueous NH_4Cl solution (0.5 mL). After filtration of insoluble precipitate through Celite, the filtrate was evaporated. Repeated flash chromatography of the residue (hexane/AcOEt 10/1, 15/1, and 30/1 → 20/1) afforded the prolinal **5** (0.0037 g, 18% (22% brsm)) and the alcohol **34** (0.0023 g, 11% (14% brsm)) as yellow oils, respectively, which exist as rotational isomers in ratios of 4/1 for **5** and of 3/1 for **34**, respectively.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR data for compounds *trans*- and *cis*-**8**, *anti*- and *syn*-**9**, *anti*- and *syn*-**10**, a mixture of **11** and **12**, **13**−**19**, (+)-DMDP (**1**), a mixture of **22** and **23**, **25**, **26**, **28**−**34**, and (−)-**5** and CIF files giving crystal data fpr **19** and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Crystallographic data are as follows. **19**: M = 253.29, monoclinic, space group $P2_1$, a = 9.6958(6) Å, b = 6.1371(4) Å, c = 10.4129(6) Å, β = 92.5870(10)°, V = 618.98(7) Å^3, Z = 2, R1 = 0.0307, wR2 = 0.0763, GOF = 1.505. **30**: M = 323.38, orthorhombic, space group $P2_12_12_1$, a = 5.69660(10) Å, b = 15.5167(4) Å, c = 19.3507(5) Å, V = 1710.46(7) Å^3, Z = 4, R1 = 0.0311, wR2 = 0.0842, GOF = 1.056. CCDC-875391 (for **19**) and CCDC-875392 (for **30**) contain 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.
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