Asymmetric Syntheses of 2-Substituted and 2,5-Disubstituted Pyrrolidines from (3*S*,5*R*,7a*R*)-5-(Benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine‡

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Benzotriazole, 2,5-dimethoxytetrahydrofuran, and (*S*)-phenylglycinol in one step gave 80% of (3*S*, 5*R*,7a*R*)-5-(benzotriazol-1-yl)-3-phenyl-[2,1-*b*]oxazolopyrrolidine (**6**), whose crystal structure was confirmed by X-ray crystallography. Novel chiral pyrrolidine synthon **6** reacts with organosilicon (allyltrimethylsilanes and vinyloxytrimethylsilanes), organophosphorus, organozinc, and Grignard reagents to afford chiral 2-substituted and 2,5-disubstituted pyrrolidines.

Introduction

Pyrrolidine derivatives are attractive synthetic targets[1] because numerous biological compounds possess pyrrolidine rings as their framework,[2] and some of them are pharmaceutically important.[3] In addition, enantiomerically pure pyrrolidines are useful chiral auxiliaries.[4]

Substituted pyrrolidines have been synthesized by (i) pyrrolidine ring construction[5] and (ii) substituent modification of a preformed ring. Many ring syntheses give racemic products, e.g., photocyclization of *N*-chloramines, reductive amination of 1,4-diketones,[5b] 1,3-dipolar cycloadditions,[5c,d] and metal-catalyzed cyclizations.[5e,f] Ring syntheses of optically active pyrrolidines are usually multistep: Rapoport *et al.* prepared chiral 2,5-disubstituted pyrrolidines from glutamic acid in 10 or more steps,[5g] while Kibayashi *et al.* made 2,5-disubstituted pyrrolidines in seven steps starting with D-mannitol.[5h]

Syntheses in which a preformed pyrrolidine ring is functionalized[6] include stepwise alkylation of *N*-nitrosopyrrolidine via deprotonation α to the nitrogen atom,[6a] conjugate addition to α,β-unsaturated 2-pyrrolidinones,[6g] and alkylation and reduction of the Lukes−Sorm dilactam.[6c] Such syntheses often derive their chirality source from an amino acid, e.g., proline[6j] or pyroglutamic acid.[6d,6e]

Endocyclic enamines (**1**) have been developed as successful synthons by Stevens (Figure 1).[7] Husson et al. have used both the 2-cyano-6-oxazolopiperidine synthon (**2b**)[8] and the lower homologue (**2a**) for the synthesis of chiral 2-substituted and 2,5-disubstituted pyrrolidines[9] including (+)-ferruginine.[10] Chiral α,β-unsaturated 2-pyrrolidinone synthons (**3**[11] and **4**[12]) have been recently used

‡ This paper is dedicated in friendship and with affection to Henk van der Plas on the occasion of his 70th anniversary.

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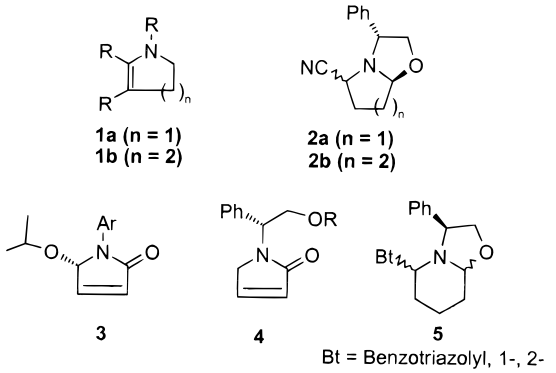


Figure 1. Synthons.

by Speckamp and Royer, respectively, for the synthesis of 3,4-disubstituted and ring-fused pyrrolidines. Despite these successes, the development of simple synthons, and thus reliable and flexible routes to complex chiral pyrrolidines, is still important.

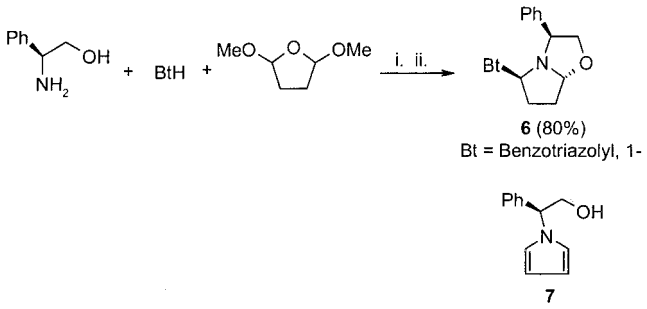
Benzotriazole is a useful auxiliary group in organic synthesis.[13] Benzotriazole methodology has been applied by Shankar et al. to synthesize polyhydroxylated piperidines as potential glycosidase inhibitors.[14] We prepared chiral 2-substituted and 2,6-disubstituted piperidines from intermediate 2-benzotriazolyl-6-oxazolopiperidine (**5**).[15] We now report the details of the preparation of 2-benzotriazolyl-5-oxazolopyrrolidine (**6**) and its application as a pyrrolidine synthon for chiral pyrrolidines (for a preliminary communication of part of this work see ref 16).

Results and Discussion

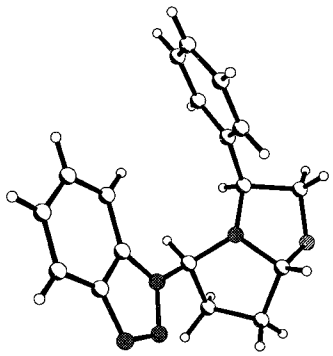
Preparation and Characterization of (3*S*,5*R*, 7a*R*)-5-(Benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine (6). Benzotriazole, (*S*)-phenylglycinol, and hydrolyzed 2,5-dimethoxytetrahydrofuran (the equivalent of succindialdehyde) at room temperature gave crystalline (3*S*,5*R*, 7a*R*)-5-(benzotriazol-1-yl)-3-phenyl[2,1-*b*]-oxazolopyrrolidine (**6**) in 80% yield on a 100 mmol scale. This reaction entails the formation of two heterocyclic rings and two new chiral centers in one step (Scheme 1) by double Robinson−Schopf condensation of the dialdehyde with the amino group and benzotriazole intercepting the initially formed iminium ion. Concentrations of HCl greater than 0.1 N or a reaction temperature higher than ambient led to the formation of byproduct **7** and lower yields of **6**. The ^{1}H and ^{13}C NMR spectra of the crude product **6** showed only one diastereoisomer; the detailed structure of **6** was shown by X-ray crystallography to be that in Scheme 1.

Compound **6** is thus even easier to prepare than is its higher homologue 2-benzotriazolyl-6-oxazolopiperidine (**5**).[15] By contrast, the cyano derivative (**2a**)[9a,c,d] was less stable than that of its 5,6-membered ring analogue (**2b**),[8a]

Scheme 1. Preparation and the X-ray Structure of Synthon 6[a]



[a] (i) 0.1 N HCl, 50 °C, 0.5 h; (ii) CH_2Cl_2, rt, 12 h.



and **2a** cannot be prepared by Robinson−Schopf condensation of succinaldehyde with phenylglycinol in the presence of KCN,[8b] the method used for **2b**. An epimeric mixture of **2a** was produced in 52% yield by the condensation of phenylglycinol, dimethoxytetrahydrofuran, and aqueous KCN at pH ∼3 over 48 h, followed by refluxing the crude reaction extract in EtOH for 96 h.[9b]

Reactions of Synthon 6 with Allylsilanes and Vinyloxysilanes To Give 2-Substituted and 2,5-Disubstituted Pyrrolidines. Synthon **6** with allyltrimethylsilane in the presence of zinc(II) bromide, tin(IV) chloride, or boron trifluoride as a Lewis acid gave the 2-substituted product (**8**) along with the elimination product (**7**) (Scheme 2). Boron trifluoride−diethyl etherate cleanly gave **8** in 40−50% yield. Synthon **6** and (2-methylprop-1-en-3-yl)trimethylsilane gave **15** (Scheme 3), which has the 2-methylpropenyl substituent at the C-2 pyrrolidine position.

The trans H-3, H-7a relationship of **6** was unchanged in **8**. A 2D shift correlation COSY experiment allowed assignment of the ^{1}H resonances, and the absolute configuration (*S*) of C-5 in **8** was ascertained by the NOE difference technique (Figure 2). Presaturation of the H-5 resonance resulted in enhancement of the signals for the H-3 proton.

Hydrogenation of intermediates **8** and **15** cleaved the chiral auxiliary and reduced the double bond to give the 2-alkylpyrrolidines **11** and **18** in nearly quantitative yields (Scheme 2 and 3).

Intermediate **8** was also reacted further with Grignard reagents to give mixtures of cis and trans epimers **9** and **10** (Table 1), which were easily separated by flash chromatography. As shown in Scheme 2 and Table 1, only two isomers were produced in this reaction. Nucleophilic substitution of the benzotriazole group at the C-2 pyrrolidine position gave one stereoisomer, with attack cis to the phenyl group. Further substitution at the C-5

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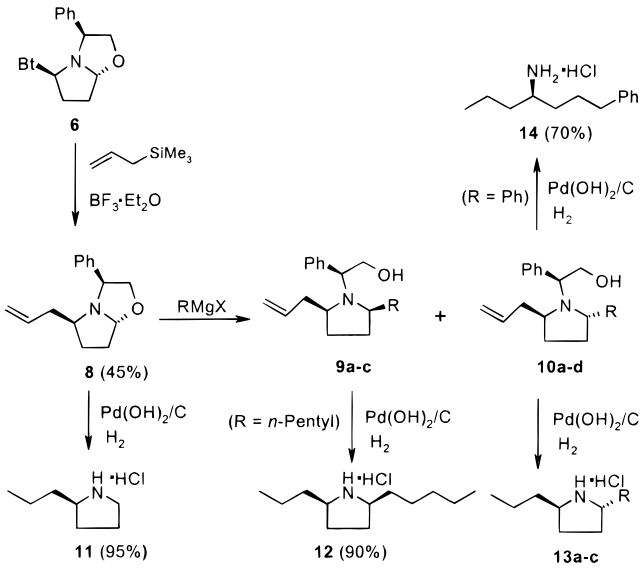
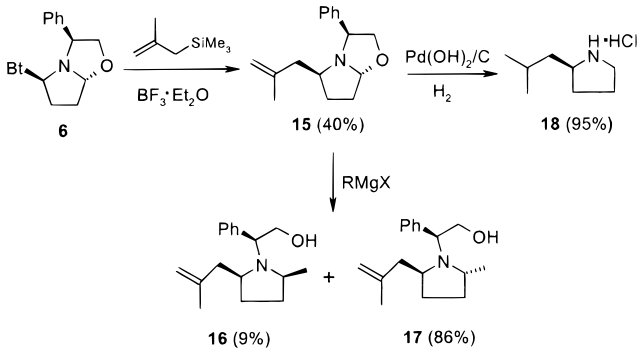
Scheme 2[a]



	R	9	10	13
a	Me	9%	81%	90%
b	*n*-Pentyl	18%	72%	95%
c	$PhCH_2CH_2$	14%	76%	95%
d	Ph		91%	

Scheme 3



pyrrolidine position gave a mixture of *cis* and *trans* isomers. The mechanism involves initial formation of an iminium ion by opening the oxazolidine ring and subsequent nucleophilic addition, which selectively attacked at the less hindered face of the molecule. The *cis*−*trans* ratio of **9**:**10** from alkyl Grignards ranged from 20:80 to 10:90, but for the phenyl group the ratio of **9**:**10** was <3:>97; only trans isomer was detected in the crude NMR spectra.

The stereochemistry of compounds **9** (*cis*) and **10** (*trans*) was determined by comparing their NMR spectra and $[\alpha]_D$ with those reported in the literature[17] and with the series *cis*-**23** and *trans*-**24** products derived from synthon **6** with excess Grignard reagents. The absolute configuration of **24b** has been elucidated by X-ray crystallography.[16] The optical rotations of *cis*-2,5-dialkyl substituted **9** and **23** were usually positive, while those of *trans*-2,5-dialkyl-substituted **10** and **24** were always negative, as shown in Tables 1 and 2.

Under hydrogenolytic conditions ($Pd(OH)_2/C$, H_2), the chiral auxiliary attached to the nitrogen atom of **9** and **10** was cleaved to afford the corresponding 2,5-dialkyl pyrrolidines (**12** and **13**). When R was a phenyl group, hydrogenolysis by pyrrolidine ring opening led to the chiral primary amine (4*R*)-1-phenyl-4-heptanamine (**14**).

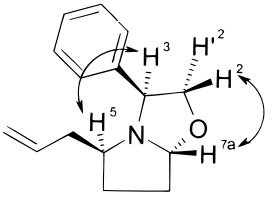


Figure 2. NOE effects in **8**.

Table 1. Reaction of Intermediate 8 with Grignard Reagents to Prepare 9 and 10

entry	R	total yield (%)	ratio **9**:**10**	$[\alpha]^{20}_D$ of **9** (*c* 1 g/mL, EtOH)	$[\alpha]^{20}_D$ of **10** (*c* 1 g/mL, EtOH)
a	Me	90	10:90	−13.0	−36.7
b	*n*-pentyl	90	20:80	+31.5	−20.9
c	$PhCH_2CH_2$	90	15:85	+56.4	−23.4
d	Ph	85	<3:97		−34.6

Table 2. Reaction of Synthon 6 with Excess Grignard Reagents to Prepare Compounds 23 and 24

entry	R	total yield (%)	ratio **23**:**24**	$[\alpha]^{20}_D$ of **23** (*c* 1 g/mL, EtOH)	$[\alpha]^{20}_D$ of **24** (*c* 1 g/mL, EtOH)
a	Ph	90	1:1	−17.6	−3.1
b	Me	76	3:1	+30.1	−23.0
c	*n*-Pr	77	5:2	+20.3	−36.7
d	*n*-pentyl	70	3:1	+14.6	−42.9
e	$PhCH_2CH_2$	90	2:1	+8.2	−25.5[a]

[a] Solvent: $CHCl_3$.

Thus, starting from 2,5-dimethoxytetrahydrofuran, optically pure 2,5-disubstituted pyrrolidines were prepared. Trans configuration products **13** dominate, which could be useful as most natural dialkyl pyrrolidines (e.g., ant alkaloids[1a,2b]) have the trans 2,5-configuration. The cis/trans stereoselectivities of several other approaches are low, e.g., 60:40 in the case of the alkylation of formamidines.[18]

Synthon **6** reacted with (α-substituted-vinyloxy)trimethylsilanes in the presence of boron trifluoride−diethyl etherate at 0 °C to produce compounds **19**, which have a substituent bearing a carbonyl group at the C-2 pyrrolidine position (Scheme 4). Compounds **19a** (R = Me) and **19b** (R = Ph) are potential intermediates for the preparation of (−)-hygrine and ruspolinone analogues.[5k,19] Synthon **6** reacted with 1-methoxy-1-trimethylsiloxy-2-methyl-1-propene to give compound **20** as an inseparable mixture of two isomers, in 64% yield.

Reactions of Synthon 6 with Phosphorus Reagents. During the last two decades, considerable efforts have been made toward the asymmetric synthesis of phosphonic analogues of naturally occurring α-amino acids.[20] Cyclic phosphonic acids, like their acyclic derivatives, also show interesting properties.

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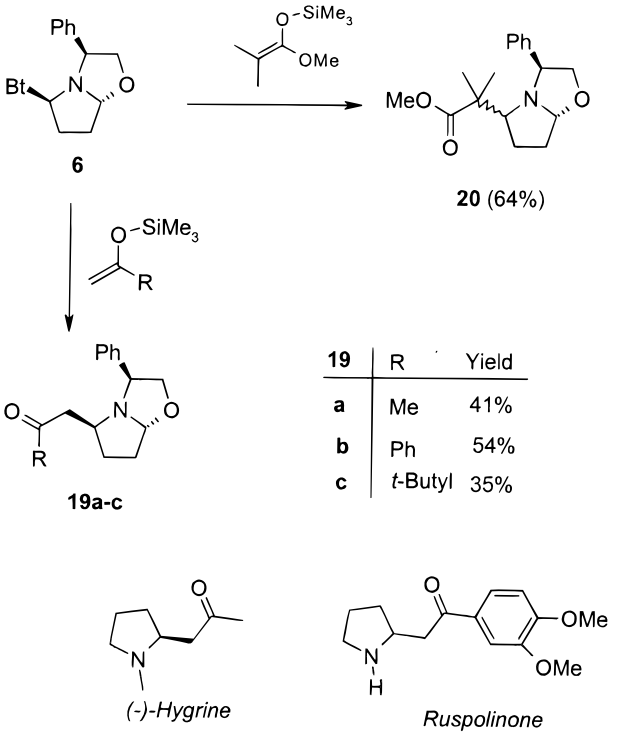
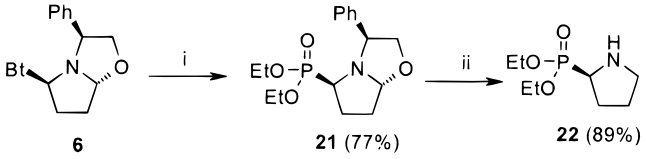
Scheme 4



19	R	Yield
a	Me	41%
b	Ph	54%
c	*t*-Butyl	35%

Scheme 5



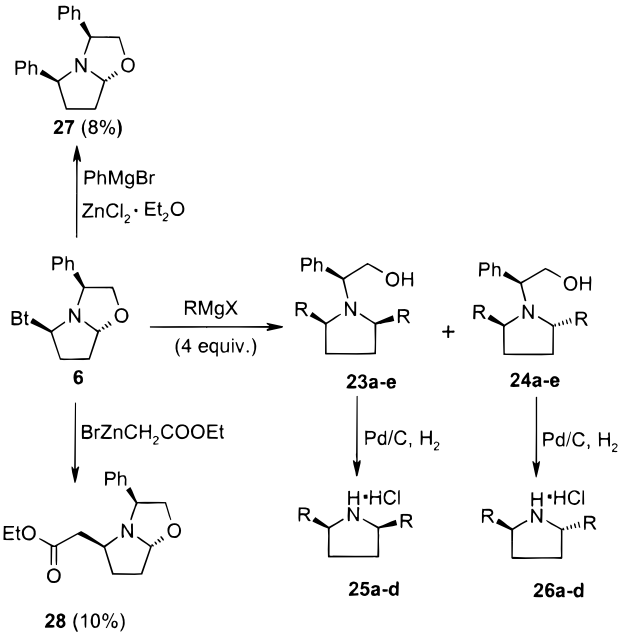
[a] Key: (i) $P(OEt)_3$, $ZnBr_2$, CH_2Cl_2, rt; (ii) Pd/C, H_2.

The Arbuzov reaction,[21] as previously employed by Husson et al. to prepare piperidin-2-ylphosphonic acid,[20c] converted **6** into the expected 2-substituted pyrrolidine phosphonate (**21**) in 77% yield in the presence of the mild Lewis acid $ZnBr_2$. Both ^1H and ^{13}C NMR spectra of **21** indicated that only one diastereoisomer was obtained. Hydrogenation of **21** gave diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate (**22**) in 63% overall yield (Scheme 5).

The reactivity of synthon **6** toward phosphorus reagents differs from that of its homologue **5** and of synthon **2b**. Lithium diethyl phosphite was used successfully in the preparation of piperidin-2-yl phosphonate from **5**,[15] but it failed to react with **6**. Furthermore, attempts to use the same procedure that gave 2-cyano-6-oxazaphosphorinane from synthon **2b**[20c] failed for synthon **6** as triethyl phosphite in the presence of $SnCl_4$ in room temperature for 24 h gave a complex mixture.

Reactions of Synthon 6 with Grignard Reagents and Organozinc Reagents: Preparation of 2,5-Disubstituted Pyrrolidines. When excess (4 equiv) Grignard reagent was reacted with synthon **6** at 0 °C, the reactions gave mixtures of the cis products (**23a**−**e**) and trans products (**24a**−**e**) in excellent total yields; each of the diastereoisomeric pairs of **23** and **24** were separated by column chromatography. Hydrogenation of **23b**−**e** and **24b**−**e** in the presence of Pd/C catalyst gave

Scheme 6



	R	23	24
a	Ph	45%	45%
b	Me	57%	19%
c	*n*-Pr	55%	22%
d	*n*-Pentyl	53%	17%
e	$PhCH_2CH_2$	60%	30%

	R	25	26
a	Me	90%	87%
b	*n*-Pr	95%	84%
c	*n*-Pentyl	92%	80%
d	$PhCH_2CH_2$	89%	76%

the corresponding cis and trans 2,5-disubstituted pyrrolidines (**25a**−**d** and **26a**−**d**) in excellent yields.

When phenylmagnesium bromide reacted with **6**, the reaction gave **23a** and **24a** in a ratio of 1:1. However, methylmagnesium bromide in this reaction gave a ratio of 3:1. Similarly, other alkyl Grignard reagents afforded **23** and **24** in ratios of about 3:1. The ratios of cis/trans **23**:**24** (Table 2) are surprising in contrast to the **9**:**10** ratios (Table 1), with *cis*-**23** being the major product.

We previously found that the C−benzotriazole bond can be cleaved selectively in the presence of a geminal C−O bond.[22] This, and the results described above, suggested that two reactive sites in the pyrrolidine ring of synthon **6** should be discriminated by mild organometallic reagents. Phenyl organozinc reagent and Reformatsky reagent did furnish the monosubstituted products **27** and **28** (a key intermediate to homohygrinic acid), respectively, but in low yields (10%) and with disubstituted and elimination byproducts (Scheme 6). Treatment of synthon **6** with 1 equiv of Grignard reagent at 0 °C gave mixtures of cis and trans 2,5-disubstituted pyrrolidines (**23** and **24**), along with a large amount of recovered starting material **6**. Many attempts, including addition of Lewis acids such as $ZnBr_2$ to the reaction mixture to assist the departure of the benzotriazolyl group, lowering the reaction temperature, and adjusting the rate of Grignard reagent addition, failed to yield the desired monosubstituted product in reasonable yield. This indicates that the two reaction centers, α-aminobenzotriazolyl at the C-2 position and α-amino ether at the

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(22) Katritzky, A. R.; Bao, W.; Qi, M.; Fali, C. N.; Prakash, I. *Tetrahedron Lett.* **1998**, in press.

C-5 position of the pyrrolidine ring, have similar reactivities toward Grignard reagents.

Conclusion

Novel chiral pyrrolidine **6**, (3*S*,5*R*,7a*R*)-5-(benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine, which was prepared from benzotriazole, 2,5-dimethoxytetrahydrofuran, and (*S*)-phenylglycinol in one step, can be used as a chiral synthon for rapid asymmetric syntheses of 2-substituted and 2,5-disubstituted pyrrolidines.

Experimental Section

General Comments. Air- and moisture-sensitive reactions were carried out under inert atmosphere (N_2 or Ar). When necessary, solvents and reagents were dried in the traditional fashion prior to use. Column chromatography was carried out on silica gel (230−400 mesh). All melting points were measured on a hot-stage apparatus and are not corrected. Optical rotations were measured with a digital polarimeter (a 1 dm cell was used in all cases). The ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solution (300 and 75 MHz, respectively), with TMS or $CDCl_3$ as internal references.

(3*S*,5*R*,7a*R*)-5-(Benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine (6). A mixture of 2,5-dimethoxytetrahydrofuran (1.3 mL, 10 mmol) and HCl aqueous solution (40 mL, 0.1 N) was refluxed for 1 h and then cooled to room temperature. A solution of benzotriazole (1.19 g, 10 mmol) and (*S*)-phenylglycinol (1.37 g, 10 mL) in methylene chloride (100 mL) was added to the cooled mixture, which was then stirred overnight. The reaction mixture was washed with NaOH aqueous solution (2 N, 3 × 30 mL) and water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from ethyl acetate to give crystalline product **6** in 80% yield: mp 139−140 °C; $[\alpha]^{20}_D = +89.0$ (*c* 0.57, EtOH); ^{1}H NMR δ 2.27−2.32 (m, 1H), 2.57−2.67 (m, 3H), 3.68−3.75 (m, 1H), 4.48−4.55 (m, 2H), 5.23−5.24 (m, 1H), 5.98−6.01 (m, 1H), 7.05−7.20 (m, 5H), 7.26−7.35 (m, 2H), 7.53 (d, J = 7.1 Hz, 1H), 7.99 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 29.6, 30.0, 68.5, 73.2, 82.4, 97.6, 111.0, 111.1, 119.8, 123.8, 126.1, 127.2, 128.4, 131.6, 140.6, 146.8. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.55; H, 5.93; N, 18.30. Found: C, 70.16; H, 6.18; N, 18.23.

Crystal data for **6** at −132 °C: $C_{18}H_{18}N_4O$, M 306.36, orthorhombic, $P2_12_12_1$, a = 5.6900(1) Å, b = 9.3343(2) Å, c = 27.1700(5) Å, V = 1511.53 (5) Å^3, Z = 4, λ (Mo Kα) = 0.710 73 Å, F(000) = 648, D_c = 1.346 gcm^{-3}, μ = 0.087 mm^{-1}, 3082 reflections, 209 parameters, R = 0.0331, R_w = 0.0763 for all data.

(2*S*)-2-Pyrrolyl-2-phenylethan-1-ol (7). The elimination product of (3*S*,5*R*,7a*R*)-5-(benzotriazol-1-yl)-3-phenyl[2,1-*b*]-oxazolopyrrolidine (**6**) was formed in the presence of Lewis acids or at high temperature: $[\alpha]^{20}_D = -21.53$ (*c* 0.85, EtOH); ^{1}H NMR δ 2.02 (s, 1H), 4.09−4.16 (m, 2H), 5.18−5.22 (t, J = 6.9 Hz, 1H), 6.20 (s, 2H), 6.79 (s, 2H), 7.11−7.14 (d, J = 6.9 Hz, 2H), 7.27−7.34 (m, 3H); ^{13}C NMR δ 64.8, 65.2, 108.6, 119.9, 126.6, 128.0, 128.7, 138.5. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.89; H, 7.31; N, 7.78.

(3*S*,5*S*,7a*R*)-5-Allyl-3-phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazole (8). To a solution of **6** (3.1 g, 10 mmol) in CH_2Cl_2 (200 mL) was added sequentially allyltrimethylsilane (4.0 mL, 25 mmol) and zinc bromide. The reaction mixture was stirred at 0 °C for 24 h. Then the reaction was quenched with 2 N NaOH and the aqueous suspension extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried with Na_2SO_4, and evaporated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate (10/1), yielded 1.03 g (45%) **8** as a colorless oil: $[\alpha]^{20}_D = +57.94$ (*c* 2.52, EtOH); ^{1}H NMR δ 1.56−1.66 (m, 1H), 1.84−1.95 (m, 1H), 2.02−2.33 (m, 4H), 2.93−3.00 (m, 1H), 3.62 (dd, J = 6.6 Hz, J = 8.4 Hz, 1H), 4.20 (t, J = 6.6 Hz, 1H), 4.37 (t, J = 7.2 Hz, 1H), 4.94−5.02 (m, 3H), 5.68−5.80 (m, 1H), 7.20−7.38 (m, 5H); ^{13}C δ 29.9, 30.2, 40.4, 66.3, 68.0, 73.0, 98.9, 116.4, 126.5, 126.9, 128.4, 135.7, 143.0. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.37; N, 6.11. Found: C, 78.35; H, 8.62; N, 6.24.

General Procedure for Hydrogenation. A solution of starting material (1 mmol) in ethanol (60 mL) with 10% $Pd(OH)_2$/C (50 mg) was charged with hydrogen at a pressure of 40 psi at room temperature for 24 h. After filtration of the catalyst, the filtrate was treated with HCl in EtOAc (2.0 M) and stirred at room temperature for 30 min. The solvent was evaporated under vacuum, and the residue was washed with ethyl ether to provide the crude product, which can be recrystallized from $CHCl_3$ and hexane or purified by column chromatography using CH_2Cl_2/MeOH as eluents.

(2*R*)-2-Propylpyrrolidium chloride (11): yield 95%; $[\alpha]^{20}_D = -3.21$ (*c* 1.34, EtOH); ^{1}H NMR δ 0.94 (t, J = 7.2 Hz, 3H), 1.41−1.48 (m, 2H), 1.61−1.79 (m, 2H), 1.92−2.13 (m, 4H), 3.27−3.47 (m, 3H), 9.23 (br s, 1H), 9.89 (br s, 1H); ^{13}C NMR δ 13.7, 20.2, 23.5, 30.3, 34.1, 44.4, 60.2; HRMS calcd for C_7H_{16}-NCl 114.1283 (M − Cl), found 114.1306.

General Procedure for 8 Reacted with Grignard Reagents To Prepare 9 and 10. To a cold solution (ice−water bath) of **8** (1 mmol) in dry THF (50 mL) was added Grignard reagent (2 mmol) dropwise under nitrogen. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was washed with NaOH (2 N, 3 × 30 mL) and water (2 × 30 mL) before being extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate from 20/1 to 5/1 as eluents) to give pure products **9** and **10**.

(2*S*)-2-[(2*S*,5*S*)-2-Allyl-5-methyltetrahydro-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (9a): yield 9%; $[\alpha]^{20}_D = -12.78$ (*c* 0.90, EtOH); ^{1}H NMR δ 1.21−1.31 (m, 4H), 1.34−1.45 (m, 2H), 1.68−1.74 (m, 1H), 2.02−2.12 (m, 1H), 2.26−2.31 (m, 1H), 2.60 (br s, 1H), 2.98−3.02 (m, 1H), 3.09−3.16 (m, 1H), 3.66−3.70 (m, 1H), 3.87−3.98 (m, 2H), 5.00−5.06 (m, 2H), 5.70−5.78 (m, 1H), 7.21−7.38 (m, 5H); ^{13}C NMR δ 21.1, 29.2, 32.2, 42.8, 56.7, 61.5, 63.9, 116.5, 127.7, 128.3, 128.9, 136.1, 137.0. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.47; N, 5.71. Found: C, 78.01; H, 9.72; N, 5.80.

(2*S*)-2-[(2*S*,5*R*)-2-Allyl-5-methyltetrahydro-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (10a): yield 81%; $[\alpha]^{20}_D = -36.74$ (*c* 0.86, EtOH); ^{1}H NMR δ 1.02 (d, J = 6.3 Hz, 3H), 1.30−1.37 (m, 1H), 1.44−1.51 (m, 1H), 1.76−1.94 (m, 3H), 2.07−2.12 (m, 1H), 2.64 (br s, 1H), 3.13−3.19 (m, 1H), 3.35−3.40 (m, 1H), 3.72−3.78 (m, 1H), 3.82−3.88 (m, 1H), 3.99−4.04 (m, 1H), 4.88−4.98 (m, 2H), 5.58−5.69 (m, 1H), 7.26−7.40 (m, 5H); ^{13}C NMR δ 19.1, 28.2, 31.7, 39.3, 56.2, 59.1, 62.9, 63.8, 116.4, 127.6, 128.3, 129.3, 136.2, 140.1. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.47; N, 5.71. Found: C, 77.87; H, 9.86; N, 5.73.

(2*S*)-2-[(2*S*,5*S*)-2-Allyl-5-phenyltetrahydro-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (10d): yield 91%; $[\alpha]^{20}_D = -34.59$ (*c* 0.85, EtOH); ^{1}H NMR δ 1.58−1.61 (m, 1H), 1.65−1.72 (m, 1H), 1.94−2.01 (m, 1H), 2.12−2.18 (m, 1H), 2.21−2.28 (m, 1H), 2.40−2.42 (m, 1H), 3.54−3.66 (m, 3H), 4.05−4.10 (m, 2H), 4.98−5.07 (m, 2H), 5.70−5.76 (m, 1H), 7.11−7.38 (m, 10H); ^{13}C NMR δ 28.1, 33.0, 37.5, 61.5, 63.1, 63.4, 63.8, 116.6, 126.4, 126.9, 127.3, 127.9, 128.2, 129.4, 136.1, 139.1, 146.7; MS m/z 308 (M + 1), 266 (80), 146 (100), 129 (50), 91 (45). Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.21; N, 4.56. Found: C, 81.93; H, 8.71; N, 4.71.

(2*S*)-2-[(2*S*,5*S*)-2-Methyl-5-(2-methyl-2-propenyl)tetrahydro-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (16): yield 9%; $[\alpha^{20}]_D = +9.52$ (*c* 0.21, EtOH); ^{1}H δ 1.08−1.21 (m, 4H), 1.31−1.45 (m, 2H), 1.50−1.73 (m, 4H), 1.95−2.08 (m, 1H), 2.20−2.30 (m, 1H), 3.05−3.08 (m, 2H), 3.64−3.66 (m, 1H), 3.85−3.91 (m, 2H), 4.58 (s, 1H), 4.66 (s, 1H), 7.17−7.37 (m, 5H); ^{13}C NMR δ 19.4, 22.4, 27.8, 31.5, 43.1, 55.9, 57.8, 62.8, 63.8, 111.8, 118.0, 127.6, 128.3, 129.4, 143.9. MS m/z 228 (10), 204 (100), 84 (100); HRMS calcd for $C_{17}H_{25}NO$ 260.2014 (M + 1), found 260.1962.

(2*S*)-2-[(2*R*,5*S*)-2-Methyl-5-(2-methyl-2-propenyl)tetrahydro-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (17): yield 86%; $[\alpha]^{20}_D = -4.52$ (*c* 1.26, EtOH); ^{1}H NMR δ 1.04 (d, J = 6.3 Hz, 3H), 1.24−1.59 (m, 2H), 1.48 (s, 3H), 1.75−2.09 (m, 4H), 3.27−

3.30 (m, 1H), 3.47−3.49 (m, 1H), 3.74−3.79 (m, 1H), 3.84−3.89 (m, 1H), 3.97−4.04 (m, 1H), 4.55 (s, 1H), 4.65 (s, 1H), 7.24−7.42 (m, 5H); ^{13}C NMR δ 19.0, 22.3, 27.6, 31.4, 42.8, 56.4, 58.3, 63.2, 63.7, 112.0, 118.0, 127.8, 128.4, 129.5, 143.6; HRMS calcd for $C_{17}H_{25}NO$ 260.2014 (M + 1), found 260.1962.

(2*S*,5*R*)-2-Pentyl-5-propylpyrrolidium Chloride (12). From hydrogenation of **9b**: yield 90%; $[\alpha]^{20}_D = +3.09$ (*c* 2.98, EtOH); ^{1}H NMR δ 0.88 (t, $J = 6.3$ Hz, 3H), 0.96 (t, $J = 6.9$ Hz, 3H), 1.30−1.50 (m, 8H), 1.80−1.88 (m, 4H), 2.00−2.17 (m, 4H), 3.46−3.47 (m, 2H), 8.93 (br s, 1H), 10.14 (br s, 1H); ^{13}C NMR δ 13.8, 14.0, 20.2, 22.5, 26.6, 28.5, 28.6, 31.5, 32.2, 34.3, 60.2, 60.4; HRMS calcd for $C_{12}H_{26}NCl$ 184.2065 (M − Cl), found 184.2066.

(2*R*,5*R*)-2-Methyl-5-propylpyrrolidium Chloride (13a). From hydrogenation of **10a**: yield 95%; $[\alpha]^{20}_D = +1.23$ (*c* 1.14, EtOH); ^{1}H NMR δ 0.98 (t, $J = 7.2$ Hz, 3H), 1.42−1.58 (m, 1H), 1.54 (d, $J = 6.6$ Hz, 3H), 1.60−1.76 (m, 4H), 1.92−2.01 (m, 1H), 2.14−2.24 (m, 2H), 3.65−3.70 (m, 1H), 3.76−3.82 (m, 1H), 9.45−9.48 (br s, 1H), 9.56−9.60 (br s, 1H); ^{13}C NMR δ 13.7, 18.0, 20.0, 30.5, 32.2, 34.6, 55.2, 59.2. Anal. Calcd for C_8H_{18}-NCl: C, 58.70; H, 11.11; N, 8.56. Found: C, 58.53; H, 11.36; N, 8.30.

(4*R*)-1-Phenyl-4-heptanaminium Chloride (14). From hydrogenation of **10d**: yield 70%; $[\alpha]^{20}_D = +2.38$ (*c* 0.42, EtOH); ^{1}H NMR δ 0.91 (t, $J = 6.9$ Hz, 3H), 1.40−1.51 (m, 2H), 1.62−1.85 (m, 6H), 2.63 (t, $J = 6.6$ Hz, 2H), 3.18−3.19 (m, 1H), 7.17−7.29 (m, 5H), 8.40 (br s, 3H); ^{13}C NMR δ 13.7, 18.6, 26.8, 32.4, 34.8, 35.3, 52.3, 111.2, 125.9, 128.4, 141.4; HRMS calcd for $C_{13}H_{22}NCl$ 192.1752 (M − Cl), found 192.1761.

General Procedure for 6 Reacted with Vinyloxytrimethylsilanes. To a solution of **6** (1.5 g, 5 mmol) in CH_2Cl_2 (100 mL) were added sequentially 2-methyl-propenyltrimethylsilane (1.2 g, 10 mmol) and $BF_3{\cdot}Et_2O$ at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Then the reaction was quenched with 2 N NaOH, and the aqueous suspension extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate (10/1), yielded pure **19**.

1-[(3*S*,5*S*,7a*R*)-3-Phenylhexahydropyrrolo[2,1-*b*][1,3]-oxazol-5-yl]acetone (19a): yield 41%; $[\alpha]^{20}_D = +55.23$ (*c* 0.88, EtOH); ^{1}H NMR δ 1.49−1.60 (m, 1H), 1.94−2.10 (m, 1H), 1.97 (s, 3H), 2.13−2.23 (m, 2H), 2.44 (dd, $J = 7.2$ Hz, $J = 16.5$ Hz, 1H), 2.65 (dd, $J = 5.8$ Hz, $J = 19.2$ Hz, 1H), 3.39−3.44 (m, 1H), 3.57−3.62 (m, 1H), 4.18 (t, $J = 6.6$ Hz, 1H), 4.35 (t, $J = 7.2$ Hz, 1H), 5.01−5.02 (m, 1H), 7.23−7.33 (m, 5H); ^{13}C NMR δ 30.0, 30.8, 50.1, 62.4, 68.3, 73.5, 98.6, 108.6, 126.5, 127.0, 128.4, 142.6, 207.9; HRMS calcd for $C_{15}H_{19}NO_2$ 246.1494 (M + 1), found 246.1419.

2-[(3*S*,5*S*,7a*R*)-3-Phenylhexahydropyrrolo[2,1-*b*][1,3]-oxazol-5-yl]-1-phenyl-1-ethanone (19b): yield 54%; $[\alpha]^{20}_D = +45.78$ (*c* 9.37, EtOH); ^{1}H NMR δ 1.56−1.63 (m, 1H), 1.95−2.02 (m, 1H), 2.16−2.34 (m, 2H), 2.98 (dd, $J = 8.1$ Hz, $J = 16.8$ Hz, 1H), 3.21 (dd, $J = 4.8$ Hz, $J = 16.8$ Hz, 1H), 3.56−3.66 (m, 2H), 4.26 (t, $J = 6.6$ Hz, 1H), 4.36 (t, $J = 7.5$ Hz, 1H), 5.04−5.05 (m, 1H), 7.18−7.41 (m, 7H), 7.48−7.53 (m, 1H), 7.84 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR δ 30.1, 31.0, 45.3, 63.0, 68.3, 73.1, 98.5, 126.5, 126.9, 128.0, 128.3, 128.4, 132.9, 137.1, 142.6, 199.1. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.90; N, 4.56. Found: C, 77.91; H, 7.03; N, 4.89.

Methyl 2-[3*S*,7a*R*)-3-Phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-yl]-2-methylpropanoate (20). The reaction of **6** with 1-methoxy-1-trimethylsiloxy-2-methyl-1-propene, using the same procedure as for the preparation **19**, gave the mixture of two diastereoisomers in ratio of 2:1. The data for the minor isomer are given in brackets. ^{1}H NMR δ 1.05 (s, 6H) [0.76 (s, 3H), 0.91 (s, 3H)], 1.61−2.11 (m, 4H), 3.24 (s, 3H) [3.55 (s, 3H)], 3.36−3.49 (m, 2H) [3.03−3.06 (m, 2H)], 4.19−4.31 (m, 2H) [3.97−4.03 (m, 2H)], 4.87−4.88 (m, 1H) [4.97−4.99 (m, 1H)], 7.16−7.30 (m, 5H); ^{13}C NMR δ 21.1 (20.6), 21.6 (22.9), 24.6 (26.4), 31.0 (31.6), 47.9 (48.2), 51.3 (51.5), 66.9 (64.4), 71.5 (72.8), 74.3 (72.9), 99.4 (99.3), 126.2 (126.7), 128.3 (127.9), 128.3 (129.2), 143.3 (139.6), 177.6 (178.0); HRMS calcd for $C_{17}H_{23}$-NO_3 290.1756 (M + 1), found 290.1754.

Diethyl (3*S*,5*R*,7a*R*)-3-Phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-yl phosphonate (21). To a solution of **6** (3.1 g, 10 mmol) in CH_2Cl_2 (200 mL) were added sequentially triethyl phosphite (3.4 mL, 20 mmol) and $ZnBr_2$ (1 mmol). The reaction mixture was stirred at 0 °C for 20 h. Then the reaction was quenched with 2 N NaOH, and the aqueous suspension was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried with Na_2SO_4, and evaporated in vacuo. Column chromatography on silica gel, eluting with hexane/EtOAc (2/1), yielded 2.57 g (77%) of **21** as a colorless oil: $[\alpha]^{20}_D = +50.02$ (*c* 4.65, EtOH); ^{1}H NMR δ 1.11(t, $J = 7.2$ Hz, 3H), 1.19 (t, $J = 6.9$ Hz, 3H), 2.00−2.18 (m, 2H), 2.22−2.32 (m, 2H), 3.22−3.25 (m, 1H), 3.63 (t, $J = 9.3$ Hz, 1H), 3.82−3.90 (m, 1H), 3.96−4.05 (m, 3H), 4.30−4.36 (m, 2H), 5.03−5.04 (m, 1H), 7.20−7.25 (m, 1H), 7.28−7.33 (m, 2H), 7.40−7.42 (m, 2H); ^{13}C NMR δ 16.2 ($J = 6.2$ Hz), 16.3 ($J = 6.0$ Hz), 25.1, 30.4 ($J = 6.6$ Hz), 61.7 ($J = 31.8$ Hz), 62.1 ($J = 10.3$ Hz), 63.9, 70.1 ($J = 5.7$ Hz), 72.6, 99.0 ($J = 0.7$ Hz), 126.6, 126.9, 128.2, 142.0. Anal. Calcd for $C_{16}H_{24}NO_4P$: C, 59.06; H, 7.45; N, 4.31. Found: C, 58.82; H, 7.72; N, 4.28.

Diethyl (2*R*)-Tetrahydro-1*H*-pyrrol-2-ylphosphonate (22). Hydrogenation of **21** through the general procedure gave **22** in 89% yield: $[\alpha]^{20}_D = -7.81$ (*c* 2.60, EtOH); ^{1}H NMR δ 1.38 (t, $J = 6.6$ Hz, 6H), 1.94−2.20 (m, 4H), 3.20−3.35 (m, 2H), 3.60−3.70 (m, 1H), 4.26 (q, $J = 6.9$ Hz), 6.46 (br s, 2H); ^{13}C NMR δ 16.4 ($J = 5.6$ Hz), 25.0 ($J = 8.7$ Hz), 26.7, 47.5 ($J = 6.3$ Hz), 52.1, 54.2, 63.0 ($J = 7.1$ Hz), 63.2 ($J = 7.2$ Hz); HRMS calcd for $C_8H_{19}NO_3PCl$ 208.1102 (M + 1), found 208.1112. Anal. Calcd for $C_8H_{19}NO_3PCl$: C, 39.43; H, 7.86; N, 5.75. Found: C, 39.69; H, 8.29; N, 5.14.

General Procedure for 6 Reacted with Excess Grignard Reagents To Prepare 23 and 24. A solution of Grignard reagent (15 mmol) was added dropwise to a cold solution (ice−water bath) of **6** (1.53 g, 5 mmol) in dry tetrahydrofuran (100 mL) under nitrogen. It was then warmed to room temperature and stirred overnight. The reaction mixture was washed with 2 N NaOH solution (3 × 30 mL) and water (2 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude products were separated by column chromatography on silica gel using hexane/ethyl acetate (20/1) as eluent to give pure **23** and **24**.

(2*S*)-2-(2*R*,5*R*)-2,5-Diphenyltetrahydro-1*H*-1-pyrrolyl-2-phenylethan-1-ol (23a): yield 45%; $[\alpha]^{20}_D = -17.64$ (*c* 0.72, EtOH); ^{1}H NMR δ 1.68−1.72 (m, 1H), 1.94−2.03 (m, 3H), 3.20−3.28 (m, 1H), 3.42−3.50 (m, 1H), 3.87−4.04 (m, 3H), 7.14 (d, $J = 6.6$ Hz, 2H), 7.23−7.47 (m, 9H), 7.57−7.63 (m, 4H); ^{13}C NMR δ 34.6, 35.3, 60.7, 62.2, 63.5, 67.3, 126.5, 127.2, 127.5, 127.6, 127.7, 128.2, 128.9, 129.5, 135.4, 143.4, 148.0; HRMS calcd for $C_{24}H_{25}NO$ 343.1936, found 344.1938 (M + 1).

(2*S*)-2-(2*R*,5*S*)-2,5-Diphenyltetrahydro-1*H*-1-pyrrolyl-2-phenylethan-1-ol (24a): yield 45%; $[\alpha]^{20}_D = -3.12$ (*c* 0.48, EtOH); ^{1}H NMR δ 1.70−1.80 (m, 2H), 2.01 (br s, 1H), 2.52−2.67 (m, 2H), 3.46−3.58 (m, 2H), 4.02 (t, $J = 6.6$ Hz, 1H), 4.49 (d, $J = 6.3$ Hz, 2H), 6.75−6.77 (d, $J = 7.2$ Hz, 2H), 7.01−7.37 (m, 13H); ^{13}C NMR δ 33.4, 63.2, 63.3, 65.7, 126.7, 127.2, 127.6, 128.3, 129.5, 138.4, 146.8; HRMS calcd for $C_{24}H_{25}NO$ 343.1936, Found 344.2014 (M + 1).

(2*S*)-2-(2*R*,5*S*)-2,5-Dimethyltetrahydro-1*H*-1-pyrrolyl-2-phenylethan-1-ol (23b): yield 57%; $[\alpha]^{20}_D = +30.10$ (*c* 0.93, EtOH); ^{1}H NMR δ 1.12 (d, $J = 6.3$ Hz, 3H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.26−1.36 (m, 1H), 1.39−1.46 (m, 2H), 1.67−1.73 (m, 1H), 2.92−2.98 (m, 1H), 3.03−3.10 (m, 1H), 3.50 (br s, 1H), 3.64−3.68 (m, 1H), 3.88−4.01 (m, 2H), 7.20−7.36 (m, 5H); ^{13}C NMR δ 21.2, 24.2, 31.8, 32.3, 52.5, 58.3, 61.3, 63.0, 127.6, 128.1, 128.9, 136.8. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.38; H, 9.78; N, 6.53.

(2*S*)-2-(2*R*,5*S*)-2,5-Dimethyltetrahydro-1*H*-1-pyrrolyl-2-phenylethan-1-ol (24b): yield 19%; $[\alpha]^{20}_D = -23.00$ (*c* 0.87, EtOH); ^{1}H NMR δ 0.93 (d, $J = 6.3$ Hz, 6H), 1.31−1.32 (m, 2H), 1.96−2.00 (m, 2H), 3.29−3.33 (m, 2H), 3.73−3.80 (m, 1H), 3.82−3.85 (m, 1H), 3.96 (t, $J = 6.9$ Hz, 1H), 7.26−7.40 (m, 5H); ^{13}C NMR δ 20.3, 31.6, 55.5, 63.3, 63.9, 127.5, 128.2, 129.3, 140.4. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.57; H, 9.69; N, 6.44.

Crystal data for **24b** at 23 °C: $C_{14}H_{21}NO$, M 219.32, monoclinic, $P2_1$, a = 8.3271(6) Å, b = 8.2785(5) Å, c = 10.1973(7) Å, β = 106.761(2)°, V = 673.10(8) Å^3, Z = 2, λ (Mo Kα) = 0.710 73 Å, $F(000)$ = 240, D_c = 1.082 g cm^{-3}, μ = 0.067 mm^{-1}, 1246 reflections, 149 parameters, R = 0.0385, R_w = 0.1038 for all data.

General Procedure for Hydrogenation of 23 and 24 To Prepare 25 and 26. Compound **23** or **24** (1 mmol) was dissolved in 60 mL of methanol, and 50 mg of 10% Pd/C catalyst was added. After hydrogenation at 40 psi of pressure for 24 h, the catalyst was filtered off, and the filtrate was treated with concentrated HCl with stirring at room temperature for 30 min. The solvent was evaporated in vacuo, and the resulting product was washed with ether to give the target product as a white solid. Recrystallization from $CHCl_3$ and hexane provided crystalline **25** and **26**.

(2*R*,5*S*)-2,5-Dimethyltetrahydro-1*H*-1-pyrrolidium Chloride (25a): yield 90%; mp 213−215 °C; ^{1}H NMR δ 1.58 (d, J = 6.0 Hz, 6H), 1.82−1.87 (m, 2H), 2.15−2.19 (m, 2H), 3.63−3.67 (m, 2H), 9.11 (br s, 1H), 10.1 (br s, 1H); ^{13}C NMR δ 17.8, 30.7, 56.2. Anal. Calcd for $C_6H_{14}NCl$: C, 53.13; H, 10.40; N, 10.33. Found: C, 52.77; H, 10.66; N, 10.06.

(2*R*,5*R*)-2,5-Dimethyltetrahydro-1*H*-1-pyrrolidium chloride (26a): yield 87%; mp 164−166 °C; $[\alpha]^{20}_D$ = +0.76 (*c* 1.19, EtOH); ^{1}H NMR δ 1.53 (d, J = 6.6 Hz, 6H), 1.65−1.72 (m, 2H), 2.21−2.24 (m, 2H), 3.82−3.84 (m, 2H), 9.58 (br s, 2H); ^{13}C NMR δ 18.2, 32.2, 54.9. Anal. Calcd for $C_6H_{14}NCl$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.09; H, 10.57; N, 10.16.

(3*S*,5*S*,7a*R*)-3,5-Diphenylhexahydropyrrolo[2,1-*b*][1,3]-oxazole (27).[17] An ether solution of zinc chloride complex (3 mL, 3 mmol) was added dropwise at 0 °C to a solution of phenylmagnesium bromide (1 mL, 3 mmol) in dry THF (30 mL). The mixture was stirred at 25 °C for 45 min and then cooled to 0 °C again. A solution of compound **8** (0.91 g, 3 mmol) in dry tetrahydrofuran (20 mL) was then added dropwise under nitrogen. The mixture was stirred at room temperature for another 30 min before being washed with 2 N NaOH solution (3 × 30 mL) and water (2 × 30 mL) and then extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude products were separated by column chromatography on silica gel using hexane/ethyl acetate (20/1) as eluent to give 0.03 g **27** and recovered 0.4 g of starting material **6**: yield 8%; $[\alpha]^{20}_D$ = +41.33 (*c* 0.60, EtOH); ^{1}H NMR δ 1.71−1.78 (m, 1H), 1.91−1.97 (m, 1H), 2.17−2.26 (m, 2H), 3.66 (dd, J = 5.4 Hz, J = 8.1 Hz, 1H), 3.95 (dd, J = 6.0 Hz, J = 9.6 Hz, 1H), 4.14 (t, J = 6.9 Hz, 1H), 4.35 (t, J = 7.2 Hz, 1H), 5.10−5.12 (m, 1H), 7.08−7.33 (m, 10H); ^{13}C NMR δ 30.4, 35.1, 66.6, 69.5, 72.0, 98.3, 126.4, 126.7, 126.9, 127.1, 128.2, 128.3, 142.8, 143.1.

Ethyl 2-[(3*S*,5*S*,7a*R*)-3-Phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-yl]acetate (28). To a solution of **6** (0.6 g, 2 mmol) in dichloromethane (50 mL) was added dropwise freshly prepared zinc reagent of ethyl 2-bromoacetate (2 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. Then the reaction was quenched with 2 N NaOH, and the aqueous suspension was extracted with dichloromethane. The combined organic extracts were washed with brine, dried with Na_2SO_4, and evaporated in vacuo. Column chromatography on silica gel, eluting with hexanes/ethyl acetate (5/1), yielded 50 mg of **28** (10%): $[\alpha]^{20}_D$ = +93.19 (*c* 2.79, EtOH); ^{1}H NMR δ 1.10 (t, J = 6.9 Hz, 3H), 1.59−1.68 (m, 1H), 1.94−2.02 (m, 1H), 2.15−2.35 (m, 3H), 2.45−2.62 (m, 1H), 3.39−3.46 (m, 1H), 3.55−3.60 (m, 1H), 3.85−3.93 (m, 2H), 4.24 (t, J = 6.9 Hz, 1H), 4.35 (t, J = 7.2 Hz, 1H), 4.99−5.02 (m, 1H), 7.22−7.36 (m, 5H); ^{13}C NMR δ 14.0, 30.0, 30.4, 41.6, 60.2, 63.6, 68.7, 73.4, 98.7, 126.4, 126.9, 128.3, 142.7, 171.8. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.70; N, 5.09. Found: C, 70.15; H, 8.08; N, 5.32.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra and CHN analyses or HRMS (if new compounds) for compounds **15**, **18**, **9b**,**c**, **10b**,**c**, **13b**,**c**, **19c**, **23c**−**e**, **24c**−**e**, **25b**−**d**, and **26b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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