

A New Synthetic Method for the Preparation of α,β-Didehydroamino Acid Derivatives by Means of a Wittig-Type Reaction. Syntheses of (2*S*, 4*S*)- and (2*R*, 4*R*)-4-Hydroxyprolines

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Ethyl *N*-Boc- and *N*-*Z*-α-tosylglycinates were reacted with a variety of aldehydes in the presence of tributylphosphine and a base to afford the corresponding α,β-didehydroamino acid derivatives with high (*Z*)-selectivity in good yields. Moreover, ethyl (4*S*)- and (4*R*)-2-(*N*-Boc-amino)-4,5-isopropylidenedioxy-2-pentenoates prepared by the present method were converted to (2*S*, 4*S*)- and (2*R*, 4*R*)-4-hydroxyprolines, respectively.

Increasing interest in α,β-didehydroamino acids has developed in recent years based both on their importance as chemical products and on their existence in biologically active natural products.[1a–g] Many reports related to the preparation of α,β-didehydroamino acids have been published.[2a–i] Moreover, intensive studies on the asymmetric hydrogenation of α,β-didehydroamino acid derivatives have also been established since they would provide a quite efficient route to optically active usual and unusual amino acid derivatives,[3a–d] which are widely used in various fields. Therefore, the development of a new and effective method for the preparation of α,β-didehydroamino acid derivatives is one of the important and attractive subjects in organic chemistry.

In previous papers, we reported that 3,4-disubstituted 5-tosyl-1,5-dihydro-2*H*-pyrrole-2-one reacted with 2-formyl pyrroles in the presence of tributylphosphine (Bu_3P) and a base to afford the corresponding C/D ring component of phycobilins,[4a–c] and ethyl *N*-*t*-butoxycarbonyl (Boc)- and *N*-benzyloxycarbonyl (*Z*)-α-tosylglycinates (**1a** and **1b**) were reacted with a variety of nitro compounds in the presence of a base to afford the corresponding α,β-didehydroamino acid derivatives with high (*Z*)-selectivity in good yields.[5]

In this paper, we now wish to report on a new method for preparing α,β-didehydroamino acid derivatives starting from **1a** or **1b** and a variety of aldehydes in the presence of Bu_3P and a base. The results are summarized in Table 1.

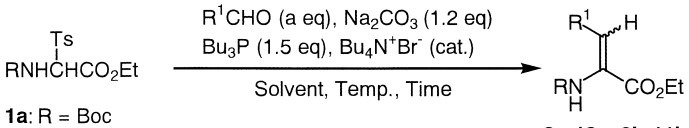
First, compound **1a** was treated with 2.0 molar amounts of acetaldehyde in the presence of 1.5 molar amounts of Bu_3P, 1.2 molar amounts of sodium carbonate, and a catalytic amount of tetrabutylammonium bromide in THF at room temperature to afford the desired ethyl 2-(*N*-Boc)amino-2-butenoate (**2a**) as a mixture of (*Z*)- and (*E*)-isomers in 96% yield, in which the (*Z*)-isomer was predominantly formed (Entry 1). The reaction of **1a** with simple aldehydes succeeded in the formation of a variety of *N*-Boc-α,β-didehydroamino acid derivatives (**3a**, **4a**, and **5a**) in satisfactory yields, respectively (Entries 2–4). Upon the treatment of **1a** with *p*-methoxybenzaldehyde, **6a** was obtained in unsatisfactory yield (Entry 5). When the reaction was carried out in toluene in the presence of 2.0 molar amounts of tetraethyl orthotitanate [$Ti(OEt)_4$], the yield of **6a** could be improved up to 70% yield (Entry 6). With 4-nitrobutanal (**13**) bearing both nitro- and aldehyde groups, only the aldehyde group reacted with **1a** chemoselectively to provide **7a** in good yield (Entry 7). Furthermore, the reaction of **1a** with *N*,*N*′,*N*″-protected 3-guanidinopropanal (**14**) underwent very smoothly at 60 °C for 1.5 h under the same reaction conditions to afford the desired product **8a** as a single isomer with (*Z*)-configuration in good yield.

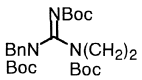
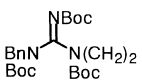
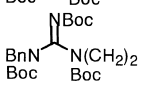
Similarly, the reaction of **1a** with 1-*Z*-indole-3-carboxaldehyde (**15**), 1-Boc-indole-3-carboxaldehyde (**16**), and 1-Boc-Imidazole-4-carboxaldehyde (**17**) afforded the corresponding **9a**, **10a**, and **11a** with only the (*Z*)-configuration in good yields, respectively (Entries 9–11). With (*R*)-isopropylideneglyceraldehyde,[6] compound **12a** with predominantly the (*Z*)-configuration (*Z*/*E* = 95/5) was obtained in 94% yield (Entry 12). In the same way, a variety of α,β-didehydroamino acid derivatives **2b**–**11b** were successfully synthesized by the reaction of **1b** and various aldehydes in good yields, respectively (except for Entry 19).

Although the precise mechanism of the present coupling reaction is still an open question, one possible reaction pathway is shown in Scheme 1. Initially, the Schiff base was generated from **1a** or **1b** and Na_2CO_3; a subsequent addition of the Bu_3P to the resulting base resulted in the formation of the ylide, which was reacted with aldehyde and converted into a four-membered cyclic intermediate. Finally, elimination of $Bu_3P{=}O$ through transition state T_2 with less steric repulsion than that of transition state T_1 occurred to provide a product with predominantly the (*Z*)-configuration.

In the past, it had been reported that (2*S*, 4*S*)-4-hydroxyproline (**28a**) has biological activities,[7a–c] and that **28a** and **28b**[8] are also useful as chiral building blocks for the syntheses of a variety of valuable substances. Concerning synthetic studies of **28**, the interconversion of (2*S*, 4*R*)-4-hydroxyproline and its enantiomer to **28** has been positively developed;[9a–c] however, there are only a few reports concerning asymmetric synthesis,

Table 1. Preparation of Dehydroamino Acid Derivatives

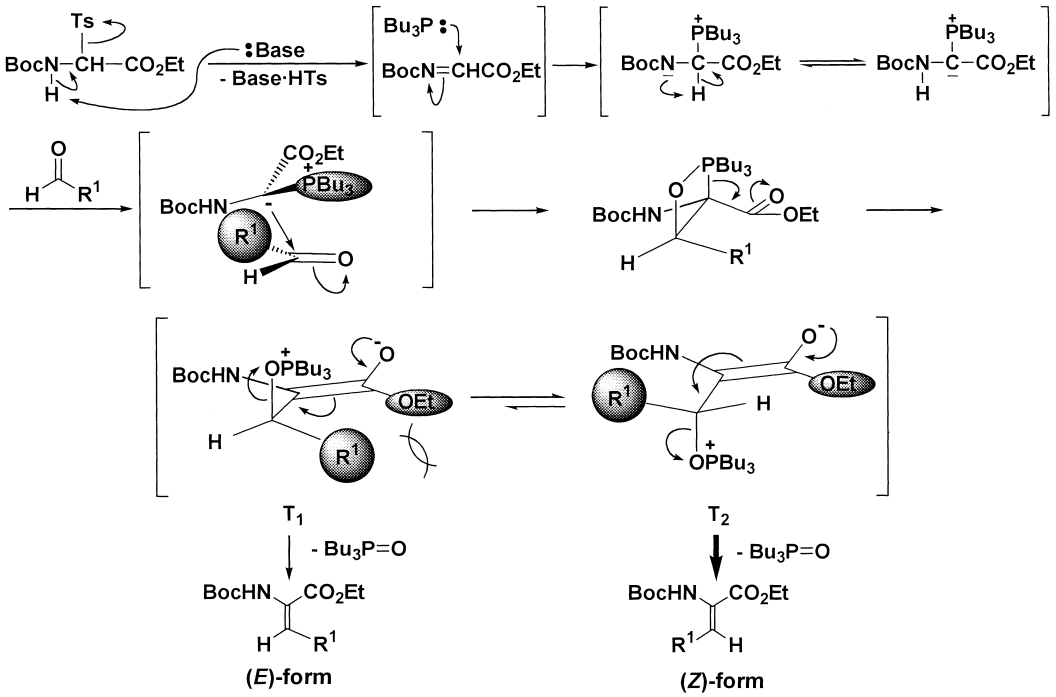


Entry	Substrate	R^1	a	Temp	Time	Solvent	Product	Yield/%	Z/E[a]
1	**1a**	Me	2.0	r.t.	overnight	THF	**2a**	96	89/11
2	**1a**	Et	2.0	r.t.	overnight	THF	**3a**	82	90/10
3	**1a**	^{i}Pr	2.0	r.t.	48 h	THF	**4a**	84	93/7
4	**1a**	Ph	2.0	r.t.	overnight	THF	**5a**	79	100/0
5	**1a**	*p*-$MeOC_6H_4$	1.5	r.t.	24 h	THF	**6a**	55	86/14
6[b]	**1a**	*p*-$MeOC_6H_4$	1.5	r.t.	24 h	$PhCH_3$	**6a**	70	89/11
7	**1a**	$O_2N(CH_2)_3$	2.0	r.t.	48 h	THF	**7a**	84	89/11
8	**1a**		2.0	60 °C	1.5 h	THF	**8a**	84	100/0
9[c]	**1a**		3.0	r.t.	67 h	$PhCH_3$	**9a**	73	100/0
10[c]	**1a**		3.0	r.t.	67 h	$PhCH_3$	**10a**	77	100/0
11	**1a**		2.0	r.t.	overnight	THF	**11a**	79	100/0
12	**1a**		2.0	r.t.	6 h	THF	**12a**	94	95/5
13	**1b**	Me	2.0	r.t.	overnight	THF	**2b**	78	85/15
14	**1b**	Et	2.0	r.t.	overnight	THF	**3b**	79	90/10
15	**1b**	^{i}Pr	2.0	r.t.	48 h	THF	**4b**	76	84/16
16	**1b**	Ph	2.0	r.t.	overnight	THF	**5b**	71	100/0
17[b]	**1b**	*p*-$MeOC_6H_4$	1.5	r.t.	24 h	$PhCH_3$	**6b**	77	93/7
18	**1b**	$O_2N(CH_2)_3$	2.0	r.t.	48 h	THF	**7b**	73	90/10
19	**1b**		2.0	r.t.	70 h	THF	**8b**	< 25	—
20	**1b**		2.0	60 °C	1.5 h	THF	**8b**	76	100/0
21[c]	**1b**		3.0	r.t.	67 h	$PhCH_3$	**9b**	60	100/0
22[c]	**1b**		3.0	r.t.	67 h	$PhCH_3$	**10b**	77	100/0
23	**1b**		2.0	r.t.	overnight	THF	**11b**	85	100/0

a) Determined by NOE measurement. b) In cases of entries 6 and 17, 2.0 molar amounts of $Ti(OEt)_4$ were added. c) In cases of entries 9, 10, 21, and 22, 3.0 molar amounts of $Ti(OEt)_4$ were added.

in which an α-amino acid derivative is used as the starting material.[10a,b] We are thus interested in the asymmetric synthesis of **28** using compound **12** (Scheme 2).

First, the hydrolysis of the isopropylidene protecting group of **12a** was carried out with 0.5 M HCl aq in ethanol at room temperature overnight to afford the corresponding diol derivative **18a** and a by-product **19a** in 85% and 11% yields, respectively. Subsequently, conversion of the diol compound **18a** to **27a** was attempted under Mitsunobu reaction conditions in CH_2Cl_2. Unfortunately, only the epoxide derivative **20** was obtained in 97% yield[11] instead of the expected **27a**. Therefore, we examined the conversion of **18a** to **23a** and the following



Scheme 1.

cyclization of **23a** to compound **25a**. Thus, in order to protect the primary hydroxy group of **18a** selectively, compound **18a** was treated with *t*-butylchlorodimethylsilane (TBDMS-Cl, 1.1 equiv) in the presence of 1.2 equivalents of triethylamine (TEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2. Compound **21a** was obtained in 84% yield, which was furthermore converted into compound **22a** in quantitative yield by protection of the secondary hydroxy group by means of *t*-butylchlorodiphenylsilane (TBDPS-Cl, 1.2 equiv) and imidazole (3 equiv) in DMF. Deprotection of the TBDMS group of **22a** was easily achieved with 1.5 M HCl aq in ethanol at room temperature for 2 h to give compound **23a** in 98% yield. The cyclization reaction was crucially dependent on the reaction temperature. Namely, when the cyclization of **23a** to **25a** was carried out at room temperature for 2 d using 2 equivalents of diethyl azodicarboxylate (DEAD) and 2 equivalents of Ph_3P in CH_2Cl_2, ethyl 2-pyrrolecarboxylate (**24**) was obtained exclusively in 52% yield, whereas the reaction at 0 °C provided the desired product **25a** in 61% yield, which was subsequently hydrogenated over 5% Pd–C in ethanol under a hydrogen atmosphere. Consequently, hydrogenation took place with over 99% diastereoselectivity to give the desired (2*S*,4*S*)-4-hydroxyproline derivative **26a** in quantitative yield, whose recrystallization from hexane gave optically pure **26a**. The stereochemistry of **26a** was determined by comparing the specific rotation value of compound **28a** derived from **26a** with that of an authentic sample.[12] Deprotection of the TBDPS group of **26a** with tetrabutylammonium fluoride (TBAF) in THF afforded **27a** in 91% yield. Subsequent hydrolysis of the ester group with lithium hydroxide, and deprotection of the *N*-Boc group with hydrogen chloride, followed by neutralization with TEA, afforded optically pure **28a**[12] in 83% yield based on **27a**.

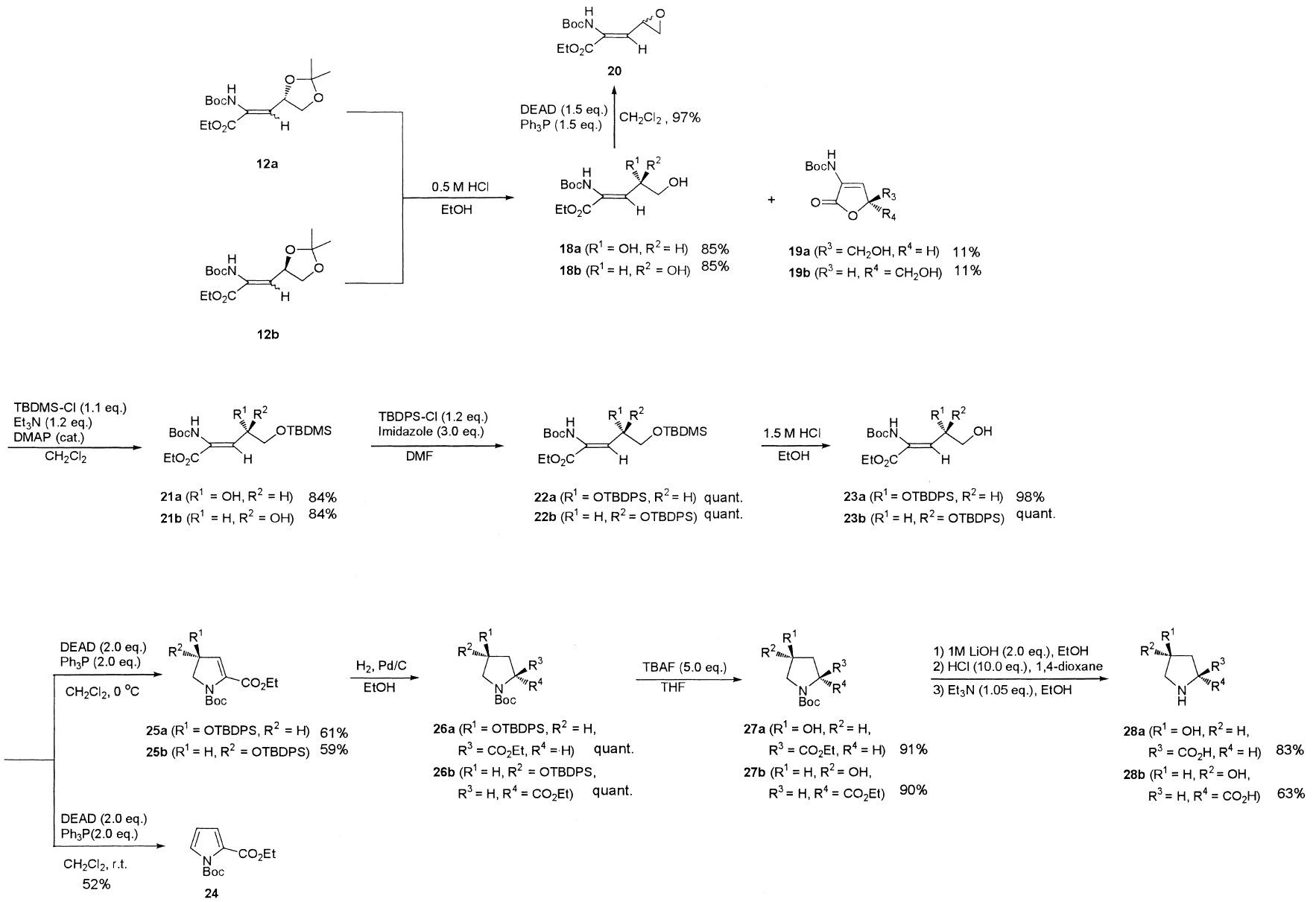
In the same pathway as described for compound **28a**, optically pure (2*R*,4*R*)-4-hydroxyproline (**28b**) was synthesized starting from compound **12b**, as shown in Scheme 2.

We developed a new method for preparing a variety of α,β-didehydroamino acid derivatives starting from **1a** or **1b** and various aldehydes by a Wittig-type reaction using Bu_3P and a base. Also, compounds **12a** and **12b**, prepared by the present coupling method, proved to be useful as starting material for the asymmetric syntheses of 4-hydroxyprolines, respectively.

Experimental

All of the melting points were determined with a micro melting apparatus (Yanagimoto Seisakusho) and were uncorrected. The ^{1}H NMR, IR, and MS spectra were recorded on JEOL JNM-LA 400FT (400 MHz) and LA 300FT (300 MHz) NMR spectrometers, a JASCO FT/IR-230 infrared spectrometer, and a JEOL SX-102A mass spectrometer, respectively. The chemical shifts of NMR are reported in the δ-scale relative to TMS as an internal standard. All of the solvents were distilled and stored over a drying agent. Thin-layer chromatography (TLC) and flash column chromatography were performed using Merck's silicagel 60 PF_{254} (Art. 7749) and Cica-merck's silicagel 60 (No. 9385-5B), respectively.

A General Procedure for Synthesis of α,β-Didehydroamino Acid Derivatives: To a solution of acetaldehyde (18 mg, 0.40 mmol), **1a** (72 mg, 0.20 mmol), and Bu_3P (61 mg, 0.30 mol) in THF (5 mL) was added a mixture of Na_2CO_3 (26 mg, 0.24 mmol) and $Bu_4N^+Br^-$ (cat.) at room temperature under a N_2 atmosphere. After the mixture was stirred at this temperature overnight, the solvent was removed in vacuo to afford a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrat-


12a
12b
0.5 M HCl
EtOH
20
DEAD (1.5 eq.)
Ph3P (1.5 eq.)
CH2Cl2, 97%
18a (R1 = OH, R2 = H) 85%
18b (R1 = H, R2 = OH) 85%
19a (R3 = CH2OH, R4 = H) 11%
19b (R3 = H, R4 = CH2OH) 11%
TBDMS-Cl (1.1 eq.)
Et3N (1.2 eq.)
DMAP (cat.)
CH2Cl2
21a (R1 = OH, R2 = H) 84%
21b (R1 = H, R2 = OH) 84%
TBDPS-Cl (1.2 eq.)
Imidazole (3.0 eq.)
DMF
22a (R1 = OTBDPS, R2 = H) quant.
22b (R1 = H, R2 = OTBDPS) quant.
1.5 M HCl
EtOH
23a (R1 = OTBDPS, R2 = H) 98%
23b (R1 = H, R2 = OTBDPS) quant.
DEAD (2.0 eq.)
Ph3P (2.0 eq.)
CH2Cl2, 0 °C
25a (R1 = OTBDPS, R2 = H) 61%
25b (R1 = H, R2 = OTBDPS) 59%
H2, Pd/C
EtOH
26a (R1 = OTBDPS, R2 = H, R3 = CO2Et, R4 = H) quant.
26b (R1 = H, R2 = OTBDPS, R3 = H, R4 = CO2Et) quant.
TBAF (5.0 eq.)
THF
27a (R1 = OH, R2 = H, R3 = CO2Et, R4 = H) 91%
27b (R1 = H, R2 = OH, R3 = H, R4 = CO2Et) 90%
1) 1M LiOH (2.0 eq.), EtOH
2) HCl (10.0 eq.), 1,4-dioxane
3) Et3N (1.05 eq.), EtOH
28a (R1 = OH, R2 = H, R3 = CO2H, R4 = H) 83%
28b (R1 = H, R2 = OH, R3 = H, R4 = CO2H) 63%
DEAD (2.0 eq.)
Ph3P(2.0 eq.)
CH2Cl2, r.t.
52%
24

Scheme 2.

ed under reduced pressure. The residue was subjected to preparative TLC (SiO_2, hexane:ethyl acetate = 5:1, v/v) to afford ethyl 2-(*N*-Boc-amino)-2-butenoate (**2a**); 44 mg, 96%: (*Z*)- and (*E*)-isomers were separable.

The physical and spectral data of compounds **2a**–**6a** and **2b**–**6b** were in agreement with those of products prepared previously.[5] Those of prepared compounds **7a**–**12a** and **7b**–**11b** are given in the following.

Ethyl 2-(*N*-Boc-amino)-6-nitro-2-hexenoate (7a) (*Z*/*E* = 89/11): A pale-yellow oil; IR of a mixture of isomers (neat) 3341, 2980, 2935, 1715, 1660, 1554, 1493, 1368, 1265, 1164, 1096, 1048, 1029, 860, 777 cm^{-1}; (*Z*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.47 (s, 9H), 2.21 (quintet, J = 7.1 Hz, 2H), 2.33 (dt, J = 7.1, 7.3 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.42 (t, J = 7.1 Hz, 2H), 6.10–6.20 (br, 1H), 6.45 (t, J = 7.3 Hz, 1H); When γ-methylene protons were irradiated, 2.3% and 9.3% of NOE were observed for the NH proton and the olefinic proton, respectively. (*E*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 1.47 (s, 9H), 2.20 (quintet, J = 7.1 Hz, 2H), 2.67 (dt, J = 7.1, 7.3 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 4.42 (t, J = 7.1 Hz, 2H), 6.65–6.75 (m, 1H + 1H). EI-MS *m*/*z* 302 (M^+; 0.6%).

Ethyl N^{α}-Boc-N'-benzyl-N',N'',N'''-tris(Boc)-α,β-didehydroargininate (8a) (*Z*/*E* = 100/0): (*Z*)-form; An oil; IR (neat) 3345, 2979, 2932, 1731, 1713, 1659, 1496, 1455, 1371, 1245, 1134, 1078, 1047, 977, 918, 854, 813, 767, 732, 701 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.28 (t, J = 7.1Hz, 3H), 1.37 (s, 9H), 1.46 (s, 9H + 9H), 1.50 (s, 9H), 2.43 (dt, J = 6.8, 7.3 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.83 (s, 2H), 6.26 (t, J = 7.3 Hz, 1H), 6.40–6.60 (br, 1H), 7.22–7.40 (m, 5H). When γ-methylene protons were irradiated, 4.0% and 11.8% of NOE were observed for the NH proton and the olefinic proton, respectively. EI-MS *m*/*z* 690 (M^+; 19.9%).

Ethyl N^{α}-Boc-N'-*Z*-α,β-didehydrotryptophanate (9a) (*Z*/*E* = 100/0): To a solution of $Ti(OEt)_4$ (68 mg, 0.30 mmol) in toluene (5 mL) was added a suspension of Bu_3P (61 mg, 0.30 mmol), 1-*Z*-indole-3-carboxaldehyde (**14**) (90 mg, 0.3 mmol), Na_2CO_3 (26 mg, 0.24 mmol), and $Bu_4N^+Br^-$ (cat.) in toluene (2 mL) at room temperature under a N_2 atmosphere; the mixture was stirred for 67 h. Then, after the addition of a saturated aqueous solution of $NaHCO_3$ to the reaction mixture, an insoluble substance was filtered and washed with ethyl acetate. The filtrate was concentrated in vacuo to afford a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to preparative TLC (SiO_2, hexane:ethyl acetate = 5:1, v/v) to afford **9a** in 73% yield (102 mg): An oil ; IR (neat) 3329, 2979, 2933, 1731, 1707, 1642, 1485, 1456, 1393, 1367, 1244, 1163, 1087, 1047, 1028, 759 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 1.37 (s, 9H), 4.32 (q, J = 7.1 Hz, 2H), 5.46 (s, 2H), 6.20–6.30 (br, 1H), 7.27–7.50 (m, 5H + 2H), 7.56 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.91 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H). When the proton at the 2-position of the indole ring was irradiated, 3.8% and 1.3% of NOE were observed for the NH proton and the olefinic proton, respectively. When the olefinic proton was irradiated, 1.8% and 12.9% of NOE were observed for the proton at the 2-position of the indole ring and the proton at the 4-position of the indole ring, respectively. EI-MS *m*/*z* 464 (M^+; 3.0%).

Ethyl N^{α}-Boc-N^{in}-Boc-α,β-didehydrotryptophanate (10a) (*Z*/*E* = 100/0): Compound **10a** was prepared from **1a** and 1-Boc-indole-3-carboxaldehyde (**15**) in the same way as described for compound **9a**. (*Z*)-form; Mp 125.0–126.0 °C (ethyl acetate-hexane); IR (KBr) 3324, 2979, 1731, 1714, 1644, 1585, 1455, 1372, 1282, 1239, 1161, 1084, 1048, 918, 895, 842, 768 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 1.68 (s, 9H), 4.33 (q, J = 7.1 Hz, 2H), 6.10–6.30 (br, 1H), 7.27–7.40 (m, 1H + 1H), 7.57 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.93 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H). Found: C, 64.00; H, 7.14; N,6.11%. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.14; N, 6.11%. When the proton at the 2-position of the indole ring was irradiated, 3.6% and 2.2% of NOE were observed for the NH proton and the olefinic proton, respectively. When the olefinic proton was irradiated, 2.3% and 12.4% of NOE were observed for the proton at the 2-position of the indole ring and the proton at the 4-position of the indole ring, respectively.

Ethyl N^{α}-Boc-N^{im}-Boc-α,β-didehydrohistidinate (11a) (*Z*/*E* = 100/0): Compound **11a** was prepared from **1a** and 1-Boc-imidazole-4-carboxaldehyde (**16**). (*Z*)-form; An oil; IR (neat) 3289, 2979, 2930, 1758, 1717, 1652, 1557, 1507, 1457, 1372, 1253, 1152, 1065, 1013, 910, 839, 771, 745 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 1.49 (s, 9H), 1.62 (s, 9H), 4.30 (q, J = 7.1 Hz, 2H), 6.43 (s, 1H), 7.38 (s, 1H), 8.09 (s, 1H), 7.91 (s, 1H), 8.96-9.06 (br, 1H). When ^{t}Bu protons of the Boc group of the imidazole ring were irradiated, 6.4% of NOE was observed for the ^{t}Bu protons of the N^{α}-Boc group. EI-MS *m*/*z* 381 (M^+; 12.4%).

Ethyl (4*S*)-2-(*N*-Boc-amino)-4,5-isopropylidenedioxy-2-pentenoate (12a) (*Z*/*E* = 95/5): Recrystallization from hexane gave pure *Z*-isomer. (*Z*)-form; Mp 81.9–83.0 °C (hexane); $[\alpha]_D^{25}$ = −11.4 ° (*c* 0.77, $CHCl_3$); IR (KBr) 3329, 2983, 2936, 1730, 1715, 1666, 1504, 1455, 1370, 1318, 1247, 1160, 1057, 1030, 849, 771 cm^{-1}; (*Z*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.39 (s, 3H), 1.45 (s, 9H), 1.47 (s, 3H), 3.84 (dd, J = 6.6, 8.5 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.34 (dd, J = 6.6, 8.5 Hz, 1H), 4.84 (ddd, J = 6.6, 8.1, 8.5 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 6.30–6.50 (br, 1H). When the γ-methine proton of the major product was irradiated, 1.5% and 3.6% of NOE were observed for the NH proton and the olefinic proton, respectively. Found: C, 57.02; H, 8.19; N, 4.35%. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44%. (*E*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.39 (s, 3H), 1.45 (s, 9H), 1.47 (s, 3H), 3.63–3.70 (m, 1H), 4.20–4.35 (m, 2H + 1H), 5.30–5.38 (m, 1H), 6.74–6.87 (m, 1H). A mixture of **12a** could be used in a subsequent reaction without recrystallization.

Ethyl 2-(*N*-*Z*-Amino)-6-nitro-2-hexenoate (7b) (*Z*/*E* = 90/10): An oil; IR of a mixture of isomers (neat) 3320, 3065, 3033, 2981, 1707, 1660, 1549, 1499, 1455, 1378, 1227, 1149, 1097, 1049, 905, 864, 772, 753, 699 cm^{-1}; (*Z*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.23 (quintet, J = 6.8 Hz, 2H), 2.33 (dt, J = 6.8 Hz, 7.3 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.38 (t, J = 6.8 Hz, 2H), 5.14 (s, 2H), 6.30–6.40 (br, 1H), 6.53 (t, J = 7.3 Hz, 1H), 7.30–7.38 (m, 5H). When γ-methyl protons were irradiated, 2.1% and 9.0% of NOE were observed for the NH proton and the olefinic proton, respectively. (*E*)-form; ^1H NMR (400 MHz; $CDCl_3$) δ 1.33 (t, J = 7.1 Hz), 2.19 (quintet, J = 6.8 Hz, 2H), 2.69 (dt, J = 6.8, 7.3 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.42 (t, J = 6.8 Hz, 2H), 5.14 (s, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.90–7.00 (br, 1H), 7.30–7.40 (m, 5H). EI-MS *m*/*z* 336 (M^+; 1.1%).

Ethyl N^{α}-*Z*-N''-Benzyl-N',N'',N'''-tris(Boc)-α,β-didehydro-

argininate (8b) (*Z*/*E* = 100/0): (*Z*)-form; An oil; IR (neat) 3331, 2979, 2934, 1731, 1715, 1651, 1498, 1455, 1369, 1247, 1141, 1078, 1050, 978, 916, 854, 813, 734, 699 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.36 (s, 9H), 1.44 (s, 9H), 1.47 (s, 9H), 2.30 (dt, J = 6.8, 7.3 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.82 (s, 2H), 5.14 (s, 2H), 6.37 (t, J = 7.3 Hz, 1H), 6.80–6.90 (br, 1H), 7.20–7.40 (m, 5H + 5H). When the γ-methylene protons were irradiated, 5.7% and 12.4% of NOE were observed for the NH proton and the olefinic proton, respectively. EI-MS m/z 724 (M^+; 6.6%)

Ethyl N^{α}-*Z*-N^{in}-*Z*-α,β-Didehydrotryptophanate (9b) (*Z*/*E* = 100/0): Compound **9b** was prepared from **1b** and 1-*Z*-indole-3-carboxaldehyde (**14**) in the same way as described for compound **9a**. (*Z*)-form; Mp 91.0–92.0 °C (ethyl acetate-hexane); IR (KBr) 3313, 2929, 2853, 1738, 1715, 1643, 1586, 1498, 1455, 1394, 1308, 1245, 1141, 1088, 757, 698 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 5.15 (s, 2H), 5.44 (s, 2H), 6.36–6.44 (br, 1H), 7.30–7.41 (m, 5H + 5H + 2H), 7.61 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.94 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H). When the proton at the 2-position of the indole ring was irradiated, 4.1% and 2.5% of NOE were observed for the NH proton and the olefinic proton, respectively. When the olefinic proton was irradiated, 2.6% and 11.9% of NOE were observed for the proton at the 2-position of the indole ring and the proton at the 4-position of the indole ring, respectively. Found: C, 69.58; H, 5.28; N, 5.39%. Calcd for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62%.

Ethyl N^{α}-*Z*-N^{in}-Boc-α,β-didehydrotryptophanate (10b) (*Z*/*E* = 100/0): Compound **10b** was prepared from **1b** and 1-Boc-indole-3-carboxaldehyde (**15**) in the same way as described for compound **9a**. (*Z*)-form; An oil; IR (neat) 3036, 2927, 2933, 1732, 1706, 1642, 1545, 1497, 1455, 1370, 1329, 1308, 1251, 1153, 1088, 1052, 1027, 907, 861, 842, 747, 698 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 1.66 (s, 9H), 4.30 (q, J = 7.1 Hz, 2H), 5.15 (s, 2H), 6.25–6.40 (br, 1H), 7.28–7.50 (m, 5H + 2H), 7.65 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.95 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H). When the proton at the 2-position of the indole ring was irradiated, 4.7% and 2.3% of NOE were observed for the NH proton and the olefinic proton, respectively. When the olefinic proton was irradiated, 2.5% and 12.0% of NOE were observed for the proton at the 2-position of the indole ring and the proton at the 4-position of the indole ring, respectively. EI-MS m/z 464 (M^+; 9.8%).

Ethyl N^{α}-*Z*-N^{im}-Boc-α,β-didehydrohistidinate (11b) (*Z*/*E* = 100/0): (*Z*)-form; An oil; IR (neat) 3274, 2982, 2943, 2917, 1766, 1732, 1652, 1555, 1473, 1371, 1253, 1149, 1061, 1014, 910, 840, 731 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 1.62 (s, 9H), 4.27 (q, J = 7.1 Hz, 2H), 5.18 (s, 2H), 6.46 (s, 1H), 7.30–7.40 (m, 5H + 1H), 8.06 (s, 1H), 9.42–9.48 (br, 1H). When ^{t}Bu protons of the Boc group of the imidazole ring were irradiated, 2.1% of NOE was observed for the benzylic protons of the *Z*-group. EI-MS m/z 415 (M^+; 21.6%).

4-Nitrobutanal (13): To a suspension of pyridinium chlorochromate (405 mg, 2. 00 mmol) and molecular sieves 4A (1.00 g) in 5 mL of CH_2Cl_2 was added a solution of 4-nitro-1-butanol (119 mg, 1.0 mmol)[5] in 0.3 mL of acetone at room temperature with vigorous stirring. After 1 h the solvent was removed in vacuo and the residue was triturated with ether. An insoluble substance was filtered off and the filtrate was concentrated under reduced pressure to afford a residue, which was subjected to preparative TLC (SiO_2; hexane:ethyl acetate = 2:1, v/v). An oily product was obtained in 47% yield (56 mg). IR (neat) 2935, 1720, 1548, 1436, 1381, 1271, 1221, 1077, 988, 947, 872, 830, 759 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 2.31 (quintet, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 4.47 (t, J = 6.8 Hz, 2H), 9.80 (S, 1H).

3-[N''-Benzyl-N',N'',N'''-tris(Boc)guanidino]-1-propanal (14): To a solution of N',N'',N'''-tris(Boc)guanidine (3.769 g, 10.49 mmol),[13] Ph_3P (4.126 g, 15.73 mmol), and benzyl alcohol (1.699 g, 15.73 mmol) in dry toluene (20 mL) was slowly added DEAD (2.740 g, 15.73 mmol, 40% toluene solution) at room temperature under a N_2 atmosphere. The solution was warmed at 60 °C for 2 h and evaporated under reduced pressure to give a residue, which was treated with CH_3OH. An insoluble substance was filtered and the filtrate was concentrated in vacuo. The residual oil was purified by silica-gel column chromatography (eluent, hexane:ethyl acetate = 20:1 v/v) to give N''-benzyl-N',N'',N'''-tris(Boc)guanidine in 81% yield (a pale yellow oil, 3.832 g). IR (neat) 3240, 2970, 2931, 1718, 1655, 1458, 1076, 980, 948, 855, 700 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.33 (s, 9H), 1.49 (s, 9H + 9H), 5.02 (s, 2H), 7.20–7.40 (m, 5H), 10.6–10.70 (br, 1H); EI-MS m/z 449 (M^+; 3.6%).

To a solution of the foregoing N''-benzyl-N',N'',N'''-tris-(Boc)guanidine (5.008 g, 11.14 mmol), PPh_3 (5.843 g, 22.28 mmol), and 1,3-propanediol (2.050 g, 22.28 mmol) in dry toluene (20 mL) was slowly added DEAD (7.760 g, 44.56 mmol, 40% toluene solution) with vigorous stirring at room temperature under a N_2 atmosphere. The solution was warmed at 60 °C for 4 h and evaporated under reduced pressure. The residue was treated with ether, and an insoluble substance was filtered. Evaporation of the filtrate and purification of the residual oil by silica-gel column chromatography (eluent, hexane:ethyl acetate = 5:1, v/v) gave the desired alcohol derivative in 60% yield (a pale-yellow oil, 3.390 g); IR (neat) 3504, 2977, 2934, 1737, 1654, 1476, 1368, 1247, 1140, 1078, 977, 854, 815, 765, 700 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.39 (s, 9H), 1.49 (s, 9H + 9H), 1.66 (tt, J = 5.6, 6.3 Hz, 2H), 3.38 (t, J = 6.3 Hz, 2H), 3.51 (t, J = 5.6 Hz, 2H), 4.82 (s, 2H), 7.22–7.40 (m, 5H). The proton of OH group was not assigned. EI-MS m/z 507 (M^+; 3.6%).

To a mixture of pyridinium chlorochromate (80 mg, 0.37 mmol) and finely powdered molecular sieves 3A (185 mg) was added a solution of the foregoing propanol derivative (127 mg, 0.25 mmol) in dry CH_2Cl_2 (1 mL) at room temperature under a N_2 atmosphere, and the mixture was stirred for 2.5 h at this temperature. The solvent was removed in vacuo to afford a residue, which was triturated with ether. An insoluble substance was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by silica-gel column chromatography (eluent, hexane:ethyl acetate = 4:1, v/v) to afford the product **14** in 68% yield (a pale-yellow oil, 86 mg); IR (neat) 2979, 2934, 1792, 1731, 1645, 1497, 1477, 1368, 1249, 1130, 1077, 977, 854, 814, 768, 701 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.37 (s, 9H), 1.46 (s, 9H), 1.50 (s, 9H), 2.64 (t, J = 7.0 Hz, 2H), 3.62 (t, J = 7.0 Hz, 2H), 4.87 (s, 2H), 7.20-7.40 (m, 5H), 9.62 (s, 1H); EI-MS m/z 505 (M^+; 9.6%).

1-*Z*-Indole-3-carboxaldehyde (15): To a solid of indole-3-carboxaldehyde (5.760 g, 40 mmol) placed in a flask was added a solution of Na_2CO_3 (9.328 g, 88 mmol) in 88 mL of water, followed by the addition of 50 mL of CH_3CN, including a catalytic amount of DMAP. Then, to the vigorously stirred solution was dropwise added Z-Cl (6.823 g, 40 mmol) at room temperature under an air atmosphere; the solution was allowed to be stirred for 24 h. After dilution with a large amount of water, the mixture was extracted with ethyl acetate several times. The ethyl acetate solu-

tion was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the product in quantitative yield (11.161 g); mp 47.0–48.0 °C (ethyl acetate–hexane); IR (KBr) 3141, 2822, 1753, 1608, 1546, 1454, 1402, 1376, 1346, 1264, 1230, 1167, 1125, 1095, 1043, 1031, 1015, 972, 781, 757, 732, 707, 691 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 5.51 (s, 2H), 7.30–7.60 (m, 5H + 1H + 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.27 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 10.09 (s, 1H). Found: C, 73.23; H, 4.72; N, 4.95%. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H; 4.69; N, 5.02%.

1-Boc-Indole-3-carboxaldehyde (16): In the same way as described for the preparation of **15** using di-*t*-butyl dicarbonate, **16** was obtained in quantitative yield. Mp 117.0–118.0 °C (ethyl acetate–hexane); IR (KBr) 3002, 2814, 1742, 1678, 1558, 1482, 1472, 1398, 1359, 1330, 1309, 1277, 1242, 1157, 1102, 1046, 839, 786, 759, 668 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.71 (s, 9H), 7.35-7.45 (m, 1H + 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H), 8.29 (d, J = 8.1 Hz, 1H), 10.11 (s, 1H). Found: C, 68.62; H, 6.14; N, 5.65%. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.36; N, 5.71%.

1-Boc-imidazole-4-carboxaldehyde (17): To a solid of 4-(hydroxymethyl)- imidazole hydrochloride (135 mg, 1.00 mmol) was added a solution of Na_2CO_3 (117 mg, 1.10 mmol) in water (2 mL), followed by the addition of a solution of a catalytic amount of DMAP in THF (2 mL). A solution of di-*t*-butyl dicarbonate (240 mg, 1.1 mmol) in THF (3 mL) was slowly added to the above-mentioned solution. After the solution was allowed to stand overnight with vigorous stirring, and follwing the addition of water, the mixture was extracted with ethyl acetate a couple of times. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. To a solution of oxalyl chloride (254 mg, 2.00 mmol) in dry CH_2Cl_2 (5 mL) was added 0.22 mL of dimethyl sulfoxide (DMSO, 3.00 mmol) at −78 °C under a N_2 atmosphere; the solution was kept at this temperature for 15 min. A solution of the foregoing crude imidazole derivative in dry CH_2Cl_2 (3 mL) was added to the above solution at −78 °C. After 15 min the mixture was gradually warmed to room temperature and concentrated in vacuo to give a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residual oil was subjected to silica-gel column chromatography (eluent, hexane:ethyl acetate = 2:1, v/v) to give the product in 47% yield (a pale-yellow crystalline, 202 mg); mp 80.0–81.0 °C (ethyl acetate–hexane); IR (KBr) 3134, 3115, 3061, 2996, 2938, 1751, 1698, 1540, 1493, 1462, 1402, 1378, 1315, 1281, 1263, 1228, 1160, 1120, 1049, 1017, 963, 891, 841, 771, 756, 668 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.65 (s, 9H), 8.03 (s, 1H), 8.14 (s, 1H), 9.94 (s, 1H). Found: C, 54.94; H, 6.15; N, 14.28%. Calcd for $C_{23}H_{30}N_2O_6$: C, 55.09; H, 6.16; N, 14.28%.

Ethyl (4*S*)-2-(*N*-Boc-amino)-4,5-dihydroxy-2-pentenoate (18a): To a solution of the acetonide **12a** (441 mg, 1.40 mmol) in EtOH (2 mL) was added 0.5 M HCl (3 mL) at room temperature under an air atmosphere. The solution was stirred at this temperature overnight and then neutralized with a saturated aqueous solution of $NaHCO_3$. The organic solvent was removed in vacuo. The resulting aqueous layer was saturated with NaCl and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, hexane:ethyl acetate = 2:1, v/v) to afford **18a** in 85% yield (327 mg). Mp 67.0–68.0 °C (ethyl acetate–hexane); $[\alpha]_D^{25}$ = +18.9 ° (*c* 0.15, $CHCl_3$); IR (KBr) 3311, 2981, 2935, 1718, 1508, 1369, 1160, 1029, 857, 779 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 1.46 (s, 9H), 2.02-2.12 (br, 1H), 2.70–2.80 (br, 1H), 3.63 (dd, J = 6.6, 11.2 Hz, 1H), 3.70 (dd, J = 3.9, 11.2 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.49 (ddd, J = 3.9, 6.6, 9.5 Hz, 1H), 6.37 (d, J = 9.5 Hz, 1H), 6.80–7.00 (br, 1H); Found: C, 52.16; H, 7.73; N, 4.88%. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09%.

Ethyl 2-(*N*-Boc-amino)-4,5-epoxy-2-pentenoate (20): To a solution of compound **18a** (73 mg, 0.265 mmol) and Ph_3P (104 mg, 0.40 mmol) in dry CH_2Cl_2 (7 mL) was dropwise added a solution of DEAD (70 mg, 0.40 mmol, 40% toluene solution) in dry CH_2Cl_2 (2 mL) at room temperature under a N_2 atmosphere; the solution was stirred for 30 min. Then, the solvent was removed in vacuo to afford a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was subjected to preparative TLC (SiO_2, hexane:ethyl acetate = 2:1, v/v) to afford the epoxide derivative **20** in 97% yield (an oil, 66 mg). IR (neat) 3340, 2980, 2934, 2871, 1731, 1714, 1505, 1392, 1368, 1257, 1161, 1102, 1075, 1024, 847, 780, 697 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 4.21 (q, J = 7.2 Hz, 2H), 4.74–4.90 (m, 2H), 5.73–5.77 (m, 1H), 6.30 (d, J = 6.1 Hz, 1H), 6.40–6.62 (br, 1H); EI-MS *m/z* 257 (M^+; 1.2%)

Ethyl (4*S*)-2-(*N*-Boc-amino)-5-*t*-butyldimethylsiloxy-4-hydroxy-2-pentenoate (21a): To a mixed solution of **18a** (440 mg, 1.60 mmol), TBDMS-Cl (270 mg, 1.8 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added TEA (202 mg, 2.00 mmol) at room temperature under a N_2 atmosphere. The solution was stirred at this temperature overnight. The solvent was removed in vacuo to afford a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (SiO_2, hexane:ethyl acetate = 4:1, v/v) to afford **21a** in 84% yield (a pale-yellow oil, 843 mg). $[\alpha]_D^{25}$ = +15.2 ° (*c* 1.55, $CHCl_3$); IR (neat) 3394, 2955, 2930, 2858, 1730, 1661, 1473, 1392, 1368, 1320, 1254, 1164, 1112, 1050, 838, 779, 669 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 0.09 (s, 3H + 3H), 0.90 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H), 1.46 (s, 9H), 3.34–3.46 (br, 1H), 3.69 (dd, J = 8.5, 9.3 Hz, 1H), 3.75 (dd, J = 5.4, 9.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.47 (ddd, J = 5.4, 8.1, 8.5 Hz, 1H), 6.29 (d, J = 8.1 Hz, 1H), 6.68–6.72 (br, 1H); EI-MS *m/z* 389 (M^+; 0.8%).

Ethyl (4*S*)-2-(*N*-Boc-amino)-5-*t*-butyldimethylsiloxy-4-*t*-butyldiphenylsiloxy-2-pentenoate (22a): Compound **21a** (514 mg, 1.30 mmol), TBDPS-Cl (726 mg, 2.60 mmol), and imidazole (270 mg, 4.00 mmol) were dissolved in DMF (5 mL) at room temperature under a N_2 atmosphere. The solution was stirred at this temperature overnight. The solution was diluted with water and then extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, hexane:ethyl acetate = 10:1, v/v) to afford **22a** in quantitative yield (a pale-yellow oil). $[\alpha]_D^{25}$ = +37.2 ° (*c* 3.45, $CHCl_3$); IR (neat) 3406, 3071, 2930, 2858, 1731, 1662, 1589, 1473, 1428, 1391, 1367, 1255, 1161, 1112, 836, 778, 739, 702

cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 0.20 (s, 3H + 3H), 1.06 (s, 9H), 1.28 (s, 9H), 1.48 (t, J = 7.1 Hz, 3H), 1.59 (s, 9H), 3.75–3.85 (m, 1H), 3.87 (dd, J = 5.0, 9.2 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.64–4.80 (m, 1H), 6.32 (d, J = 7.1 Hz, 1H), 6.58–6.80 (br, 1H), 7.48–7,65 (m, 3H + 3H), 7.84–7.90 (m, 2H + 2H). EI-MS m/z 627 (M^+; 0.4%).

Ethyl (4*S*)-2-(*N*-Boc-amino)-4-*t*-butyldiphenylsiloxy-5-hydroxy-2-pentenoate (23a): To a solution of the starting material **22a** (363 mg, 0.58 mmol) in EtOH (3.0 mL) was added dropwise 1.5 M HCl (0.6 mL) at room temperature under an air atmosphere. The solution was stirred at this temperature for 2 h and then neutralized with a saturated aqueous solution of $NaHCO_3$. The organic solvent was removed in vacuo. The resulting aqueous layer was saturated with NaCl and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, hexane:ethyl acetate = 5:1, v/v) to afford the desired product **23a** in 98% yield (a pale-yellow oil, 297 mg). $[\alpha]_D^{25}$ = −27.1 ° (c 1.04, $CHCl_3$); IR (neat) 3404, 2932, 2858, 1726, 1474, 1428, 1367, 1251, 1161, 1111, 822, 741, 703 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.06 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H), 3.69 (dd, J = 6.6, 10.8 Hz, 1H), 3.70–3.81 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.52–4.56 (m, 1H), 4.64–5.75 (br, 1H), 6.33 (d, J = 9.3 Hz, 1H), 7.60–7.64 (br, 1H), 7.32–7.45 (m, 3H + 3H) 7.60–7.65 (m, 2H + 2H); EI-MS m/z 513 (M^+; 0.1 %).

Ethyl 1-Boc-2-pyrrolecarboxylate (24): To a solution of Ph_3P (283 mg, 1.08 mmol) in dry CH_2Cl_2 (7 mL) was added DEAD (188 mg, 1.08 mmol, 40% tuluene solution) at 0 °C under a N_2 atmosphere. To the solution was slowly added a solution of **23a** (267 mg, 0.52 mmol) in dry CH_2Cl_2 (7 mL) over a period of 1.5 h at this temperature. After stirring for 20 h at room temperature the solvent was removed in vacuo to give a residue, which was partitioned between ether and water. The aqueous layer was extracted with ether and the combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual oil was subjected to preparative TLC (SiO_2, hexane:ethyl acetate = 10:1, v/v) to afford pyrrole compound **24** in 52% yield (a pale-yellow oil, 65 mg). IR (neat) 2980, 2931, 1751, 1726, 1449, 1419, 1394, 1370, 1349, 1318, 1269,1213, 1194, 1159, 1094, 1064, 849, 775, 744, 705 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.35 (t, J = 7.2 Hz, 3H), 1.58 (s, 9H), 4.23 (q, J = 7.2 Hz, 2H), 6.16 (dd, J = 1.7, 3.3 Hz, 1H), 6.83 (dd, J = 1.5, 3.3 Hz, 1H), 7.31 (dd, J = 1.7, 2.8 Hz, 1H); EI-MS m/z 239 (M^+; 6.6%).

Ethyl (4*S*)-*N*-Boc-4-*t*-butyldiphenylsiloxy-α,β-didehydroprolinate (25a): To a solution of Ph_3P (787 mg, 3.00 mmol) in CH_2Cl_2 (15 mL) was added DEAD (323 mg, 3.04 mmol, 40% toluene solution) at 0 ° C under a N_2 atmosphere. Then, a solution of **23a** (695 mg, 1.35 mmol) in CH_2Cl_2 (15 mL) was added dropwise over a period of 2 h at 0 ° C. The solution was stirred at 0 ° C for 2 d. The solvent was removed in vacuo to afford a residue, which was partitioned between ether and water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was subjected to preparative TLC (SiO_2, hexane:ethyl acetate = 10:1, v/v) to afford **25a** in 59% yield (a pale-yellow oil, 20 mg). $[\alpha]_D^{25}$ = +55.5 ° (c 1.00, $CHCl_3$); IR (neat) 3072, 2935, 2859, 1735, 1706, 1629, 1454, 1431, 1364, 1300, 1238, 1177, 1113, 1069, 1000, 915, 823, 736, 701 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.05 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 3.74 (dd, J = 7.7, 12.5 Hz, 1H), 3.82 (dd, J = 3.9, 12.5 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.82–4.91 (m, 1H), 5.46 (d, J = 2.8 Hz, 1H), 7.30–7.50 (m, 3H + 3H), 7.60–7.69 (m, 2H + 2H); EI-MS m/z 495 (M^+; 11.9 %).

Ethyl(2*S*,4*S*)-*N*-Boc-4-*t*-butyldiphenylsiloxyprolinate (26a): Compound **25a** (1.096 g, 2.20 mmol) was hydrogenated over 5% palladium on carbon (329 mg) in EtOH (15 mL) at room temperature under a H_2 atmosphere for 1 d. The catalyst was filtered through a pad of celite, and the filtrate was removed in vacuo to afford the desired product in quantitative yield (ds; > 99%). The crude product was subjected to a HPLC analysis to determine the diastereoselectivity [column, CAPCELL PAK (Shiseido) UG-120 (4.6 Å–250 nm); buffer A, 0.1% aqueous TFA; B, 80% CH_3CN (0.1% TFA); linear gradient, 50–95% B over 40 min; flow rate, 1.0 mL/min, detection at 210 nm]. Recrystallization from hexane afforded pure **26a** as a single isomer. Mp 93.5–94.5 °C (hexane); $[\alpha]_D^{25}$ = −44.6 ° (c 1.00, $CHCl_3$); IR (KBr) 2978, 2930, 2857, 1759, 1702 ,1588, 1471, 1429, 1395, 1220, 1191, 1157, 1111, 1083, 1054, 918, 822, 752, 742, 706 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.02 and 1.03 (s, 9H, rotamer, ^{t}Bu) 1.30 (t, J = 7.2 Hz, 3H), 1.41 and 1.44 (s, 9H, rotamer, ^{t}Bu), 2.12–2.24 (m, 1H + 1H), 3.37–3.46 (m, 1H), 3.52–3.57 (m, 1H), 4.16–4.33 (m, 2H + 1H + 1H), 7.35–7.46 (m, 3H + 3H), 7.60–7.65 (m, 2H + 2H); Found: C, 67.36; H, 8.04; N, 2.81%. Calcd for $C_{28}H_{39}NO_5Si$: C, 67.57; H, 7.90; N, 2.81%.

Ethyl (2*S*, 4*S*)-*N*-Boc-4-hydroxyprolinate (27a): To a solution of **26a** (845 mg, 1.70 mmol) in THF (5 mL) was added 1 M TBAF solution in THF (8.5 mL, 8.5 mmol) at room temperature under an air atmosphere. The solution was stirred at the temperature overnight. The solvent was removed in vacuo to afford a residue, which was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, hexane:ethyl acetate = 1:1, v/v) to afford the product **27a** in 91% yield (a pale-yellow oil, 598 mg). $[\alpha]_D^{25}$ = −6.91 ° (c 0.86, $CHCl_3$); IR (neat) 3454, 2979, 2935, 1751, 1701, 1477, 1404, 1367, 1256, 1192, 1161, 1123, 1089, 1047, 972, 906, 858, 755 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.27 and 1.28 (t, J = 7.1 Hz, 3H, rotamer, CH_3), 1.39 and 1.43 (s, 9H, rotamer, ^{t}Bu), 2.00–2.07 (m, 1H), 2.24–2.35 (m, 1H), 3.28–3.44 (br, 1H) 3.46–3.54 (m, 1H), 3.58–3.68 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.27–4.33 (m, 1H + 1H); EI-MS m/z 257 (M^+; 0.2 %).

(2*S*, 4*S*)-4-Hydroxyproline (28a): To a solution of **27a** (386 mg, 1.50 mmol) in EtOH (5 mL) was added 1.0 M LiOH aq (3.0 mL) at room temperature under an air atmosphere. The solution was stirred at room temperature for 2 h. The organic solvent was removed in vacuo. The resulting aqueous layer was extracted with ether once. The aqueous layer was acidified with 10% citric acid (pH 3), saturated with NaCl, and then extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting crystalline was treated with 10 equivalents of hydrogen chloride (2 M hydrogen chloride in 1,4-dioxane, 5.0 mL) at room temperature for 19 h under an air atmosphere. Then, the solvent was removed in vacuo to afford the hydrogen chloride salt, which was treated with TEA (92 mg, 0.91 mmol) in cooled EtOH (3 mL). The resulting desired product was filtered and recrystallization from H_2O–EtOH afforded **28a** in 83% yield. Mp 250.0–252.0 ° C (decomp) (H_2O–EtOH); $[\alpha]_D^{25}$ = −57.7 ° (c 0.65, H_2O); IR (KBr) 3215, 2995, 2938 1630. 1561, 1433, 1384, 1327, 1311, 1264, 1197, 1177, 1088, 1070, 1040,

1001, 976, 920, 869, 831, 811, 735, 680 cm^{-1}; ^1H NMR (400 MHz; D_2O) δ 2.22–2.28 (m, 1H), 2.50–2.55 (m, 1H), 3.36 (dd, J = 3.9, 12.5 Hz, 1H), 3.44–3.48 (m, 1H), 4.21 (dd, J = 3.9, 10.5 Hz, 1H), 4.56–4.67 (m, 1H); HRMS (FAB) ($M^+ + 1$) Found: m/z 132.0672. Calcd for $C_5H_{10}NO_3$: 132.0660. [Lit,[13] Mp 248 ° C (decomp), $[\alpha]_D^{25} = -58.0$ ° (c 2.00, H_2O)]

The NMR and IR data of compounds **12b**, **18b**, **21b**–**23b**, and **25b**–**28b** were satisfactorily in accodance with those described for the enantiomers obtained above.

Ethyl (4*R*)-2-(*N*-Boc-amino)-4,5-isopropylidenedioxy-2-pentenoate (12b): **12b** was prepared from **1a** and (*S*)-isopropylideneglyceraldehyde.[6] Yield: 94%; (*Z*/*E* = 95/5) ; Mp 75.0–76.5 ° C (hexane); $[\alpha]_D^{25} = +12.3$ ° (c 0.77, $CHCl_3$).

Ethyl (4*R*)-2-(*N*-Boc-amino)-4,5-dihydroxy-2-pentenoate (18b): Yield: 85% ; Mp 67.0–68.0 ° C (ethyl acetate–hexane); $[\alpha]_D^{25} = -18.2$ ° (c 1.57, $CHCl_3$).

Ethyl (4*R*)-2-(*N*-Boc-amino)-5-*t*-butyldimethylsiloxy-4-hydroxy-2-pentenoate (21b): Yield: 84%; a pale yellow oil; $[\alpha]_D^{25} = -15.1$ ° (c 1.10, $CHCl_3$).

Ethyl (4*R*)-2-(*N*-Boc-amino)-5-*t*-butyldimethylsiloxy-4-*t*-butyldiphenylsiloxy-2-pentenoate (22b): Yield: Quantitative; a pale yellow oil; $[\alpha]_D^{25} = -37.0$ ° (c 0.72, $CHCl_3$).

Ethyl (4*R*)-2-(*N*-Boc-amino)-4-*t*-butyldiphenylsiloxy-5-hydroxy-2-pentenoate (23b): Yield: Quantitative; a pale-yellow oil; $[\alpha]_D^{25} = +26.5$ ° (c 1.04, $CHCl_3$).

Ethyl (4*R*)-*N*-Boc-4-*t*-butyldiphenylsiloxy-α,β-didehydroprolinate (25b): Yield: 59%; a pale yellow oil; $[\alpha]_D^{25} = -55.9$ ° (c 0.96, $CHCl_3$).

Ethyl (2*R*, 4*R*)-*N*-Boc-4-*t*-butyldiphenylsiloxyprolinate (26b): Yield: Quantitative. Recrystallization from hexane afforded pure **26b.** Mp 94.0–95.0 ° C (hexane); $[\alpha]_D^{25} = +45.0$ ° (c 1.85, $CHCl_3$).

Ethyl (2*R*, 4*R*)-*N*-Boc-4-hydroxyprolinate (27b): Yield: 90%; a pale-yellow oil; $[\alpha]_D^{25} = +7.15$ ° (c 0.95, $CHCl_3$).

(2*R*, 4*R*)-4-hydroxyproline (28b): Yield: 63% ; Mp 245.0–248.0 ° C (decomp) (H_2O–EtOH); $[\alpha]_D^{25} = +58.6$ ° (c 0.65, H_2O) [Lit,[8b] Mp 252–257 ° C (decomp), $[\alpha]_D^{25} = +58.6$ ° (c 2.00, H_2O)].

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