Chiral Tricyclic Iminolactone Derived from (1*R*)-(+)-Camphor as a Glycine Equivalent for the Asymmetric Synthesis of α-Amino Acids

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The development of a highly efficient and stereoselective methodology for the preparation of α-amino acids is described. The chiral template, tricyclic iminolactone **7**, was synthesized from (1*R*)-(+)-camphor in five steps in 50% overall yield. Alkylation of iminolactone **7** afforded the α-monosubstituted products in good yields (74−96%) and excellent diastereoselectivities (>98%). Hydrolysis of the alkylated iminolactones furnished the desired α-amino acids in good yields and enantioselectivities with nearly quantitative recovery of the chiral auxiliary **4**.

Introduction

Nonproteinogenic amino acids have received tremendous attention recently.[1] They are widely used for biological, biochemical, and pharmaceutical studies.[2] They have also been utilized as chiral starting materials in organic synthesis and for the preparation of chiral auxiliaries.[3] Rapid progress in the development of active peptides requires the ready availability of a large number of structurally diverse D-amino acids.[4] Consequently, an efficient and convenient general method for the preparation of optically pure enantiomers of α-substituted α-amino acids would be of general interest.[5]

As part of our effort to develop synthetic procedures for the preparation of optically active α-amino acids, we have investigated the utility of compounds derived from camphor, a versatile and inexpensive chiral starting material in asymmetric synthesis,[6] as chiral auxiliaries. In developing an asymmetric glycine equivalent, we focused our attention on the camphor-based tricyclic iminolactone **7** for the following reasons: (1) A cyclic system will allow for a more rigid transition state than the corresponding acyclic one, which could enhance the steric effect of the auxiliary in controlling the stereochemistry of the reaction. (2) Unlike acyclic esters, lactones give rise to only the *Z*-enolates, which in turn will provide a single alkylated product if the electrophile approaches specifically from one of the enolate reaction faces. (3) The C_{12}-methyl group of camphor could block the top face of the alkylation step and thus result in good stereoselectivity. (4) Both the imine and the lactone functionalities can be hydrolyzed easily to form the amino acids with the possibility of recovering the chiral auxiliary. (5) Camphor is inexpensive and readily available. Therefore, iminolactone **7** is expected to form a rigid transition state upon deprotonation and the electrophile is expected to come in from the less hindered bottom side of the lactone to produce the alkylated product in high diastereomeric purity. We now report a practical and highly stereoselective route to the synthesis of α-amino acids via this tricyclic iminolactone derivative of camphor.

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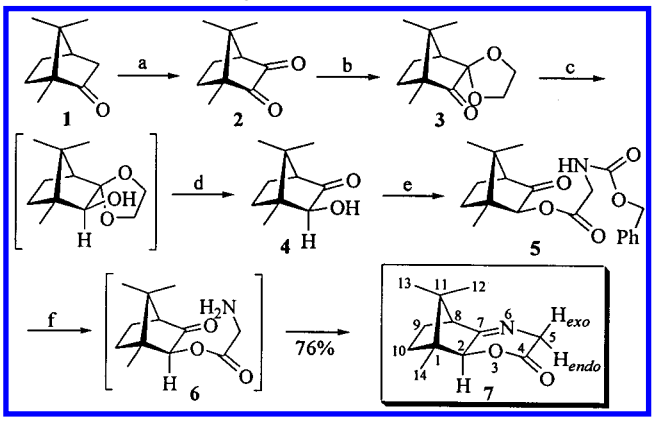
Scheme 1. Synthesis of Iminolactone 7[a]

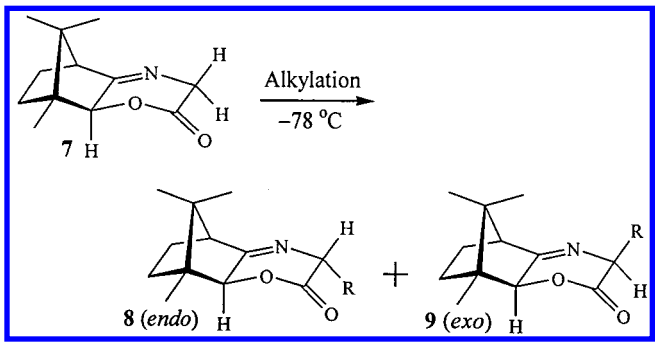


[a] Key: (a) SeO_2/Ac_2O, reflux, 17 h, 100%; (b) ethylene glycol, TsOH, benzene, 78%; (c) $NaBH_4$, Et_2O/CH_3OH (1:1); (d) cold H_2SO_4, 94%; (e) Z-GlyOH, DMAP, DCC, THF, rt, 16 h, 98%; (f) H_2 (1 atm), Pd/C, room temperature, 14 h.

The synthesis of tricyclic iminolactone **7** from camphor is outlined in Scheme 1. Thus, (1*R*)-(+)-camphor was first treated with selenium dioxide to give (1*R*)-(+)-camphorquinone (**2**) as a yellow solid in quantitative yield.[7] Selective acetalization of the less hindered carbonyl group was then accomplished using ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene with azeotropic removal of water to afford the desired monoacetal **3** in 78% yield.[8,9] The remaining carbonyl group was then reduced with sodium borohydride at ca. 0 °C followed by the removal of the acetal with aqueous sulfuric acid to give the 2-*exo*-hydroxyepicamphor (**4**) as the sole isomer in 94% isolated yield.[10] Hydroxyketone **4** was then treated with *N*-Cbz-glycine, DCC, and DMAP in dry THF to furnish ester **5** in quantitative yield after column chromatography. The Cbz group was removed by hydrogenolysis in absolute ethanol under a hydrogen atmosphere (1 atm) using 5% palladium on carbon as catalyst for 14 h. Concomitant cyclization to the imine occurred simultaneously during hydrogenation to give rise to the desired chiral template **7** in 76% isolated yield over two steps.[11,12]

The assignment of the C_{5endo}-H and the C_{5exo}-H of compound **7** was based on the following observations: (a) The C_{5exo}-H (4.54 ppm) of the iminolactone **7** was a doublet with a large geminal coupling constant ($J = 18.0$ Hz) due to the lack of long-range coupling between it and the C_2-H. (b) The C_{5endo}-H (3.88 ppm), on the other hand, appeared as a doublet of doublets ($J = 18.0$, 1.6 Hz). The long-range coupling is possible for this proton since the C−H bond is nearly parallel to the π-orbital of the imine double bond, which in turn is almost parallel to the C_2-H bond. (c) The C_2-H of compound **7** is a doublet ($J = 1.6$ Hz) because it couples with the C_{5endo}-H. The exceptionally large difference ($\Delta\Delta\delta = 0.66$ ppm) between the chemical shifts of the two C_5-protons on the lactone ring suggests that the chemical environments of the two protons are considerably different.

Table 1. Alkylation of the Tricyclic Iminolactone 7



entry	solvent	base	E^+	yield[a] (%)	endo/exo[b]	% de
1	THF/HMPA	$KOBu^t$	CH_3I	71	3:1	50
2	THF/HMPA	LDA	CH_3I	81	>99:1	>98
3	THF/HMPA	$KOBu^t$	CH_2=CH-CH_2Br	58	>99:1	>98
4	THF/HMPA	LDA	CH_2=CH-CH_2Br	93	>99:1	>98
5	THF/HMPA	$KOBu^t$	$C_6H_5CH_2Br$	85[c]	1.2:1.3	
6	THF	$KOBu^t$	$C_6H_5CH_2Br$	58[d]	1:>99	>98
7	THF/HMPA	*n*-BuLi	$C_6H_5CH_2Br$	51 (75)[e]	>99:1	>98
8	THF	LDA	$C_6H_5CH_2Br$	59 (81)[e]	>99:1	>98
9	THF/HMPA	LDA	$C_6H_5CH_2Br$	83 (96)[e]	>99:1	>98

[a] The reported yields are isolated yields after column chromatography. [b] The ratios were estimated by NMR integrations of the crude reaction mixtures on a Varian Mercury-400 NMR spectrometer. [c] The yield is composed of endo, exo, and dialkylated products in a ratio of 1.2:1.3:1. [d] The yield is composed of exo and dialkylated products in a 1.4:1 ratio. [e] The yields in parentheses are based on recovered starting material.

Alkylation of the tricyclic iminolactone **7** was carried out at −78 °C using various combinations of different bases, solvent systems, additives, and electrophiles. The results of the alkylation reactions of the enolate of **7** were strongly dependent on the reaction conditions employed. The electrophile was injected slowly using a syringe pump with the needle contacting the wall of the neck, and thus, the reagent was dripped along the flask wall to cool it to the reaction temperature before the electrophile reached the reaction mixture.[13] The results in Table 1 clearly show that the combination of lithium diisopropylamide (LDA) and HMPA gave the best yields. In every case except one, extremely high diastereoselectivity was realized.[14]

The stereochemistry of the two monomethylation products was revealed by the NMR coupling pattern of the

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(9) Approximately 16% of the diacetal was also obtained in the reaction, which can be hydrolyzed to regenerate camphorquinone. As a result, the yield of the C_3 carbonyl monoprotected camphorquinone is 95% based on recovered camphorquinone. Under milder conditions, the diacetal can be converted selectively to a monoacetal with the more hindered carbonyl group being protected (2-acetal), which can be utilized to prepare α-amino acids of the opposite configuration.

(10) The *exo*-stereochemistry of the hydroxyl group in compound **4** was verified by the absence of long-range coupling between the C_2-H, which exists as a singlet, and C_6-H because the C_2-H cannot form a W-shaped conformer with the C_{6exo}-H and is parallel to the C_{6endo}-H. Therefore, the C_2-H and C_6-H do not have a long-range coupling.

(11) Intermediate **6** was obtained as its hydrochloride salt by adding a few drops of 2 N hydrochloric acid when the hydrogenation was interrupted after 2 h. The structure of intermediate **6** was confirmed by both NMR and MS spectra.

(12) All new compounds gave satisfactory analytical and spectral data. The elemental composition of all new compounds was established by combustion or mass spectrometric analysis.

(13) This proved to be crucial in obtaining a high diastereoselectivity since direct addition of the alkyl halide to the reaction resulted in a significant loss of stereoselectivity.

(14) This served as a strong indication that the alkylation of the enolate occurred exclusively from the bottom face. The NMR spectrum of the crude methylation reaction was carefully examined and there was no sign of the *exo*-methylated product within the NMR detection limits.

Table 2. Alkylation of Iminolactone 7[a]

entry	T (°C)	E^+	yield[b] (%)	products	endo/exo[c]	% de
1	−78	CH_3I	81	**8a** + **9a**	>99:1	>98
2	−78	$CH_2{=}CHCH_2Br$	93	**8b** + **9b**	>99:1	>98
3	−30	$C_6H_5CH_2Br$	86	**8c** + **9c**	6:1	71
4	−78	$C_6H_5CH_2Br$	83 (96)[d]	**8c** + **9c**	>99:1	>98
5	−78	CH_3CH_2I	74	**8d** + **9d**	>99:1	>98
6	−78	$CH_3(CH_2)_2I$	59 (88)[d]	**8e** + **9e**	>99:1	>98
7	−78	$CH_3(CH_2)_3I$	52 (84)[d]	**8f** + **9f**	>99:1	>98
8	−78	$(CH_3)_2C{=}O$	68	**8g** + **9g**	95:5	90
9	−78	$CH_2{=}CHCO_2Bu^t$	74	**8h** + **9h**	>99:1	>98

[a] The reaction was carried out in THF/HMPA with LDA as the base. [b] The reported yields are isolated yields after column chromatograph. [c] The ratios were estimated by NMR integrations of the crude reaction mixtures on a Varian Mercury-400 NMR spectrometer. [d] The yields in parentheses are based on recovered starting material.

C_{5exo}-H and C_{5endo}-H. The C_{5endo}-H of the exo-methylated product is a quartet of doublets (3.84 ppm, J = 7.2, 1.2 Hz) while the C_2-proton is a doublet (4.33 ppm, J = 1.2 Hz). Long-range coupling between the C_{5endo} proton and C_2-proton is allowed only when the two protons are parallel to each other as well as to the π-orbital of the imine double bond in this rigid ring system. Thus, the existence of long-range coupling between these two protons indicates that the methyl group is exo. On the contrary, the C_{5exo}-proton of the endo product appears as a quartet (4.55 ppm, J = 7.6 Hz) while the C_2-proton appears as a singlet (4.37 ppm). The absence of long-range coupling supports the assignment of an *endo*-methyl group.

Likewise, the stereochemistry of the two endo- and exo-monobenzylated products also can be determined by the NMR coupling pattern of the C_{5exo}-H and C_{5endo}-H. The C_{5endo}-H of the exo product **9c** is a doublet of doublets of doublets (3.95 ppm, J = 1.2, 4.4, 4.8 Hz) and the C_2-proton is a doublet (4.27 ppm, J = 1.2 Hz). Furthermore, the chemical shift of the C_2-proton is close to that of the exo-methylated product (4.27 vs 4.33 ppm). On the other hand, the C_{5exo}-proton of the endo-benzylated product appears as a doublet of doublets (4.84 ppm, J = 4.8, 5.4 Hz) while the C_2-proton appears as a singlet (2.51 ppm). The chemical shift of the C_2-proton is 1.76 ppm higher field than that of the corresponding endo-methylated compound, presumably due to the shielding effect of the phenyl group, which serves as a further evidence for the endo stereochemistry of the benzyl group.

It is noteworthy that methylation of compound **7** using $KOBu^t$ as the base at −78 °C resulted in considerably lower facial selectivity (**8a**/**9a** = 3/1) compared to that utilizing LDA (Table 1, entries 1 and 2). Similarly, benzylation of iminolactone **7** with $KOBu^t$ resulted in a reversal of stereoselectivity but with a poor diastereomeric ratio (**8c**/**9c** = 1.2/1.3) (Table 1, entry 5). Furthermore, complete reversal of stereochemistry of the benzylated product was observed when the reaction was performed in THF alone (Table 1, entry 6). On the contrary, extremely high diastereoselectivity was achieved in allylation regardless of the base used (Table 1, entries 3 and 4).

The alkylation was then conducted using the optimum reaction conditions developed in Table 1. As summarized in Table 2, the alkylation reaction generated the monoalkylated products in high yields with very high control of the stereochemistry of the newly formed stereocenter for a wide range of electrophiles. Moreover, the reaction

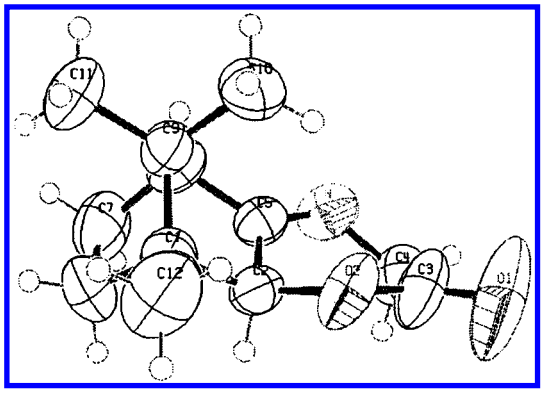

Figure 1. X-ray structure of compound **7**.

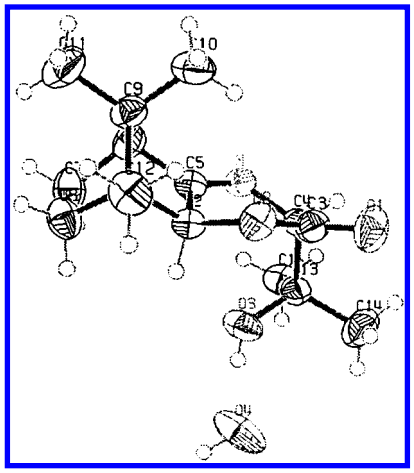

Figure 2. X-ray structure of compound **8g**.

temperature seems to play an important role in determining the facial selectivity, as much lower diastereomeric ratio was obtained when the reaction was performed at −30 °C (Table 2, entry 3). In addition, the aldol reaction and Michael addition of the enolate also delivered the desired products smoothly with good facial selectivities (Table 2, entries 8 and 9) demonstrating the generality of the reaction.

X-ray crystallographic determination of single crystals of compounds **7** and **8g**, obtained by recrystallization from a mixture of ethyl acetate and hexane, provided the structures presented in Figure 1 and Figure 2.[15] A salient feature in the crystallographic structure in Figure 1 is that the iminolactone ring fused with the rigid camphor skeleton is in a boat conformation with the C_2-proton and the C_{5endo}-proton being at the flagpole positions. The aforementioned two hydrogens are both parallel to the π-orbitals of the C=N double bond, which supports the above assigned NMR coupling pattern. In addition, the stereochemistry of the alkylated iminolactones is confirmed unequivocally by the fact that the hydroxypropyl group of compound **8g** is at the endo position in its X-ray structure.

Hydrolysis of the alkylated iminolactones in 8 N HCl solution at 87 °C for 2 h[16] afforded the corresponding D-α-amino acids in good yields and enantiomeric excesses (Table 3). The *R*-configuration of the resulting amino

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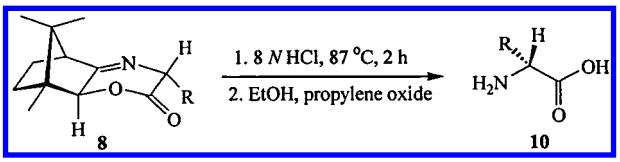
Table 3. Hydrolysis of the Alkylated Iminolactones 8



entry	R	amino acid (%)	recovered auxiliary (%)	ee[a] (%)	$[\alpha]^{22}_D$
1	CH_3	70	94	94	−9.0[b]
2	CH_2=$CHCH_2$	78	97	98	+36.4[c]
3	$C_6H_5CH_2$	82	97	96	+33.7[c]

[a] Ee values were determined by HPLC analysis utilizing a Daicel Crownpak CR(+) column. [b] The optical rotations were measured in 2 N HCl solution on a Perkin-Elmer PE-241 polarimeter. [c] The optical rotations were recorded in H_2O solution.

acids, determined by comparing the optical rotation of the products with literature values, is in accord with the assigned stereochemistry of the alkylated iminolactones. In addition, the chiral auxiliary **4** was also recovered in excellent yield. The configuration of the α-amino acids is in agreement with that assigned to the respective precursors. The recovered chiral auxiliary **4** was recycled to prepare the iminolactone **7**, which exhibited the same optical purity as that of the one derived from freshly synthesized compound **4**.

In summary, an efficient and practical method for the preparation of α-amino acids starting from inexpensive and readily available (1*R*)-(+)-camphor has been developed. Good chemical yields and excellent diastereoselectivities were realized to produce the α-amino acids in high optical purity. The fact that the chiral auxiliary can be recycled without loss of optical integrity renders the present method an economical method for the preparation of α-monosubstituted α-amino acids. The preparation of α-amino acids of the opposite configuration can be achieved by starting from the (1*S*)-(−)-camphor. Consequently, our method is amenable to the synthesis of α-amino acids of either stereochemistry.

Experimental Section

General Methods. All alkylation reactions were conducted in flame-dried round-bottom or modified long-neck flasks fitted with rubber septa under an argon atmosphere unless otherwise noted. Solvents and reagents were dried prior to use as required. Diisopropylamine and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride immediately prior to use, THF was distilled from sodium benzophenone ketyl, *n*-butylithium in hexane (nominally 1.6 M) was purchased from Aldrich and titrated[17] before each use. Thin-layer chromatography plates visualized by exposure to ultraviolet light and/or immersion in a staining solution (phosphomolybdic acid) followed by heating on a hot plate. Flash chromatography was carried out utilizing silica gel 60, 70−230 mesh ASTM. Medium-pressure liquid chromatography was carried out using Merck Lobar prepacked silica gel columns and a Fluid Metering, Inc., FMI Lab Pump. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 or 600 MHz; ^{13}C NMR spectra were recorded at 100 or 150 MHz. Chloroform (δ = 7.27 ppm) or deuterium oxide (δ = 4.63 ppm) was used as internal standard in ^{1}H NMR spectra. The center peak of deuteriochloroform (δ = 77.0 ppm) was used as internal standard in ^{13}C NMR spectra. Mass spectra (EI) were obtained at 70 eV. The optical rotations were measured in $CHCl_3$ solution with a cuvette of 1 dm length. The ee value of the α-amino acids obtained from hydrolysis of the alkylated iminolactones was determined by measuring the optical rotation of the amino acids or by HPLC analysis on a Crownpak CR(+) column. X-ray data were collected on a Bruker CCD Smart-1000 diffractometer equipped with graphite-monochromator Mo Kα radiation (λ = 0.710 73 Å).

Camphorquinone (2).[8a] To a 250 mL flask were added sequentially acetic anhydride (50 mL), (1*R*)-(+)-camphor (30.42 g, 200 mmol), and selenium dioxide (51.04 g, 460 mmol). The mixture was heated to reflux (oil bath temperature ca. 170 °C) for 17 h. The reaction was then cooled to room temperature and filtered to remove the black selenium precipitate. Addition of cold water to the filtrate, cooled in an ice bath, resulted in the precipitation of a yellow solid, and the mixture was stirred for another 5 min. The yellow solids were filtered and washed with cold water. The filtrate was neutralized with saturated aqueous sodium hydroxide and then extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and filtered and solvent removed to afford camphorquinone as a yellow solid that was combined with the previous precipitate (33.1 g, 99.6%). The ^{1}H NMR of the camphorquinone indicated that the crude camphorquinone is pure enough for the subsequent reactions and therefore was used without further purification: mp 197−198 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (d, J = 5.6 Hz, 1H), 2.08∼2.28 (m, 1H), 1.99−1.82 (m, 1H), 1.71−1.56 (m, 2H), 1.11 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H); IR (NaCl, $CHCl_3$) 3040 (m), 2980 (m), 1775 (m), 1760 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_{10}H_{14}O_2$ M^+ 166.0994, found M^+ 166.0987.

(1*R*,4*S*)-(-)-1,7,7-Trimethyl-3,3-ethylenedioxybicyclo-[2.2.1]heptan-2-one (3).[8b] A solution of camphorquinone (8.32 g, 50 mmol), *p*-toluenesulfonic acid monohydrate (0.48 g, 2.5 mmol). and ethylene glycol (4 mL, 71.8 mmol) in benzene (60 mL) was heated under reflux using a Dean−Stark trap for 24 h. Benzene was removed, and the residue was dissolved in EtOAc (40 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and filtered and solvent removed. Column chromatography (EtOAc/hexane = 1:20) afforded the desired acetal (8.20 g, 78%) and the over-protected diacetal (2.10 g, 16%). Acetal: mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 4.34−4.28 (m, 1H), 4.21−4.15 (m, 1H), 4.06−3.95 (m, 2H), 2.03−1.94 (m, 1H), 1.96 (d, J = 4.8 Hz, 1H), 1.87−1.76 (m, 1H), 1.72−1.53 (m, 2H), 1.02 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H); IR (NaCl, $CHCl_3$) 2971 (s), 2899 (m), 1752 (s) cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{18}O_3$ M^+ 210.1250, found M^+ 210.1256. Diacetal: mp 59−60 °C; IR (NaCl, $CHCl_3$) 2961 (m), 2893 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.98−3.75 (m, 8H), 1.99−1.92 (m, 1H), 1.83−1.77 (m, 1H), 1.69 (d, J = 4.8 Hz, 1H), 1.59−1.52 (m, 1H), 1.39−1.32 (m, 1H), 1.18 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 114.8, 113.8, 65.9, 65.0, 64.5, 64.2, 53.3, 52.7, 44.5, 29.3, 21.0, 20.9, 20.7, 9.8; MS *m*/*z* 254 (M^+, 23.5), 239 (10.5), 170 (15.9), 141 (56.0), 127 (55.8), 113 (100.0), 99 (96.3), 69 (49.3), 55 (55.3), 53 (16.0).

(1*S*,3*S*,4*R*)-3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (4).[3] To a solution of acetal **3** (5.80 g 27.6 mmol) in ether (30 mL) and methanol (30 mL), cooled in an ice bath, was added sodium borohydride (1.26 g) in small batches over 10 min. The reaction mixture was stirred in an ice bath for 3.5 h. The reaction was washed with water, and the organic layer was evaporated to leave an oil that was cooled to about 0 °C and was mixed with ice-cold concentrated sulfuric acid−water (v/v = 1:1, 60 mL). Ice (10 g) was added after 15 min, and the mixture was extracted with ether. The ether layer was washed with brine and water, dried ($MgSO_4$), and filtered and solvent evaporated while the bath temperature of the rotary evaporator was kept under 30 °C to give the 2-*exo*-hydroxyepicamphor as a white powder (4.36 g, 94%): mp 218−220 °C; IR (NaCl, $CHCl_3$) 3444 (br), 2959 (m), 1746 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.54 (d, J = 2.8 Hz, 1H), 2.32 (d, J = 2.8 Hz, 1H), 2.17 (d, J = 4.4 Hz, 1H), 1.96−1.82 (m, 2H), 1.47−1.35 (m, 2H), 1.04 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 79.5, 58.6, 49.2, 46.5, 33.9, 21.1, 20.3, 18.8, 10.2; MS *m*/*z* 168 (M^+, 53.8), 153 (3.0), 140 (12.0), 125 (31.6), 107 (7.3), 100 (11.7), 83 (100.0), 69 (23.4), 55 (25.4), 53 (3.8).

(17) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

(*1R,2S,4S*)-Benzyloxycarbonylaminoacetic Acid 1,7,7-Trimethyl-3-oxobicyclo[2.2.1]hept-2-yl Ester (5). A solution of 2-*exo*-hydroxyepicamphor (5.09 g, 30.2 mmol), Cbz-glycine (7.58 g, 36.3 mmol, 1.2 equiv), and 4-*N*,*N*-(dimethylamino)pyridine (DMAP, 1.85 g, 15.1 mmol, 0.5 equiv) in THF (120 mL) in a 250 mL flask was stirred at 0 °C for 15 min, and dicyclohexylcarbodiimide (DCC, 9.35 g, 45.4 mmol, 1.5 equiv) in THF (30 mL) was then added dropwise to the solution via a syringe. The reaction was stirred at 0 °C for 2 h and then at room temperature for 16 h. Precipitated 1,3-dicyclohexylurea (DCU) was removed by filtration and the filtrate concentrated under reduced pressure. Purification by flash column chromatography (EtOAc/hexane = 1:8) gave the ester as a colorless viscous oil (10.73 g, 98.8%). The oil solidified upon standing or evacuating with a vacuum pump: mp 72−74 °C; IR (NaCl, $CHCl_3$) 3360 (br), 2961 (m), 1758 (s), 1750 (s) cm^{-1}; $[\alpha]^{22}_D = -94.6$ (c = 2.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36−7.35 (m, 5H), 5.24 (s, 1H), 5.12 (s, 2H), 4.90 (s, 1H), 4.15−4.02 (m, 2H), 2.21−2.20 (d, J = 4.0 Hz, 1H), 2.10−1.84 (m, 2H), 1.62−1.44 (m, 2H), 0.97 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 212.4, 169.7, 156.5, 136.4, 128.8, 128.4, 79.4, 67.3, 58.9, 49.7, 46.8, 42.9, 33.7, 21.0, 20.6, 18.7, 10.6; HRMS m/z calcd for $C_{20}H_{25}NO_5$ M^+ 359.1735, found M^+ 359.1733.

(1*R*,2*S*,8*S*)-1,11,11-Trimethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (7). A 100 mL two-necked flask was charged with ester **5** (5.40 g, 15 mmol) and 5% palladium on activated carbon (0.60 g). The flask was then evacuated and filled with hydrogen three times. Dry ethanol (40 mL) was added to the mixture followed by evacuation and filling with hydrogen one more time. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature (ca. 24 °C) for 14 h. The catalyst was removed by filtration, and the filtrate was concentrated to afford the crude product. Column chromagraphy purification (EtOAc/hexane = 1:4) furnished the desired iminolactone as a colorless solid (2.36 g, 76%): mp 63−64 °C; $[\alpha]^{22}_D$ −265.6 (c = 2.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.52 (d, J = 18 Hz, 1H), 4.32 (d, J = 1.6 Hz, 1H), 3.90 (dd, J = 1.6, 18 Hz, 1H), 2.45 (d, J = 4.4 Hz, 1H), 2.05−1.98 (m, 1H), 1.95−1.88 (m, 1H), 1.59−1.52 (m, 1H), 1.43−1.36 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.8, 168.8, 81.7, 53.2, 52.5, 49.4, 48.9, 34.0, 21.6, 20.0, 19.3, 9.8; IR (NaCl, $CHCl_3$) 2962 (m), 1751 (s), 1695 (m) cm^{-1}; HRMS m/z calcd for $C_{12}H_{17}NO_2$ M^+ 207.1264, found M^+ 207.1268. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.48; H, 8.20; N, 6.75. Found: C, 69.44; H, 8.25; N, 6.72.

Alkylation of Iminolactones. General Procedure A. KOBu^t (1 M) in THF (1.54 mL, 1.54 mmol, 1.1 equiv) was added to a dry 25 mL long-neck flask, immersed in a circulating cooler (FTS systems, Model MC 880A1) kept at −30 °C under an argon atmosphere. Iminolactone **7** (0.29 g, 1.4 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min. The resulting mixture was stirred at −30 °C for 90 min followed by the addition of HMPA (0.73 mL, 4.2 mmol, 3 equiv). After the temperature of the cooler was lowered to −78 °C, a solution of alkyl halide (2.1 mmol, 1.5 equiv) in dry THF (10 mL), precooled to 0 °C, was injected slowly using a syringe pump over 15 min with the needle contacting the wall of the neck allowing the reagent to cool to the reaction temperature before it reached the reaction mixture by dripping along the flask wall. The well-stirred reaction was then kept at −78 °C for 10 h.

Aqueous acetic acid solution (2 M, 2 mL) was added to the mixture to quench the reaction. The reaction was allowed to warm to room temperature and then was washed with saturated LiCl solution, dried ($MgSO_4$), concentrated, and purified by column chromatography to yield the desired compounds.

General Procedure B. Diisopropylamine (216 μL, 1.54 mmol, 1.1 equiv) was added to a 25 mL long-neck flask, immersed in a circulating cooler kept at −30 °C under an argon atmosphere, containing a solution of dry THF (1.2 mL) and *n*-BuLi (1.6 M, 962 μL, 1.54 mmol, 1.1 equiv), and the mixture was stirred for 30 min at −30 °C.

To the freshly prepared LDA solution, the same alkylation procedures used above were followed to provide the desired products.

(1*R*,2*S*,5*R*,8*S*)-1,5,11,11-Tetramethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (8a): $[\alpha]^{22}_D$ −85.6 (c =1.09, $CHCl_3$); R_f 0.23 (hexane/EtOAc = 2/1); mp 83−84 °C; IR (NaCl, $CHCl_3$) 2962 (ms), 1747 (s), 1695 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.55 (q, J = 7.6 Hz, 1H), 4.37 (s, 1H), 2.38 (d, J = 4.4 Hz, 1H), 2.04−1.91 (m, 1H), 1.99−1.82 (m, 1H), 1.57−1.48 (m, 1H), 1.41−1.32 (m, 1H), 1.41 (d, J = 7.6 Hz, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.3, 172.0, 80.4, 57.4, 53.6, 49.7, 48.2, 34.4, 21.3, 19.9, 19.3, 16.3, 9.7; HRMS m/z calcd for $C_{13}H_{19}NO_2$ M^+ 221.1416, found M^+ 221.1407. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33; Found: C, 70.52; H, 8.60; N, 6.35.

(1*R*,2*S*,5*S*,8*S*)-1,5,11,11-Tetramethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (9a): $[\alpha]^{22}_D$ +291.9 (c =1.29, $CHCl_3$); mp 161−162 °C; IR (NaCl, $CHCl_3$) 2953 (ms), 1744 (s), 1690 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.33 (d, J = 1.2 Hz, 1H), 3.84 (qd, J = 7.2, 1.2 Hz, 1H), 2.42 (d, J = 4.4 Hz, 1H), 2.06−1.96 (m, 1H), 1.95∼1.87 (m, 1H), 1.67 (d, J = 7.2 Hz, 3H), 1.59−1.52 (m, 1H), 1.44−1.34 (m, 1H), 1.10 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.7, 171.5, 81.9, 56.7, 52.9, 49.3, 49.0, 33.9, 21.6, 20.0, 19.8, 17.2, 9.9; HRMS m/z calcd for $C_{13}H_{19}NO_2$ M^+ 221.1416, found M^+ 221.1406. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.54; H, 8.61; N, 6.31.

(1*R*,2*S*,5*R*,8*S*)-5-Allyl-1,11,11-trimethyl-3-oxa-6-aza-tricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8b): $[\alpha]^{22}_D$ −17.1 (c = 1.88, $CHCl_3$); R_f 0.32 (hexane/EtOAc = 2/1); ^1H NMR ($CDCl_3$) δ 5.84 (ddt, J = 17.2, 9.6, 7.2 Hz, 1H), 5.20 (dd, J = 17.2, 1.6 Hz, 1H), 5.16 (dd, J = 9.6, 1.6 Hz, 1H), 4.57 (t, J = 7.2 Hz, 1H), 4.39 (s, 1H), 2.61−2.46 (m, 1H), 2.42 (d, J = 4.4 Hz, 1H), 2.07−1.85 (m, 2H), 1.82−1.77 (m, 1H), 1.59−1.50 (m, 1H), 1.43−1.33 (m, 1H), 1.06 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.0, 170.8, 132.8, 119.2, 81.1, 62.1, 53.9, 50.0, 48.4, 39.1, 34.7, 21.8, 20.2, 19.5, 10.0; HRMS m/z calcd for $C_{15}H_{21}NO_2$ M^+ 247.1572, found M^+ 247.1578. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.82; H, 8.49; N, 5.62.

(1*R*,2*S*,5*R*,8*S*)-5-Benzyl-1,11,11-trimethyl-3-oxa-6-aza-tricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8c): $[\alpha]^{22}_D$ −11.4 (c = 2.07, $CHCl_3$); R_f 0.27 (hexane/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 3032 (s), 1734 (s), 1705 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28−7.15 (m, 5H), 4.83 (t, J = 5.4 Hz, 1H), 3.44−3.38 (dd, J = 5.4, 13.8 Hz, 1H), 3.16−3.11 (dd, J = 5.4, 13.8 Hz, 1H), 2.51 (s, 1H), 2.34 (d, J = 4.8 Hz, 1H), 1.89−1.82 (m, 1H), 1.68−1.60 (m, 1H), 1.40−1.33 (m, 1H), 0.87 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H), 0.72−0.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 180.4, 171.4, 136.2, 130.1, 128.7, 127.4, 80.9, 62.7, 53.8, 49.0, 48.0, 38.0, 34.4, 21.2, 19.9, 19.1, 9.3; HRMS m/z calcd for $C_{19}H_{23}NO_2$ M^+ 297.1729, found M^+ 297.1728. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.80; H, 7.81; N, 4.67.

(1*R*,2*S*,5*S*,8*S*)-5-Benzyl-1,11,11-trimethyl-3-oxa-6-aza-tricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (9c): $[\alpha]^{22}_D$ −223.5 (c =1.01, $CHCl_3$); R_f 0.42 (hexane/EtOAc = 2/1); mp 68−69 °C; IR (NaCl, $CHCl_3$) 2961 (m), 1746 (s), 1693 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.22 (m, 5H), 4.27 (d, J = 1.2 Hz, 1H), 3.97−3.93 (m, 1H), 3.58−3.53 (dd, J = 4.8, 14.4 Hz, 1H), 3.26−3.20 (dd, J = 8.4, 14.4 Hz, 1H), 2.43 (d, J = 4.4 Hz, 1H), 2.00−1.84 (m, 2H), 1.56−1.49 (m, 1H), 1.38−1.31 (m, 1H), 1.08 (s, 3H), 0.95 (s, 3H), 0.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5, 170.5, 138.7, 129.6, 128.3, 126.4, 81.7, 62.6, 53.0, 49.3, 48.9, 37.2, 33.9, 21.6, 20.0, 19.3, 9.9; MS m/z 297 (M^+, 58.9), 269 (6.5), 253 (8.2), 238 (6.3), 206 (13.7), 178 (22.6), 162 (100.0), 148 (36.6), 131 (32.7), 91 (80.4), 83 (12.0), 77 (11.6), 55 (11.2); HRMS m/z calcd for $C_{19}H_{23}NO_2$ M^+ 297.1729, found M^+ 297.1729. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.77; H, 7.81; N, 4.66.

(1*R*,2*S*,5*R*,8*S*)-5-Ethyl-1,11,11-trimethyl-3-oxa-6-aza-tricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8d): $[\alpha]^{22}_D$ −46.7 (c = 2.17, $CHCl_3$); R_f 0.30 (hexane/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 1742 (s), 1604 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40 (t, J = 8 Hz, 1H), 4.38 (s, 1H), 2.41 (d, J = 4.4 Hz, 1H), 2.06−1.97 (m, 1H), 1.93−1.86 (m, 1H), 1.82−1.74 (m, 2H), 1.59−1.52 (m, 1H),

1.41−1.34 (m, 1H), 1.11 (t, J = 7.6 Hz, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.2, 171.0, 80.5, 63.7, 53.6, 49.6, 48.1, 34.4, 24.9, 21.4, 19.9, 19.3, 11.1, 9.7; HRMS m/z calcd for $C_{14}H_{21}NO_2$ M^+ 235.1572, found M^+ 235.1574. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95; Found: C, 71.50; H, 8.97; N, 6.01.

(1*R*,2*S*,5*R*,8*S*)-1,11,11-Trimethyl-5-propyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8e): $[\alpha]^{22}_D$ −40.2 (c = 1.39, $CHCl_3$); R_f 0.40 (hexane/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 2960 (ms), 1747 (s), 1697 (m) cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 4.49 (t, J = 7.2 Hz, 1H), 4.40 (s, 1H), 2.41 (d, J = 4.4 Hz, 1H), 2.08−1.86 (m, 2H), 1.72−1.70 (m, 2H), 1.58−1.53 (m, 3H), 1.42−1.38 (m, 1H), 1.07 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H), 0.97 (s, 3H) 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.0, 171.1, 80.5, 61.9, 53.6, 49.6, 48.0, 34.3, 33.4, 21.4, 19.9, 19.6, 19.2, 13.5, 9.7; MS m/z 249 (M^+, 22.8), 221 (10.1), 205 (42.6), 190 (74.4), 176 (100.0), 162 (51.0), 148 (11.9), 110 (10.1), 91 (12.4), 71 (42.6), 55 (20.0); HRMS m/z calcd for $C_{15}H_{23}NO_2$ M^+ 249.1729, found M^+ 249.1732. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.30; H, 9.33; N, 5.58.

(1*R*,2*S*,5*R*,8*S*)-5-Butyl-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8f): $[\alpha]^{22}_D$ −43.8 (c = 1.43, $CHCl_3$); R_f 0.46 (hexane/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 2958 (s), 1747 (s), 1697 (m) cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 4.46 (t, J = 8 Hz, 1H), 4.39 (s, 1H), 2.40 (d, J = 4.4 Hz, 1H), 2.08−1.84 (m, 2H), 1.72−1.68 (m, 2H), 1.59−1.38 (m, 6H), 1.07 (s, 3H), 0.97 (s, 3H), 0.94−0.90 (t, J = 8 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.0, 171.1, 80.4, 62.1, 53.5, 49.6, 48.0, 34.3, 31.0, 28.4, 22.1, 21.3, 19.8, 19.2, 13.6, 9.6; MS m/z 263 (M^+, 15.2), 235 (8.7), 204 (44.9), 176 (100.0), 162 (44.8), 149 (24.4), 134 (13.5), 95 (14.3), 91 (26.0), 67 (29.8), 55 (45.3), 54 (26.6); HRMS m/z calcd for $C_{16}H_{25}NO_2$ M^+ 263.1885, found M^+ 263.1879. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.99; H, 9.61; N, 5.29.

(1*R*,2*S*,5*R*,8*S*)-5-(1-Hydroxy-1-methylethyl)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (8g): $[\alpha]^{22}_D$ −15.6 (c = 1.06, $CHCl_3$); mp 159−160 °C; R_f 0.52 (hexane/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 3400 (br), 1752 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.67 (s, 1H), 4.41 (s, 1H), 2.44 (d, J = 4.4 Hz, 1H), 2.05−1.98 (m, 1H), 1.91−1.84 (m, 1H), 1.65−1.58 (m, 1H), 1.51 (s, 3H), 1.42−1.36 (m, 1H), 1.40 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.6, 169.6, 82.2, 75.3, 70.3, 54.1, 49.5, 48.2, 34.6, 28.8, 28.1, 21.6, 20.0, 19.3, 9.7; HRMS m/z calcd for $C_{15}H_{23}NO_3$ M^+ 265.1678, found M^+ 265.1670.

(1*R*,2*S*,5*S*,8*S*)-5-(1-Hydroxy-1-methylethyl)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (9g): $[\alpha]^{22}_D$ −198.0 (c = 0.96, $CHCl_3$); mp 73−74 °C; R_f 0.28 (hexane/EtOAc = 2/1); ^{1}H NMR ($CDCl_3$) δ 4.26 (d, J = 1.6 Hz, 1H), 3.93 (s, 1H, OH), 3.56 (d, J = 1.6 Hz, 1H), 2.44 (d, J = 4.8 Hz, 1H), 2.06−1.85 (m, 2H), 1.64−1.56 (m, 1H), 1.41−1.35 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.08 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.1, 170.5, 81.9, 71.9, 68.0, 53.1, 49.3, 48.9, 33.8, 26.5, 24.5, 21.5, 19.9, 19.3, 9.9; HRMS m/z calcd for $C_{15}H_{23}NO_3$ M^+ 265.1678, found M^+ 265.1667.

3-[(1*R*,2*S*,8*S*)-1,11,11-Trimethyl-4-oxo-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-5-yl]propionic acid *tert*-butyl ester (8h): $[\alpha]^{22}_D$ −41.2 (c = 2.78, $CHCl_3$); IR (NaCl, $CHCl_3$) 2983 (ms), 1742 (s), 1604 (m) cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 4.46 (s, 1H), 4.43 (t, J = 7.6 Hz, 1H), 2.47 (t, J = 7.2 Hz, 2H), 2.39 (d, J = 4.4 Hz, 1H), 2.07−1.98 (m, 2H), 2.05−1.86 (m, 2H), 1.66−1.53 (m, 1H), 1.48−1.36 (m, 1H), 1.45 (s, 9H), 1.07 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 180.3, 171.8, 170.7, 80.8, 80.4, 61.7, 53.7, 49.6, 48.1, 34.3, 31.9, 28.0, 26.1, 19.9, 19.2, 9.7; MS: m/z 335 (M^+, 5.6), 279 (66), 262 (29), 251 (12), 220 (100); HRMS m/z calcd for $C_{19}H_{29}NO_4$ M^+ 335.2097, found M^+ 335.2107. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.00; H, 8.75; N, 4.14.

General Procedure for the Hydrolysis of Alkylated Iminolactones. Compound **8** (0.4 mmol) was dissolved in 8 N HCl (2 mL) in a sealed tube with a Teflon screw cap and heated at 87 °C for 2 h. After the mixture was cooled to room temperature, water (2 mL) was added, and the mixture was extracted with diethyl ether. The chiral auxiliary **4** was recovered from the ether layer after the removal of solvent. The aqueous layer was evaporated under reduced pressure (40 mmHg) and the residue was dissolved in EtOH (2 mL). Propylene oxide (1.5 mL) was then added, and the mixture was stirred at room temperature for 30 min during which time white solids precipitated. The precipitate was collected by filtration, washed successively with cold EtOH and Et_2O, and air-dried to afford the desired α-amino acid.

D-Alanine (10a): 25 mg, 70%;$[\alpha]^{22}_D$ −9.0 (c = 1.15, 2 N HCl); lit.[18] ^{1}H NMR (D_2O) δ 3.64−3.58 (q, J = 7.2 Hz, 1H), 1.31 (d, J = 7.2 Hz, 3H), recovered **4** (63 mg, 94%).

D-α-Allylglycine (10b): 35 mg, 78%; $[\alpha]^{22}_D$ = +36.4° (c = 1.34, H_2O); lit.[19] ^{1}H NMR (D_2O) δ 5.65−5.47 (m, 1H), 5.12−5.03 (m, 2H), 3.63−3.57 (dd, J = 5.6, 6.8 Hz, 1H), 3.01−2.96 (m, 2H); recovered **4** (65 mg, 97%).

D-Phenylalanine (10c): 64 mg, 82%; $[\alpha]^{22}_D$ = +33.7 (c = 2.67, H_2O); ^{1}H NMR (D_2O) δ 7.31 (lit.[20] 7.18) (m, 5H), 3.81 (lit.[20] 3.75) (dd, J = 4.4, 8.0 Hz, 1H), 3.15 (lit.[20]3.11) (dd, J = 4.4, 14.0 Hz, 1H), 2.96 (lit.[20] 2.85) (dd, J = 8.0, 14.0 Hz, 1H); recovered **4** (65 mg, 97%).

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Supporting Information Available: X-ray data of compounds **7** and **8g**. The material is available free of charge via the Internet at http://pubs.acs.org.

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