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Selective Synthesis of Either Enantiomer of α-Amino Acids by Switching the Regiochemistry of the Tricyclic Iminolactones Prepared from a Single Chiral Source

Peng-Fei Xu† and Ta-Jung Lu*,‡

Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 40227, Republic of China, and College of Chemistry and Chemical Engineering, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, PRC

tjlu@mail.nchu.edu.tw

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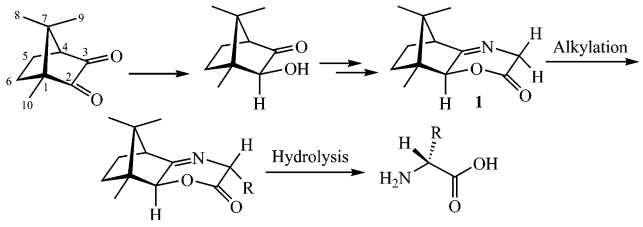
Abstract: Preparation of L-α-amino acids was easily accomplished simply by exchanging the position of the lactone group of our recently reported chiral template **1** from C_2 to C_3. The new chiral template **7** was prepared in 54% overall yield over five steps from (1*R*)-(+)-camphor. Alkylation of iminolactone **7** afforded the α-monosubstituted products in good yields and excellent diastereoselectivities (>98%). Hydrolysis of the alkylated iminolactones furnished the desired L-α-amino acids in good yields and ee with nearly quantitative recovery of chiral auxiliary **4**.

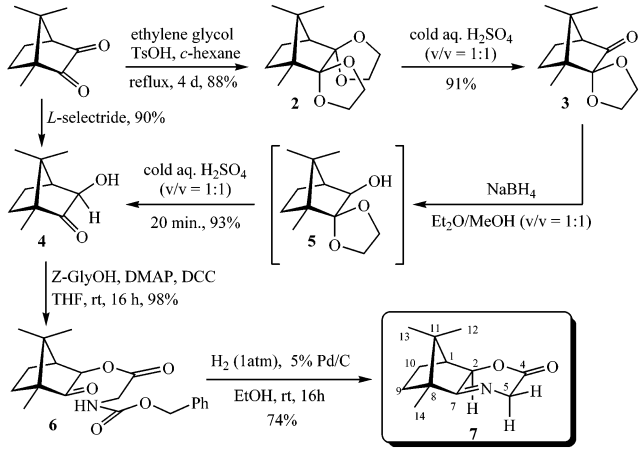
Our laboratories have been interested in the design, synthesis, and application of camphor-based chiral auxiliaries. We reported recently a highly stereocontrolled asymmetric alkylation of a tricyclic glycinate **1** derived from (1*R*)-(+)-camphor to provide D-α-amino acids in high yields with excellent level of stereoselectivity, Scheme 1.[1,2]

In principle, the antipode of the α-amino acid can be synthesized if the unnatural (1*S*)-(−)-camphor is utilized through the same sequence. Unfortunately, the unnatural camphor is much more expensive than the natural *d*-camphor, making it an uneconomical route. We have envisioned a more practical method that only requires switching the position of the hydroxyl group of the chiral auxiliary from C_2 to C_3. Namely, if the C_3-carbonyl group on (1*R*)-(+)-camphorquinone can be selectively reduced to a hydroxyl group, the resulting 3-*exo*-hydroxycamphor (**4**) should provide the enantiomer of the α-amino acid derived from 2-*exo*-hydroxyepicamphor. Thus, from the same cheap and easily accessible chiral source both enantiomers of α-amino acids can be produced. From a synthetic viewpoint, the fact that not both enantiomers of a chiral auxiliary are always readily available, a method which provides both enantiomers of products by using chiral auxiliaries derived from a single chiral source is most attractive and desirable.[3] We now would like to present our results on switching stereoselectivity by simply altering the position of the lactone group on the chiral template that delivered L-α-amino acids in high enantiomeric purity.

SCHEME 1



SCHEME 2



As depicted in Scheme 2, the required iminolactone **7** was prepared readily from camphorquinone. Regioselective reduction of the less hindered C_3-carbonyl group on (1*R*)-(+)-camphorquinone was accomplished by L-Selectride reduction to afford the 3-*exo*-hydroxycamphor in good yields but contaminated with side products.[4] Alternatively, camphorquinone was transformed into compound **4** through three highly efficient steps in 74% overall yield. Thus, camphorquinone was first refluxed with ethylene glycol in cyclohexane in the presence of catalytic amount of *p*-toluenesulfonic acid for 4 days to give a mixture of the diacetal **2** and two monoacetals (2-

† Lanzhou University.
‡ National Chung-Hsing University.

(1) Xu, P.-F.; Chen, Y.-S.; Lin, S.-I.; Lu, T.-J. *J. Org. Chem.* **2002**, *67*, 2309.

(2) For reviews on the asymmetric synthesis of α-amino acids, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (b) Williams, R. M. *Methods Mol. Med.* **1999**, *23*, 339. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321. (d) Calmes, M.; Daunis, J. *Amino acids* **1999**, *16*, 215. (e) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, *1337*, 7. (f) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (g) Meffre, P.; Le Goffic, F. *Amino Acids* **1996**, *11*, 313. (h) North, M. *Contemp. Org. Synth.* **1996**, *3*, 323. (i) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (j) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (k) Lu, T.-J. *Chemistry* (*The Chinese Chem. Soc., Taiwan China*) **1992**, *50*, 51. (l) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, 1989. (m) El Achqar, A.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319 and references cited therein.

(3) Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H. *Tetrahedron: Asymmetry* **1993**, *4*, 629.

(4) (a) Kouklovsky, C.; Pouilhes, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672. (b) Banks, M. R.; Blake, A. J.; Cadogan, J. I. G.; Doyle, A. A.; Gosney, I.; Hodgson, P. K. G.; Thorburn, P. *Tetrahedron* **1996**, *52*, 4079. Reduction utilizing the procedures reported in these two articles afforded the desired 3-*exo*-hydroxycamphor and the 2-*exo*-hydroxyepicamphor in a 6:1 ratio in a combined yield of 90%. Morris and Ryder also have pointed out that they and Professor G. Helmchen's laboratories were unable to reproduce Professor Langlois's results (Morris, D. G.; Ryder, K. S. *Synthesis* **1997**, 620).

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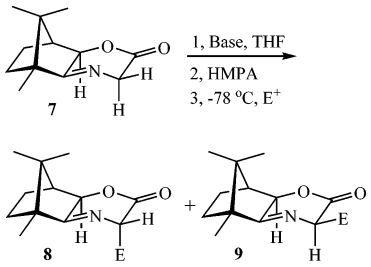
and 3-acetals) in 99% combined yield. The diacetal (62%) can be easily separated from the mixture of monoacetals (36%) by flash column chromatography.[5,6] Conversion of the mixture of monoacetals into the diacetal in 73% was accomplished smoothly by subjecting the mixture to the above reaction conditions. Therefore, the total yield of the diacetal is 88% from camphorquinone over two steps. The less hindered C_3-dioxolane of the diacetal was then selectively removed easily to furnish the 2-acetal **3** by stirring it with an ice-cold aqueous sulfuric acid solution at 0 °C for 30 min. Subsequent reduction of the C_3-carbonyl with $NaBH_4$ gave intermediate **5**, which was hydrolyzed to provide the hydroxyketone **4**. The 3-*exo*-hydroxycamphor underwent coupling reaction with Cbz-glycine under standard conditions to give rise to the ester **6** in 98% yield. Deprotection of the Cbz group and cyclization occurred simultaneously during catalytic hydrogenation to generate the desired iminolactone **7** in 74% yield.

Like its regioisomer **1**, iminolactone **7** showed a significant behavior in its NMR spectra with respect to the chemical shift and coupling pattern for the two hydrogens at C-5. Some distinctive features are: (a) The C_{5exo}-H (4.57 ppm) is a doublet with a large geminal coupling constant (J = 18.0 Hz). (b) The C_{5endo}-H (3.92 ppm) has a long-range coupling with the C_2-H and appears as a doublet of doublets (J = 18.0, 1.6 Hz). (c) The C_2-H (4.49 ppm) is a doublet (J = 1.6 Hz) as it couples to the C_{5endo}-H. (d) The chemical shifts of the two C_5-protons display a remarkably large difference ($\Delta\Delta\delta$ = 0.65 ppm), indicating the chemical environments of the two protons are considerably different.

The nature of solvent, additives, and bases is known to affect the facial selectivity in alkylation reactions. Thus, treatment of compound **7** with 1.1 equiv of KOBu^t or LDA at −30 °C for 30 min generated the corresponding anions that reacted with a variety of different electrophiles for 14 h.[7] Depending on the base and quenching electrophile, the alkylation afforded monosubstituted iminolactones in good yields and different levels of diastereoselectivity. The results in Table 1 clearly show that lithium diisopropylamide (LDA) gave the best yields. The diastereoselectivity realized in the alkylation reactions are extremely high with compound **8** as the major product.[8] In addition, the aldol reaction of the enolate also delivered the desired products smoothly with good facial selectivities (entry 9, Table 1).

The stereochemistry of the two monomethylation products was revealed by NMR coupling pattern of the C_{5exo}-H and C_{5endo}-H. The C_{5endo}-H of the *exo*-methylated product is a quartet of doublets (3.92 ppm, J = 7.2, 1.2 Hz) and the C_2-proton is a doublet (4.51 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 pi-orbital of the imine double bond in this rigid ring system. Thus, the existence of long-range coupling between these two protons clearly indicates that the methyl group is exo. On the contrary, the C_{5exo}-proton of the endo product appears as a quartet (4.63 ppm, J = 7.6 Hz) while the C_2-proton appears as a singlet (4.59 ppm). The absence of long-range coupling supports the assignment of an *endo*-methyl group.

TABLE 1. Alkylation of the Tricyclic Iminolactone 7



entry	base	E^+	yield[a] (%)	product	endo/exo[b]	% de
1	LDA	CH_3I	78	**8a** + **9a**	>99:1	>98
2	KOBu^t	CH_3I	70	**8a** + **9a**	5:3	
3	LDA	CH_2=$CHCH_2Br$	90	**8b** + **9b**	>99:1	>98
4	LDA	$C_6H_5CH_2Br$	88	**8c** + **9c**	>99:1	>98
5	KOBu^t	$C_6H_5CH_2Br$	79	**8c** + **9c**	1:5	67
6	LDA	CH_3CH_2I	68 (89)[c]	**8d** + **9d**	>99:1	>98
7	LDA	$CH_3(CH_2)_2I$	56 (85)[c]	**8e** + **9e**	>99:1	>98
8	LDA	$CH_3(CH_2)_3I$	59 (81)[c]	**8f** + **9f**	>99:1	>98
9	LDA	$(CH_3)_2C$=O	64 (90)[c]	**8g** + **9g**	7:1	75

[a] The reported yields are isolated yields after column separation. [b] The ratios were estimated by NMR integrations of the crude reaction mixtures. [c] The yields in the parentheses are the yields based on recovered starting material.

Likewise, the stereochemistry of the two endo and exo monobenzylated products also can be determined by 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 doublet of doublet (3.94 ppm, J = 4.8, 4.4, 1.2 Hz) and the C_2-proton is a doublet (4.43 ppm, J = 1.2 Hz), indicating long-range coupling between the C_{5endo}-proton and C_2-proton. Furthermore, the chemical shift of the C_2-proton is close to that of the *exo*-methylated product (4.43 vs 4.51 ppm). On the other hand, the C_{5exo}-proton of the *endo*-benzylated product appears as a doublet of doublet (4.87 ppm, J = 5.2, 4.8 Hz), while the C_2-proton appears as a singlet (2.63 ppm). The chemical shift of the C_2-proton is 1.80 ppm higher field than that of the corresponding *endo*-methylated, one presumably due to the shielding effect of the phenyl group which serves as further evidence for the endo stereochemistry of the benzyl group.

One thing noteworthy is that methylation of compound **7** using KOBu^t as the base at −78 °C gave considerably lower stereoselectivity (**8a**/**9a** = 5/3) as compared to that of utilizing LDA (Table 1, entries 1 and 2). Similarly, benzylation of iminolactone **7** with KOBu^t resulted in reversed facial selectivity but poor diastereomeric ratio (**8c**/**9c** = 1/5) (Table 1, entries 4 and 5).[9]

X-ray crystallographic determination of single crystals of compounds **7** and **8d**,**f** obtained by recrystallization

(5) When camphorquinone was refluxed in toluene under similar conditions for 10 h gave the diacetal (39%) and a mixture of two monoacetals (60%).

(6) Verdaguer, X.; Marchueta, I.; Tormo, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Helv. Chim. Acta* **1998**, *81*, 78.

(7) The optimum conditions for the alkylation of iminolactone reported in ref 1 were used in this study.

(8) 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 examined very carefully and there was no sign of the *exo*-methylated product as far as the NMR detection limit can tell.

(9) Similar trend also was observed in the alkylation of iminolactone **1**, see ref 1.

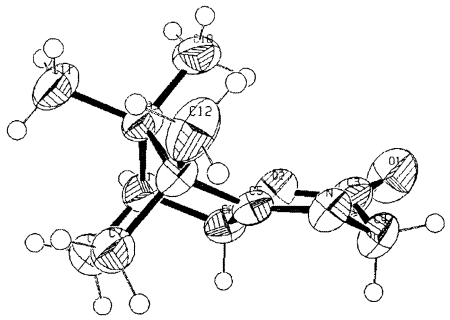


FIGURE 1. X-ray structure of compound **7**.

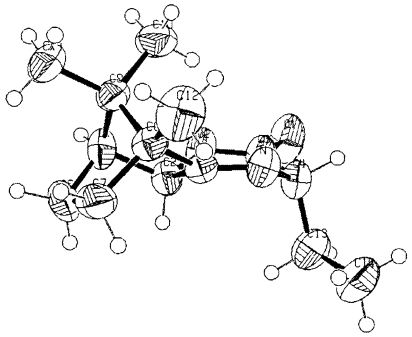


FIGURE 2. X-ray structure of compound **8d**.

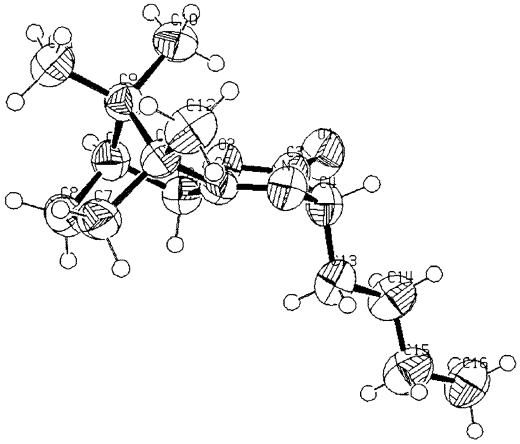
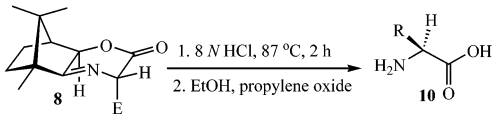


FIGURE 3. X-ray structure of compound **8f**.

from a mixture of ethyl acetate and hexane provided the structures presented in Figures 1−3.[10] A significant feature in the crystallographic structure among three compounds 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 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 are confirmed unequivocally by the fact that the hydroxypropyl group of compounds **8d** and **8f** are at the endo position in their X-ray structures (Table 2).

Upon hydrolysis of the alkylated iminolactones in 8 N HCl solution at 87 °C for 2 h,[11] the corresponding α-amino acids were obtained in good yields and enantiomeric excesses. In addition, the chiral auxiliary **4** was also recovered in nearly quantitative 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**.

TABLE 2. Hydrolysis of the Alkylated Iminolactones



entry	R	amino acid (%)	recovered auxiliary (%)	ee[a] (%)	$[\alpha]^{22}_D$
1	CH_2=$CHCH_2$	70	96	94	−33.4[b]
2	$C_6H_5CH_2$	74	94	96	−32.9[b]

[a] ee (%) values are determined by HPLC analysis utilizing a Dicel Crownpak CR(+) column. [b] The optical rotations were measured in H_2O solution.

In summary, we have developed an efficient and practical method for the preparation of natural α-amino acids starting from inexpensive and readily available (1*R*)-(+)-camphor. Good chemical yields and excellent diastereoselectivity 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. Simple switching the regiochemistry of the chiral auxiliary, derived from the same starting material, allow the preparation of α-amino acids of the opposite configuration. Consequently, our method is amenable to the synthesis of α-amino acids of either stereochemistry.

Experimental Section

(1*R*,4*S*)-2,2,3,3-Bis(ethylenedioxy)-1,7,7-trimethylbicyclo-[2.2.1]heptane (2).[6] A stirred solution of camphorquinone (9.96 g, 60 mmol), *p*-toluenesulfonic acid (0.571 g, 3.0 mmol), and ethylene glycol (16.2 mL, 300 mmol) in cyclohexane (80 mL) was heated under reflux using a Dean−Stark trap and was monitored by TLC. Additional quantities of ethylene glycol (5 mL after 15 h and 2.5 mL after 40 h) and TsOH (150 mg after 60 h) were added to the mixture. After 4 days, the reaction mixture was washed with 10% aqueous sodium hydroxide and brine, dried ($MgSO_4$), and filtered, and the cyclohexane was removed under reduced pressure. The crude product was separated by flash column (EtOAc/hexane = 1:20) to provide the desired diacetal (9.45 g, 62%) and a mixture of two monoprotected acetals (4.54 g, 36%). The mixture of monoacetals was resubmitted to the above reaction conditions to afford the diacetal (4.01 g, 73%) and recovered some monoacetal starting material (0.9 g, 20%). Diacetal **2**: R_f 0.19 (hexane/EtOAc = 4/1), mp 59−60 °C; ^{1}H NMR 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 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); IR (NaCl, $CHCl_3$) 2961 (m), 2893 (m), cm^{-1}.

(1*S*,4*S*)-3,3-Ethylenedioxy-4,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (3). To a flask containing a solution of diacetal **2**

(10) Michael N. Burnett and Carroll K. Johnson, ORTEP−III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996.

(11) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2223.

(5.09 g 20.0 mmol), cooled in an ice bath, was added an ice-cold solution of concentrated sulfuric acid−water (v/v = 1:1, 40 mL) with stirring. After 5 min. ethanol (5 mL) was added, and the reaction was stirred at 0 °C for 30 min. The reaction was extracted with diethyl ether. The combined ether layer was washed with brine and water, dried ($MgSO_4$), and filtered, and solvent was evaporated to give the title compound as a white powder (3.83 g, 91%). 2-Acetal **3**: mp 42−44 °C; $[\alpha]^{23}_D = +45.3$ ($c = 1.96$, $CHCl_3$); IR (NaCl, $CHCl_3$) 2962 (s), 2896 (m), 1758 (s) cm^{-1}; ^1H NMR δ 4.31−4.25 (m, 1H), 4.19−4.12 (m, 1H), 4.02−3.91 (m, 2H), 2.17 (d, $J = 5.6$ Hz, 1H), 2.09−2.02 (m, 1H), 1.97−1.88 (m, 1H), 1.62−1.51 (m, 2H), 1.04 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); ^{13}C NMR δ 216.5, 107.3, 66.3, 64.8, 59.2, 51.3, 43.7, 29.2, 22.7, 21.5, 18.2, 8.7; MS *m*/*z* 210 (M^+, 7.8), 182 (68.7), 165 (8.3), 113 (100.0), 99 (63.7), 95 (12.4), 69 (56.7), 67 (16.1), 55 (14.3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.56; H, 8.61.

(1*R*,3*R*,4*S*)-1,7,7-Trimethyl-2,2-ethylenedioxybicyclo[2.2.1]-heptan-3-ol (5). To a solution of 2-acetal **3** (6.31 g, 30.0 mmol) in ether (30 mL) and methanol (30 mL), cooled in an ice bath, was added sodium borohydride (1.36 g, 36 mmol, 1.2 equiv) in small batches over 10 min. The reaction mixture was stirred in an ice bath for 3 h. The reaction was washed with water, dried ($MgSO_4$), and filtered, and the organic layer was concentrated to leave an oil (6.16 g, 97%): $[\alpha]^{23}_D = -26.0$ ($c = 1.11$, $CHCl_3$); IR (NaCl, $CHCl_3$) 3473 (br), 2952 (s), 2885 (m) cm^{-1}; ^1H NMR δ 4.07−4.03 (m, 1H), 3.99−3.95 (m, 1H), 3.87−3.82 (m, 1H), 3.77−3.71 (m, 1H), 3.43 (d, $J = 5.2$ Hz, 1H), 2.54 (d, $J = 5.2$ Hz, 1H), 1.83−1.65 (m, 3H), 1.36−1.30 (m, 1H), 1.16−1.10 (m, 1H), 1.07 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H); MS *m*/*z* 212 (M^+, 16.8), 197 (6.4), 155 (54.5), 141 (74.3), 127 (15.4), 113 (24.5), 95 (20.4), 73 (100.0), 69 (45.9), 55 (23.8). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.93; H, 9.49.

(1*R*,3*R*,4*S*)-3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (4).[3] **Method A.** To a flask containing crude compound **5** (6.37 g, 30 mmol), cooled to about 0 °C, and was added an ice-cold solution of concentrated sulfuric acid−water (v/v = 1:1, 40 mL). Ice (10 g) was added after 15 min, and the mixture was extracted with ether. The combined ether layer was washed with brine and water, dried ($MgSO_4$), and filtered, and solvent was evaporated to give the 3-*exo*-hydroxycamphor as a white solid (4.84 g, 93%): mp 166−168 °C; IR (NaCl, $CHCl_3$) 3442 (br), 2957 (s), 1744 (s) cm^{-1}; ^1H NMR δ 3.74 (s, 1H), 2.10 (d, $J = 4.4$ Hz, 1H), 2.06−1.97 (m, 1H), 1.70−1.63 (m, 1H), 1.49−1.35 (m, 2H), 0.99 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H); ^{13}C NMR δ 220.2, 77.4, 57.0, 49.3, 46.8, 28.6, 25.2, 21.0, 20.1, 9.0; 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).

Method B. L-Selectride (25 mL of a 1.0 M solution, 25 mmol, 1.1 equiv) was added to a solution of camphorquinone (3.69 g, 22.2 mmol) in dry THF (80 mL) at −78 °C under argon. The reaction mixture was allowed to stir at −78 °C for 3.5 h, quenched by the addition of a 3 M solution of hydrochloric acid in methanol (40 mL), and stirred at the same temperature for another 20 min. The THF was then removed by a rotavapor, and the resulting aqueous layer was extracted into dichloromethane. Drying ($MgSO_4$), filtration, and evaporation in vacuo of the combined dichloromethane extract gave an unpleasant smelling yellow liquid. The liquid was purified by flash chromatography (hexane/ether = 9:1−3:1) to give a clear colorless oil (3.36 g, 90%) as an inseparable 6:1 mixture of hydroxycamphor **4** and 2-*exo*-hydroxyepicamphor.

(1*S*,3*R*,4*S*)-Benzyloxycarbonylaminoacetic Acid 1,7,7-Trimethyl-3-oxobicyclo[2.2.1]hept-2-yl Ester (6). A solution of 3-*exo*-hydroxycamphor **4** (4.80 g, 28.53 mmol), Cbz-glycine (6.58 g, 31.48 mmol, 1.1 equiv), and *N*,*N*-(dimethylamino)-pyridine (DMAP, 1.74 g, 14.26 mmol, 0.5 equiv) in THF (100 mL) in a 250 mL round-bottomed flask was stirred at 0 °C for 15 min, and dicyclohexylcarbodiimide (DCC, 8.83 g, 42.80 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 rt for 16 h. Precipitated 1,3-dicyclohexylurea was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (EtOAc/hexane = 1:8) gave the ester as a colorless oil (10.04 g, 98%): $[\alpha]^{23}_D = +45.6$ ($c = 1.94$, $CHCl_3$); IR (NaCl, $CHCl_3$) 3366 (br), 3033 (m), 1754 (s), 1746 (s) cm^{-1}; ^1H NMR δ 7.36−7.34 (m, 5H), 5.24 (b, 1H), 5.12 (s, 2H), 4.84 (s, 1H), 4.02 (d, $J = 5.6$ Hz, 2H), 2.13 (d, $J = 4.4$ Hz, 1H), 1.79−1.62 (m, 2H), 1.58−1.43 (m, 2H), 0.95 (s, 6H), 0.92 (s, 3H); ^{13}C NMR δ 213.6, 169.3, 156.2, 136.1, 128.4, 128.3, 128.1, 128.0, 67.0, 57.2, 48.2, 46.5, 42.7, 28.4, 24.7, 20.6, 19.5, 9.0; MS *m*/*z* 359 (M^+, 23.1), 316 (1.2), 258 (2.8), 224 (6.6), 192 (15.2), 152 (32.3), 139 (66.2), 108 (52.0), 91 (100.0), 83 (25.4), 55 (20.2); HRMS *m*/*e* calcd for $C_{20}H_{25}NO_5$ M^+ 359.1738, found M^+ 359.1733. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.85; H, 6.98; N, 3.92.

(1*S*,2*R*,8*R*)-8,11,11-Trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]-undec-6-en-4-one (7). To a 100 mL two-necked flask was charged with ester **6** (7.19 g, 20 mmol) and 5% palladium on activated carbon (0.90 g). The flask was then evacuated and filled with hydrogen three times. Freshly dried ethanol (60 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 rt for 14 h. The catalyst was removed by filtration and the filtrate was concentrated to afford the crude product. The residue was purified by column chromagraphy (EtOAc/hexane = 1:4) to furnish the desired iminolactone as a colorless solid (3.07 g, 74%): mp 103−104 °C; $[\alpha]^{22}_D = +266.3$ ($c = 1.35$, $CHCl_3$); IR (NaCl, $CHCl_3$) 2972 (m), 1758 (s), 1685 (m) cm^{-1}; ^1H NMR δ 4.57 (d, $J = 18$ Hz, 1H), 4.49 (d, $J = 1.6$ Hz, 1H), 3.95−3.90 (dd, $J = 18$ Hz, 1.6 Hz, 1H), 2.28 (d, $J = 4.8$ Hz, 1H), 2.13−2.06 (m, 1H), 1.83−1.75 (m, 1H), 1.62−1.55 (m, 1H), 1.41−1.34 (m, 1H), 1.07 (s, 3H), 0.98 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 169.2, 79.9, 52.9, 49.3, 47.7, 29.7, 25.6, 20.2, 19.9, 10.1; MS *m*/*z* 207 (M^+, 64.0), 192 (5.1), 179 (100.0), 164 (13.7), 150 (32.0), 136 (31.9), 111 (51.2), 110 (22.7), 82 (44.0), 69 (54.7), 55 (15.4), 53 (10.7); HRMS *m*/*e* calcd for $C_{12}H_{17}NO_2$ M^+ 207.1268, found M^+ 207.1259. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.48; H, 8.27; N, 6.75. Found: C, 69.54; H, 8.26; N, 6.44.

Alkylation of Iminolactone. General Procedure. 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.

Iminolactone (292 mg, 1.4 mmol) in dry THF (8 mL) was added dropwise over a period of 10 min into the above fleshly prepared LDA solution at −30 °C, and the resulting solution was stirred at −30 °C for 90 min. Hexamethylphosphoric triamide (HMPA) (distilled from CaH_2, 0.73 mL, 4.2 mmol, 3 equiv) was then added to the reaction mixture, which was subsequently cooled to −78 °C. While the reaction mixture was kept at −78 °C, a solution of alkyl halides (4.2 mmol, 3 equiv) in dry THF (8 mL), precooled to 0 °C, was slowly added to the reaction with the needle contacting the wall of the flask over 10 min.[1] The well-stirred reaction was kept at −78 °C for another 14 h.

A solution of aqueous acetic acid (2 M, 2 mL) was added to the mixture to quench the reaction. The reaction was warmed to rt, washed with saturated aqueous LiCl, dried ($MgSO_4$), and concentrated to give the crude product. The crude product was purified by column chromatography to yield desired compounds.

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Supporting Information Available: Spectral and analytical data for compounds **8a**−**g** and **9a**,**c**,**g**; general procedure and reaction yields for hydrolysis of alkylated iminolactones; and X-ray data of compounds **7** and **8d**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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