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Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids by Diastereoselective Alkylation of Camphor-Based Tricyclic Iminolactone

Peng-Fei Xu,[†] Shuo Li,[†] Ta-Jung Lu,*[,‡] Chen-Chang Wu,[‡] Botao Fan,[§] and Georgia Golfis[§]

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, PRC, Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 40227, Republic of China, and ITODYS-CNRS UMR 7086, University Paris 7, 1 rue Guy de la Brosse, 75005 Paris, France

tjlu@dragon.nchu.edu.tw

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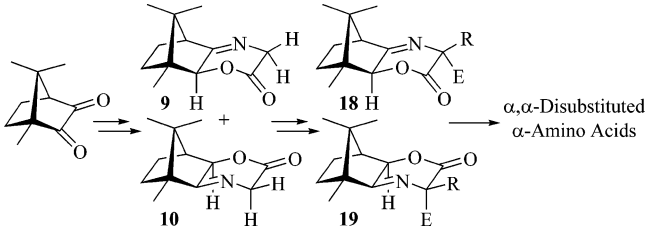

A novel and convenient route for the preparation of chiral tricyclic iminolactones **9** and **10** from camphorquinone has been developed. Alkylation of iminolactones **9** and **10** provided iminolactones **16** and **17** in high yields which were, in turn, alkylated again to afford the α,α-disubstituted products in good yields (70−90%) and excellent diastereoselectivities (>98%). Hydrolysis of the alkylated iminolactones furnished the desired α,α-disubstituted α-amino acids in good yields and high enantiomeric excesses with good recovery yields of the chiral auxiliary **12** and **13**. The extremely high endo-face selectivity for alkylation is discussed using semiempirical (MOPAC 93) calculations.

Introduction

Optically active nonproteinogenic amino acids[1] are valuable compounds of high interest not only owing to their remarkable pharmacological and biological activities but also for their role as an investigative topographic probe for bioactive conformations of peptides and the mechanisms of enzyme reactions.[2] There is a growing demand for optically active, ideally enantiomerically pure, uncommon amino acids resulting from the recent progresses in molecular biology and protein engineering technologies.[3] Numerous methods to synthesize these compounds have been reported, such as Schöllkopf's bislactim ether **1**,[4] Williams' diphenyloxazinones **2**,[5] Seebach's oxazolidinones **3**,[6] Oba and Alcaraz's diketopiperazine **4**[7] and **5**,[8] Cativiela's pinanone derivative **6**,[9] as well as Nájera's oxazinone **7**,[10] and pyrazinone **8**.[11] There is a promising trend in the area

[†] Lanzhou University.
[‡] National Chung-Hsing University.
[§] University Paris 7.

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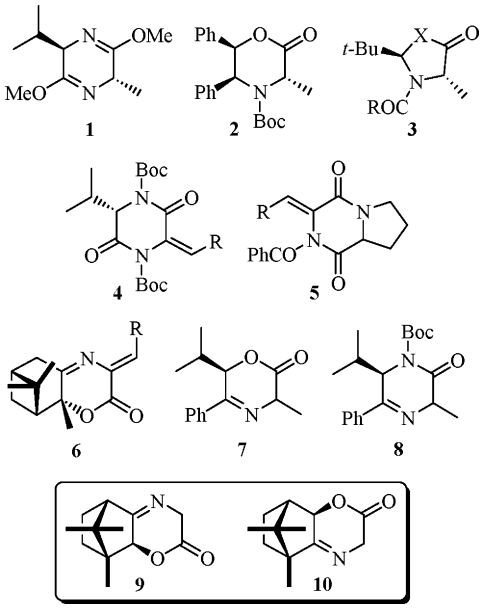
of chiral phase-transfer catalyst (PTC) catalyzed α-alkylation of glycine derivatives.[12] Most of these chiral templates, derived from alanine or acting as alanine equivalents, are very useful in the synthesis of α-methyl α-amino acids.[13] Unfortunately, the majority of them are not readily amenable to the synthesis of non-α-methyl α,α-disubstituted α-amino acids.

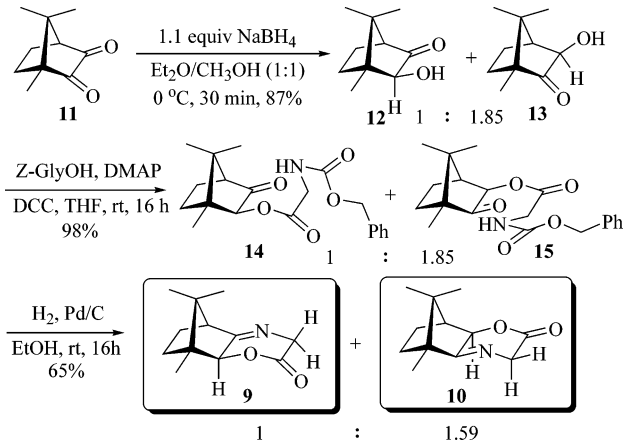
Numerous methods have been developed for the synthesis of α-amino acids, while chiral glycine equivalents occupy an important niche in amino acid synthesis.[14] Recently, we have reported two novel chiral tricyclic iminolactones, (1*R*,2*S*,8*S*)-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.$0^{2,7}$]undec-6-en-4-one (**9**)[15] and (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 (**10**),[16] prepared from (1*R*)-(+)-camphor as glycine equivalents, which have been successfully applied to the asymmetric synthesis of α-monosubstituted α-amino acids. In this paper, we report a new and shorter synthesis of compounds **9** and **10** as well as their application to the asymmetric synthesis of α,α-disubstituted α-amino acids.



Results and Discussion

A new route for the preparation of chiral tricyclic iminolactones **9** and **10** from camphorquinone is illustrated in Scheme 1.

SCHEME 1



1. The two carbonyl groups of camphorquinone were reduced with sodium borohydride at ca. 0 °C in a diethyl ether/methanol (v/v = 1:1) mixture to afford 2-*exo*-hydroxyepicamphor (**12**) and 3-*exo*-hydroxycamphor (**13**) in a ratio of 1:1.85 as an inseparable mixture. The mixture of hydroxy ketones **12** and **13** was esterified with *N*-Cbz-glycine, DMAP, and DCC in dry THF to yield again a 1:1.85 ratio of inseparable mixture of regioisomers **14** and **15** in 98% yield as a viscous oil after column chromatography. The deprotection of the Cbz group by catalytic hydrogenation was carried out in absolute ethanol under a hydrogen atmosphere (1 atm) in the presence of 5% palladium on active carbon as a catalyst for 4 h, and the reaction mixture was then stirred for another 12 h at rt after removal of the hydrogen balloon. Fortunately, two easily separable iminolactones **9** and **10** were obtained after flash chromatography in a ratio of 1:1.59 (**9**: $R_f = 0.14$, **10**: $R_f = 0.38$; EtOAc/hexanes = 1:2).

In accord with our previous results, excellent stereoselectivity has been achieved in the alkylation of iminolactones **9** and **10** when LDA was employed as the base to give the monoalkylated products **16** and **17**, respectively, as the sole detectable products in good yields (Scheme 2). The alkylation of compounds **16** and **17** was performed under the same conditions used in the alkylation of iminolactones **9** and **10** except 1.3 equiv of LDA was utilized, and the results are collected in Table 1. Interestingly, the enolates of iminolactones **16** and **17** always attack the electrophiles from the endo face regardless the size of the electrophiles and generate the stereocenter with virtually complete diastereoselectivity. Consequently, the configuration of the α,α-disubstitued α-amino acid can be controlled by employing proper order of alkylations of iminolactones **9** and **10**.

Encouraged by the above results, alkylation of mixtures of compounds **16** and **20**, as well as **17** and **21** were carried out using the same reaction conditions as above. As anticipated, excellent results were observed as summarized in Table 2.

The chemical shifts of characteristic protons of compounds **18** and **19** are compiled in Table 3.[17] The C_2-H of compound **18a** appears at a much higher field (δ 2.24) than those of the same proton of compounds **18b** and **18c** (δ 4.27 and 4.25) revealing that it is shielded by the phenyl group of the *endo*-benzyl substituent. The C_2-H of compounds **18e** and **18d** appear

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(17) Like their monosubstituted iminolactones, compounds **18** and **19** exhibit similar distinctive proton NMR absorptions, which are unique to the rigid structure systems; see refs 13 and 14.

SCHEME 2

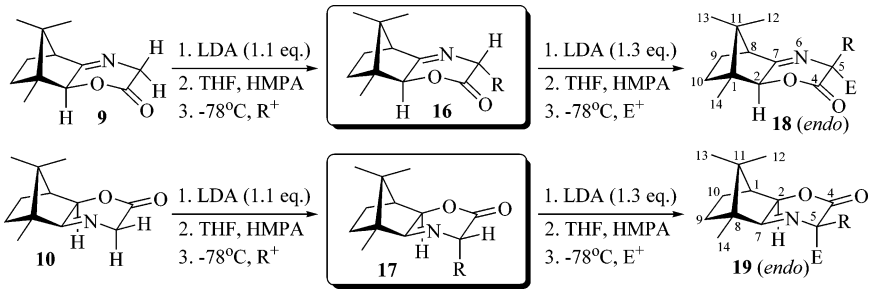
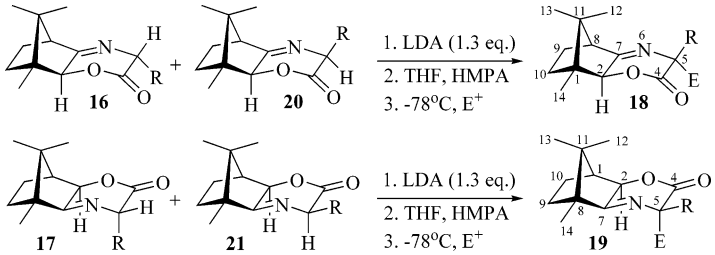


TABLE 1. Alkylation of Alkylated Tricylic Iminolactone 16 and 17

entry	substrate	R	E^+	product	yield[a] (%)	endo/exo[b]	% de[c]
1	**16**	CH_3	$C_6H_5CH_2Br$	**18a**	80	>99:1	>98
2	**16**	$C_6H_5CH_2$	CH_3I	**18b**	82	>99:1	>98
3	**16**	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	**18c**	75	>99:1	>98
4	**16**	$C_6H_5CH_2$	$C_6H_5CH_2Br$	**18d**	74 (90)[d]		
5	**16**	CH_2=$CHCH_2$	$C_6H_5CH_2Br$	**18e**	78	>99:1	>98
6	**16**	CH_2=$CHCH_2$	$CH_3(CH_2)_3I$	**18f**	80	>99:1	>98
7	**17**	CH_3	$C_6H_5CH_2Br$	**19a**	75	>99:1	>98
8	**17**	$C_6H_5CH_2$	CH_3I	**19b**	88	>99:1	>98
9	**17**	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	**19c**	85	>99:1	>98
10	**17**	CH_2=$CHCH_2$	$C_6H_5CH_2Br$	**19d**	90	>99:1	>98
11	**17**	$C_6H_5CH_2$	H^+	**19e**	71	>99:1	>98
12	**17**	CH_3	CH_2=$CHCH_2Br$	**19f**	75	>99:1	>98

[a] The reported yields are isolated yields after column separation. [b] The ratios were estimated by NMR integrations of the crude reaction mixtures on a Varian Mercury-400 NMR spectrometer. [c] The diastereomeric excesses were determined by HPLC analyses of the crude reaction mixture. [d] The numbers in parentheses are the yields based on recovered starting material.

TABLE 2. Alkylation of Mixtures of Monosubstituted Iminolactones



entry	substrate	R	E^+	product	yield[a] (%)	endo/exo[b]	% de[c]
1	**16** + **20**	CH_3	$C_6H_5CH_2$	**18a**	80 (88)[d]	>99:1	>98
2	**16** + **20**	$C_6H_5CH_2$	CH_3	**18b**	82	>99:1	>98
3	**16** + **20**	$C_6H_5CH_2$	CH_2=$CHCH_2$	**18c**	81	>99:1	>98
4	**16** + **20**	CH_3	CH_2=$CHCH_2$	**18g**	93	>99:1	>98
5	**17** + **21**	CH_3	$C_6H_5CH_2$	**19a**	91	>99:1	>98
6	**17** + **21**	$C_6H_5CH_2$	CH_3	**19b**	83	>99:1	>98
7	**17** + **21**	$C_6H_5CH_2$	CH_2=$CHCH_2$	**19c**	86	>99:1	>98

[a] The reported yields are isolated yields after column separation. [b] The ratios were estimated by NMR integrations of the crude reaction mixtures on a Varian Mercury-400 NMR spectrometer. [c] The diastereomeric excesses were determined by HPLC analyses of the crude reaction mixture. [d] The number in parentheses is the yield based on recovered starting material.

at a still higher field (δ 2.04 and 1.87) than that of compound **18a**, suggesting that the *exo*-allyl is larger than the corresponding methyl group and the *exo*-benzyl is larger still which forces the *endo*-benzyl group more and more downward. Hence, the phenyl group gets closer and closer to C_2-H resulting in more effective shielding. Similar chemical shift changes are observed for the $C_{10\alpha}$−H of compounds **18a**−**e**, further supporting the assigned endo-stereochemistry of products **18a**−**e**. On the other hand, the C_{12}-CH_3 of compounds **18a**−**e** show an opposite trend, indicating that the methyl group is shielded by the *exo*-benzyl group more and more effectively from compounds **18b** to **18c** and to **18d**. Exactly the same trends can be found for compounds **19a**−**e**, suggesting that the electrophiles reacted with the enolate from the bottom face to afford the endo isomers as the predominant product.

TABLE 3. Chemical Shifts (ppm) of Characteristic Protons of Compounds 18 and 19

compd	R	E	δ_{C_2-H}	$\delta_{C_{10\alpha}-H}$	$\delta_{C_{12}-CH_3}$
18a	CH_3	$C_6H_5CH_2$	2.24	0.68−0.62	0.75
18b	$C_6H_5CH_2$	CH_3	4.27	1.33−1.29	0.21
18c	$C_6H_5CH_2$	CH_2=$CHCH_2$	4.25	1.30−1.21	0.05
18d	$C_6H_5CH_2$	$C_6H_5CH_2$	1.87	0.48−0.42	−0.18
18e	CH_2=$CHCH_2$	$C_6H_5CH_2$	2.04	0.57−0.50	0.73
19a	CH_3	$C_6H_5CH_2$	2.40	0.66−0.62	0.69
19b	$C_6H_5CH_2$	CH_3	4.43	1.32−1.26	0.09
19c	$C_6H_5CH_2$	CH_2=$CHCH_2$	4.41	1.25−1.19	−0.07
19d	CH_2=$CHCH_2$	$C_6H_5CH_2$	2.18	0.59−0.56	0.67
19e	$C_6H_5CH_2$	H	4.43	1.35−1.28	0.71

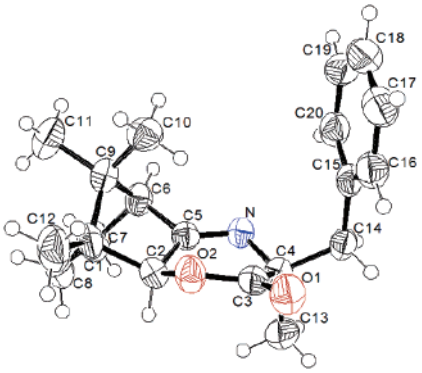


FIGURE 1. X-ray structure of compound **18b**.

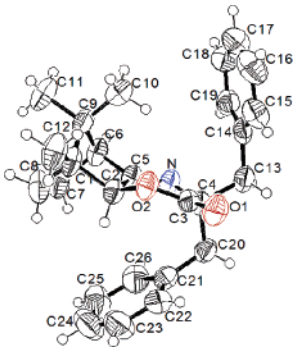


FIGURE 2. X-ray structure of compound **18d**.

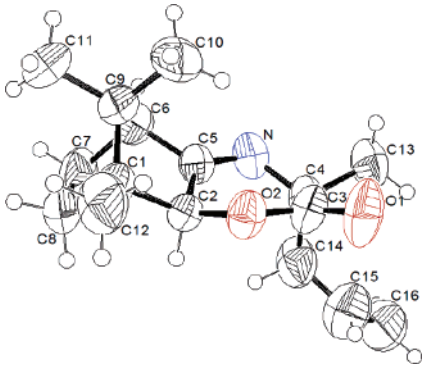


FIGURE 3. X-ray structure of compound **18g**.

Recrystallization from ethyl acetate and hexanes afforded compounds **18b**, **18d**, **18g**, and **19e**. Their X-ray crystallographic structures are shown in the Figures 1−4, respectively.[18] It is evident that the iminolactone ring, fused with the rigid camphor frame, is in a boat conformation with the C_2-proton and the C_{5endo}-group at the flagpole positions. The X-ray structure of compound **18b** clearly demonstrates that its C_{12}-CH_3 is situated in front of the shielding zone of the phenyl ring of the *exo*-benzyl group, explaining its unusual upfield position in ^{1}H NMR. The phenyl ring of the *exo*-benzyl group of compound **18d** is pushed further up by the *endo*-benzyl group, which shields the C_{12}-CH_3 more effectively, and thus, the signal of this methyl appeared at δ −0.18. Moreover, the C_2-H falls in the shielding cone of the phenyl ring of the *endo*-benzyl group of compound **18d**, making it to appear at δ 1.87, which is considerably higher field than the corresponding C_2-H of other alkylated iminolactones. Consequently, the absolute stereochemistry established by the X-ray structures is in accord with the observed characteristic ^{1}H NMR absorptions (Table 3). As a result, the attack of the enolate takes place from the endo face is established unequivocally.

(18) The X-ray crystallographic structures of compounds **18b**, **18d**, **18g**, and **19e** have been submitted to the Cambridge Crystallographic Data Centre. The CCDC numbers for compounds **18b**, **18d**, **18g**, and **19e** are CCDC 277545, CCDC 277543, CCDC 277544 and, CCDC 277542, respectively.

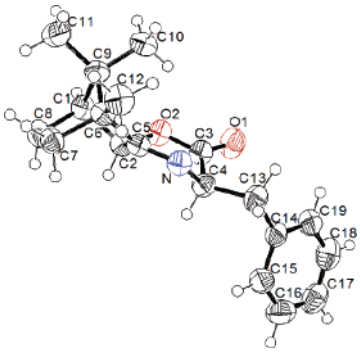


FIGURE 4. X-ray structure of compound **19e**.

TABLE 4. Hydrolysis of the Dialkylated Iminolactones 18 and 19

entry	R	E	amino acid (%)	recovered auxiliary (%)	ee[a] (%)	$[\alpha]^{22}_D$[b]
18a	CH_3	$C_6H_5CH_2$	86	80	98.2	+21.6
18b	$C_6H_5CH_2$	CH_3	88	82	97.7	−21.5
18c	$C_6H_5CH_2$	CH_2=$CHCH_2$	82	75	98.1	+26.8
19a	CH_3	$C_6H_5CH_2$	89	80	98.2	−21.6
19b	$C_6H_5CH_2$	CH_3	89	85	97.7	−21.5
19c	$C_6H_5CH_2$	CH_2=$CHCH_2$	87	84	98.9	−27.0
19f	CH_3	CH_2=$CHCH_2$	90	85	98.2	−28.0

[a] ee (%) values are determined by comparison with [α] values in the literature; see the Experimental Section. [b] The optical rotations were measured in H_2O solution on a Perkin-Elmer PE-241 polarimeter.

Representative dialkylated tricyclic iminolactones **18** and **19** were hydrolyzed with 2 N NaOH at rt for 2 h and then with 6 N HCl at 92 °C for 3 h[10] to afford the corresponding optically active α,α-disubstituented α-amino acids in good yields (Table 4) and enantiomeric excesses with good recovery yields of the chiral auxiliaries **12** and **13**. The configuration of the α-amino acids is in agreement with that assigned to the respective dialkylated tricyclic iminolactone precursors.

Theoretical Investigation

To gain an insight on the mechanism of and to look for an explanation for the high stereoselectivity of the substitution reaction from an energetic point of view, we turned to a systematic quantum chemistry study.[19]

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SCHEME 3

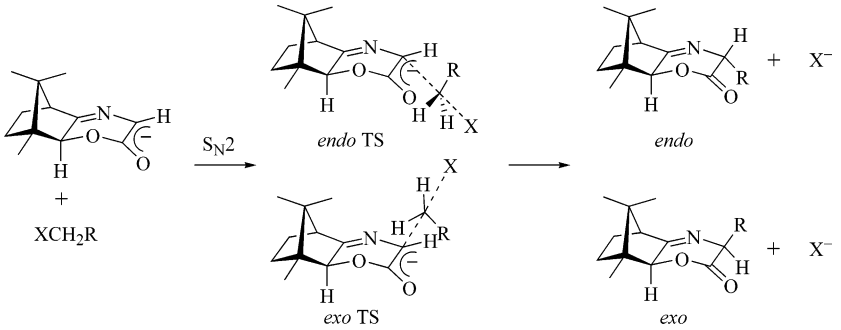


TABLE 5. Energies for Endo and Exo S_N2 Mechanisms (kcal/mol)[a]

	endo TS			exo TS			
substituent (RX)	E_a	ΔE	$\Delta E'$	E_a	ΔE	$\Delta E'$	ΔE_a
CH_3I	29.84	26.06	−1.37	34.52	29.92	−0.65	4.68
CH_3CH_2I	35.87	32.22	−0.72	41.64	36.24	0.37	5.77
$CH_3CH_2CH_2I$	36.12	33.08	0.97	40.79	37.08	0.99	4.67
$CH_3CH_2CH_2CH_2I$	36.04	32.99	1.71	40.23	36.98	2.11	4.19
$CH_2{=}CHCH_2Br$	28.83	25.68	−5.69	32.99	29.15	−4.18	4.16
$C_6H_5CH_2Br$	29.73	26.48	−5.66	33.75	29.91	−5.70	4.02

[a] $E_a = E$(TS) − E(reaction intermediate); $\Delta E = E_{ts} - E_{total}$(reactants*). Reactants*: enolate of iminolactone; $\Delta E' = E_{total}$(products) − E_{total}(reactants). $\Delta E_a = E_a$(exo TS) − E_a(endo TS)

Because of the large amount to be computed, semiempirical method AM1,[20] proven to be reliable for the calculation of transition state,[21] was employed. Full geometry optimization were carried out at the RHF level, using the Broyden−Fletcher−Goldfarb−Shanno function minimizer (BFGS).[22] All calculations were performed on an SGI workstation using AM1 computation implemented in MOPAC 93.[23]

Monosubstitution. The S_N2 mechanism of monosubstitution of the tricyclic iminolactone was studied first (Scheme 3), and the calculated results are summarized in Table 5.

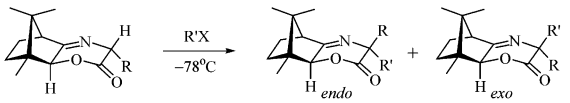
All the results were obtained in the gas phase. The differences in heat of formation for the reactants and the products are small (Table 5); however, when the difference between the enthalpies of formation for HI (g) and I^- (aq) (about 20 kcal/mol) is taken into account, the reaction become exothermal and highly energetically favored.

The activation energies, calculated without the consideration of solvation effect, for all reactions are found in the range from 28 to 41 kcal/mol. The differences in E_a range from 4.02 to 5.77 kcal/mol depending on the reaction. This result is in agreement with experimental data in which the endo diastereomer is the predominant product.[15,16] Since the difference between the enthalpy of formation of the endo product and exo product is small, indicating that the high facial selectivity observed is not controlled by thermodynamics; instead, the S_N2 reaction is most likely kinetically controlled.

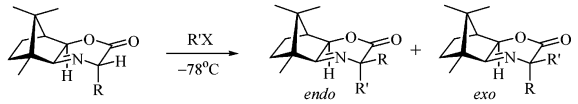
The geometry of the intermediate is depicted in Figure 5 for the illustrated reaction (MeI). The intermolecular distances in the intermediate indicate that the approach from the axial (endo) direction is easier than that from the equatorial (exo) direction (3.01 Å against 3.30 Å). This difference in distance decreases in the corresponding transition states (Figure 6). The steric hindrance resulting from the C_{12}-methyl group is presumably the major factor for the observed high facial selectivity. The electrostatic potential isodensity surfaces of the two transition states obtained from ab initio calculations are shown in Figure 7. It is observed that the presence of the methyl group pushes the nucleophilic attack to deviate from the principal axis.

Disubstitution. The substitution reactions of the two isomeric iminolactones were studied next:

Compound 16



Compound 17



R = $-CH_3$ (R^1), $-CH_2C_6H_5$ (R^2), $-CH_2CH{=}CH_2$ (R^3)

X = Br, I

R' = $-CH_3$ (R'^1), $-CH_2C_6H_5$ (R'^2), $-CH_2CH{=}CH_2$ (R'^3), $-(CH_2)_3CH_3$ (R'^4)

The reactions, like in the case of monosubstitution, can proceed easily since the energy barriers are relatively low. Furthermore, in both compounds **16** and **17**, the *endo* attack is favored by kinetics. Figures 8 and 9 show, respectively, two examples of the transition state for reactions of compounds **16** and **17**. Compared with monosubstitution, the distances between the leaving atom (X) and its binding carbon, and between this carbon atom and the enolate, are both slightly elongated, which might be due to the presence of the first substituent. In Table 6, the energy differences between these two nucleophilic attacks for compounds **16** and **17** are compared. The differences range from 1.32 to 5.57 kcal/mol depending on the reactions, which

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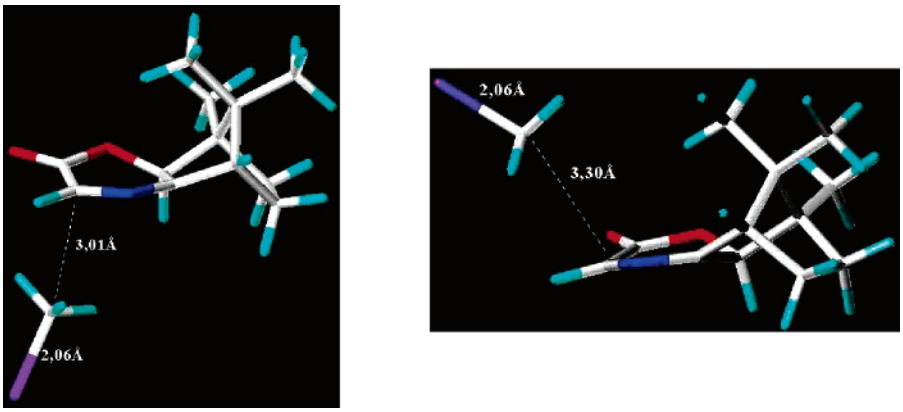

FIGURE 5. Geometries of endo and exo intermediates: (left) axial nucleophilic attack; (right) equatorial nucleophilic attack.

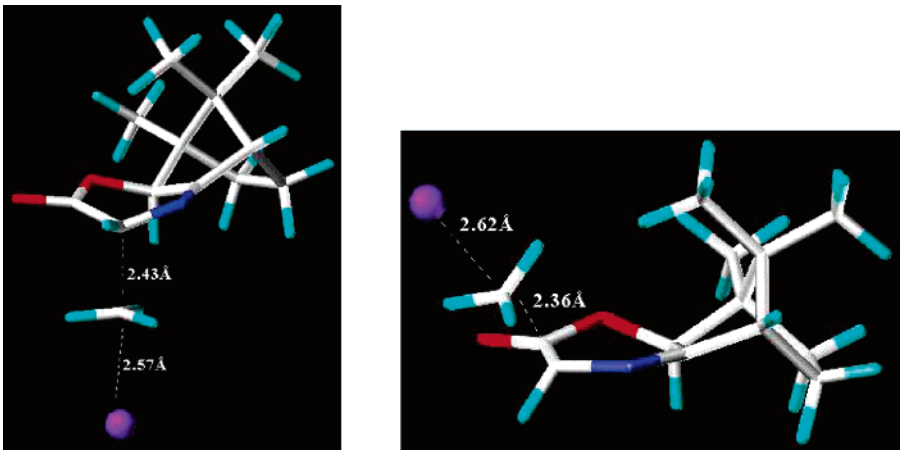

FIGURE 6. Geometries of endo and exo transition states: (left) axial nucleophilic attack; (right) equatorial nucleophilic attack.

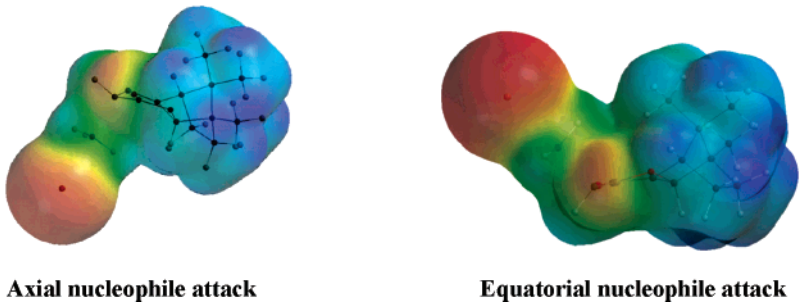

FIGURE 7. Electrostatic potential isodensity surfaces of two transition states (equatorial and axial nucleophilic attacks), obtained from ab initio calculations.

are similar to the situations for monosubstitution reactions. The results suggest that the attack is more favored from the endo direction to furnish the major product with R′ at the axial position. This is in good agreement with experimental results and can explain the high stereoselectivity of this type of reaction.

Ab Initio Calculations. To validate the AM1 semiempirical results, ab initio calculations for two transition states were carried out at the HF level using the DFT method. The B3LYP (Beck's three-parameter hybrid exchange function and the Lee−Yang−Parr correlation function) and the Pople 6-31G(d) basis set were used for the calculations except for the I atom, which was treated with the 3-21G* basis set. All calculations were performed with Gaussian 98 software at an SGI Octane 2 workstation. The geometries obtained from this computation, shown in Figure 10, are very close to those optimized (Figure 6, 2.43 Å) using the AM1 method.

The structures of both transition states have been verified by the calculation of frequency. For each geometry, we obtained one imaginary frequency (−338.98 cm^{-1} for axial attack TS and −383.37 cm^{-1} for equatorial attack TS). Moreover, the energy difference between the two transition states (axial and equatorial attack) is 3.30 kcal/mol ($\Delta E = E_e - E_a$). In AM1 calculations for this system, the energy difference is 3.86 kcal/

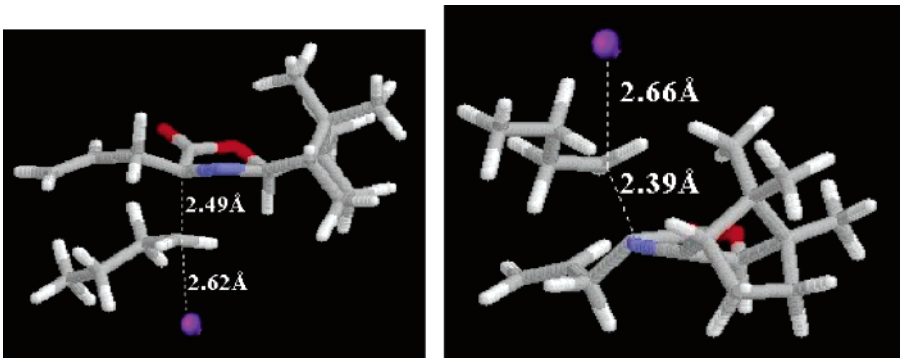

FIGURE 8. Geometries of transition states for alkylation of compound 16 (R = $CH_2CH{=}CH_2$, R′ = *n*-Bu): (left) axial nucleophile attack; (right) equatorial nucleophile attack.

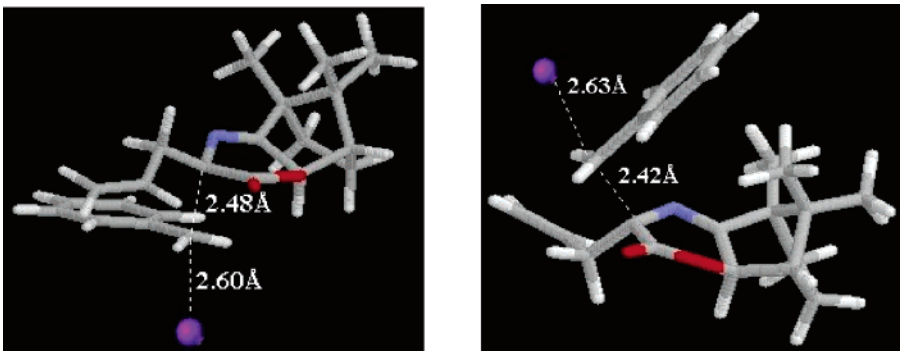

FIGURE 9. Geometries of transition states for alkylation of isomer **2** (R = $CH_2CH{=}CH_2$, R′ = $CH_2C_6H_5$): (left) axial nucleophilic attack; (right) equatorial nucleophilic attack.

TABLE 6. Energy Difference between Exo and Endo Attack (kcal/mol)

reaction compd **16**					reaction compd **17**				
R	R′	ΔE_{exo}	ΔE_{endo}	$\Delta(\Delta E)^a$	R	R′	ΔE_{exo}	ΔE_{endo}	$\Delta(\Delta E)^a$
CH_3	$CH_2C_6H_5$	35.58	32.25	3.33	CH_3	$CH_2C_6H_5$	35.40	32.15	3.25
$CH_2{=}CHCH_2$	$CH_2C_6H_5$	38.80	35.91	2.89	$CH_2{=}CHCH_2$	$CH_2C_6H_5$	38.25	36.10	2.15
$CH_2{=}CHCH_2$	*n*-Bu	41.19	39.62	1.57	$CH_2C_6H_5$	$CH_2C_6H_5$	36.77	33.05	3.72
$CH_2C_6H_5$	CH_3	36.63	31.06	5.57	$CH_2C_6H_5$	$CH_2{=}CHCH_2$	37.42	33.76	3.66
$CH_2C_6H_5$	$CH_2{=}CHCH_2$	37.31	35.99	1.32					
$CH_2C_6H_5$	$CH_2C_6H_5$	37.02	34.77	2.25					

[a] $\Delta(\Delta E) = \Delta E_{exo} - \Delta E_{endo}$.

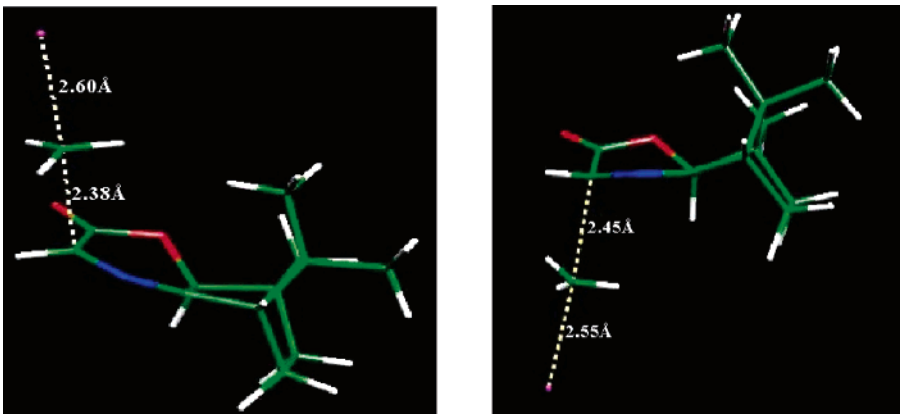

FIGURE 10. Geometries of transition states obtained from ab initio calculations.

mol. Therefore, the results obtained from AM1 computations can be considered as valid. Furthermore, the systematic errors should be reduced again for a such comparative study.

Conclusion

In conclusion, we have developed an efficient and practical method for the preparation of α,α-disubstituented α-amino acids

starting from inexpensive and readily available (1*R*)-(+)-camphor. Good chemical yields and excellent diastereoselectivity were realized to produce the α,α-disubstituted α-amino acids in high optical purity. The fact that the chiral auxiliaries can be recycled without loss of optical integrity renders the present method an economical method for the preparation of α,α-disubstituted α-amino acids. Consequently, our method makes it possible to synthesize a wide range of α,α-disubstituted α-amino acids of either stereochemistry.

Experimental Section

General Methods. All alkylation reactions were conducted in flame-dried, long-necked (15 cm), round-bottomed flasks fitted with rubber septa under an argon atmosphere. 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, and *n*-butylithium in hexanes (nominally 1.6 M) was purchased from a commercial supplier and titrated before each use. Thin-layer chromatography plates were 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. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz; ^{13}C NMR spectra were recorded at 100 MHz. Chloroform (δ = 7.27 ppm) or deuterium oxide (δ = 4.60 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. The optical rotations were measured in $CHCl_3$ solution with a cuvette of 1 dm length. For chiral alkylations, diastereomeric ratios were determined by the integration of the ^{1}H NMR spectra. The ee value of the α-amino acids obtained from hydrolysis of the alkylated iminolactones was determined by measuring the optical rotation or by HPLC analysis on a Crownpak CR(+) column.

(1*S*,3*S*,4*R*)-3-Hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one (12) and (1*R*,3*R*,4*S*)-3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one (13). To a solution of camphorquinone **11** (4.986 g 30.0 mmol) in a mixture of ether (30 mL) and methanol (30 mL), cooled in an ice bath, was added sodium borohydride (0.298 g, 7.88 mmol, 1.05 equiv) in small batches, and the reaction mixture was stirred in an ice bath for 30 min by which time the color of the reaction changed into pale yellow. The reaction was then washed with cold water (3 × 10 mL), dried ($MgSO_4$), filtered, and the organic layer was evaporated to give a white powder as an inseparable mixture of two hydroxy ketones. The ^{1}H NMR of the crude reaction indicated that the hydroxyl ketones were pure enough for the subsequent reactions and therefore was used without further purification (4.39 g, 87%; **12**/**13** = 1:1.85).

(1*R*,2*S*,4*S*)-Benzyloxycarbonylaminoacetic Acid 1,7,7-Trimethyl-3-oxobicyclo[2.2.1]hept-2-yl Ester (14) and (1*S*,2*R*,4*R*)-Benzyloxycarbonylaminoacetic Acid 4,7,7-Trimethyl-3-oxobicyclo-[2.2.1]hept-2-yl Ester (15). A solution of the mixture of 2-*exo*-hydroxyepicamphor (**12**) and 3-*exo*-hydroxycamphor (**13**) (5.046 g, 30.0 mmol), Cbz-glycine (6.897 g, 33.0 mmol, 1.1 equiv), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 1.833 g, 15.0 mmol, 0.5 equiv) in THF (120 mL) in a 250 mL flask was stirred at 0 °C for 15 min, and a solution of dicyclohexylcarbodiimide (DCC, 9.285 g, 45.0 mmol, 1.5 equiv) in THF (30 mL) was then added dropwise to the reaction via a syringe pump over 40 min. 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 reduce pressure. Purification of the residue by flash column chromatography (EtOAc/hexanes = 1:8) gave an inseparable mixture of two esters as a colorless viscous oil (10.56 g, 98%; **14**/**15** = 1:1.85).

(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 (9) and (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 (10). A 100 mL two-necked flask containing the mixture of esters **14** and **15** (5.408 g, 15 mmol) and 5% palladium on activated carbon (0.604 g) was evacuated and filled with hydrogen three times. Freshly dried 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 rt (ca. 25 °C) for 14 h. The catalyst was removed by filtration, and the filtrate was concentrated to afford the crude products. The residue was purified by column chromatography (EtOAc/hexanes = 1:4) to furnish the desired iminolactones **9** (0.78 g, 25%) and **10** (1.24 g, 40%).

Iminolactone **9**: mp 63−64 °C; $[\alpha]^{22}_D$ −265.6 (c = 2.34, $CHCl_3$); ^{1}H NMR δ 4.52 (d, J = 18 Hz, 1H), 4.32 (d, J = 1.6 Hz), 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 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*/*e* calcd for $C_{12}H_{17}NO_2$ M^+ 207.1268, found M^+ 207.1264. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.48; H, 8.27; N, 6.75. Found: C, 69.44; H, 8.25; N, 6.72.

Iminolactone **10**: 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}; ^{1}H NMR δ 4.56 (d, J = 18 Hz, 1H), 4.49 (d, J = 1.6 Hz, 1H), 3.95−3.90 (dd, J = 18 Hz, 1.6 Hz), 2.28 (d, J = 4.8 Hz), 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 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.

General Procedure for the Alkylation of Tricyclic Iminolactones (9, 10, 16, and 17). Diisopropylamine (216 μL, 1.54 mmol, 1.1 equiv) was added to a solution of dry THF (1.2 mL) and *n*-BuLi (1.6 *M*, 962 μL, 1.54 mmol, 1.1 equiv) at −30 °C and was then stirred at −30 °C for 30 min under an argon atmosphere.

Iminolactone (292 mg, 1.4 mmol) in dry THF (10 mL) was added dropwise over a period of 10 min to the above freshly prepared LDA solution via a syringe at −30 °C, and the resulting solution was stirred at −30 °C for 90 min. After the addition of HMPA (0.73 mL, 4.2 mmol, 3 equiv), the reaction mixture was cooled to −78 °C. A 0 °C solution of alkyl halide (4.2 mmol, 3 equiv) in dry THF (10 mL) was added to the reaction mixture via a syringe pump with the needle contacting the wall of the neck of the reaction vessel over 10 min. The well-stirred reaction was kept at −78 °C for 12 h.

Aqueous acetic acid solution (2 M, 2 mL) was added to the mixture to quench the reaction. The reaction was warmed to room temperature, washed with satd aqueous LiCl (3 × 3 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude product. The crude reaction was purified by column chromatography to yield the purified products.

(1*R*,2*S*,5*R*,8*S*)-5-Benzyl-1,5,11,11-tetramethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18a): 347 mg (yield 80%); $[\alpha]^{22}_D$ −32.7 (c = 2.29, $CHCl_3$); R_f 0.33 (hexanes/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 2963 (s), 2882 (m), 1741 (s), 1698 (m) cm^{-1}; ^{1}H NMR δ 7.30−7.15 (m, 5H), 3.34 (d, J = 13.6 Hz, 1H), 2.92 (d, J = 13.6 Hz, 1H), 2.32 (d, J = 4.4 Hz, 1H), 2.24 (s, 1H), 1.90−1.78 (m, 1H), 1.72 (s, 3H), 1.68−1.54 (m, 1H), 1.41−1.34 (m, 1H), 0.86 (s, 3H), 0.81 (s, 3H), 0.75 (s, 3H), 0.68−0.62 (m, 1H); ^{13}C NMR δ 178.5, 174.1, 136.2, 130.5, 128.6, 127.4, 81.5, 64.9, 54.0, 49.0, 48.0, 46.0, 34.5, 29.5, 21.1, 19.8, 19.2, 9.4; MS *m*/*z* 311 (M^+, 1.3), 282 (0.8), 267 (62.0), 252 (30.1), 220 (6.7), 192 (18.5), 176 (100.0), 148 (18.2), 117 (8.6), 91 (41.6), 83 (7.5), 55 (6.9); HRMS *m*/*e* calcd for $C_{20}H_{25}NO_2$ M^+ 311.1886, found M^+ 311.1888. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.10; H, 8.24; N, 4.45.

(1*R*,2*S*,5*S*,8*S*)-5-Benzyl-1,5,11,11-tetramethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18b): 356 mg (yield 82%); $[\alpha]^{22}_D$ −70.7 (*c* = 1.27, $CHCl_3$); R_f 0.34 (hexanes/EtOAc = 2/1); mp 118−120 °C; IR (NaCl, $CHCl_3$) 3032 (ms), 2965 (m), 1743 (s), 1701 (m) cm^{-1}; ^{1}H NMR *δ* 7.34−7.13 (m, 5H), 4.27 (s, 1H), 3.50−3.47 (d, *J* = 13.2 Hz, 1H), 3.13−3.09 (d, *J* = 13.2 Hz, 1H), 2.29 (d, *J* = 4.4 Hz, 1H), 1.98−1.79 (m, 2H), 1.59 (s, 1H), 1.46 (m, 1H), 1.41−1.34 (s, 3H), 1.33−1.29 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H), 0.21 (s, 3H); ^{13}C NMR *δ* 176.6, 173.0, 136.9, 131.3, 127.6, 126.4, 80.5, 63.7, 53.8, 49.6, 48.1, 46.7, 34.5, 23.8, 21.2, 19.3, 19.1, 9.7; MS *m*/*z* 311 (M$^+$, 43.8), 296 (2.2), 267 (47.1), 252 (30.4), 220 (34.6), 192 (22.4), 176 (100.0), 148 (22.3), 117 (11.2), 91 (55.7), 83 (15.8), 55 (12.0); HRMS *m*/*e* calcd for $C_{20}H_{25}NO_2$ M$^+$ 311.1886, found M$^+$ 311.1896. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.21; H, 8.15; N, 4.60.

(1*R*,2*S*,5*S*,8*S*)-5-Allyl-5-benzyl-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18c): 354 mg (yield 75%); $[\alpha]^{22}_D$ −12.0 (*c* = 1.39, $CHCl_3$); R_f 0.49 (hexanes/EtOAc = 2/1); ^{1}H NMR *δ* 7.29−7.11 (m, 5H), 5.89−5.76 (m, 1H), 5.22−5.17 (m, 2H), 4.25 (s, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 3.09 (d, *J* = 12.8 Hz), 2.67 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.44 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.27 (d, *J* = 4.8 Hz, 1H), 1.97−1.89 (m, 1H), 1.83−1.72 (m, 1H), 1.54−1.46 (m, 1H), 1.30−1.21 (m, 1H), 0.90 (s, 3H), 0.80 (s, 3H), 0.05 (s, 3H); ^{13}C NMR *δ* 177.2, 172.1, 136.5, 131.7, 131.3, 127.6, 126.3, 120.1, 81.2, 70.0, 53.8, 49.3, 47.9, 45.7, 43.1, 34.6, 21.5, 19.1, 18.7, 9.4; MS *m*/*z* 337 (M$^+$, 22.6), 293 (85.8), 278 (38.7), 252 (26.5), 250 (22.2), 202 (78.3), 174 (12.2), 160 (15.0), 128 (12.6), 91 (100.0), 83 (16.0), 55 (20.4); HRMS *m*/*e* calcd for $C_{22}H_{27}NO_2$ M$^+$ 337.2042, found M$^+$ 337.2050. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.26; H, 8.12; N, 4.30.

(1*R*,2*S*,8*S*)-5,5-Dibenzyl-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18d). 400 mg (yield 74%); $[\alpha]^{22}_D$ −41.9 (*c* = 1.03, $CHCl_3$); mp 146−147 °C; IR (NaCl, $CHCl_3$) 2960 (ms), 2928 (m), 1738 (s), 1705 (m) cm^{-1}; ^{1}H NMR *δ* 7.29−7.26 (m, 6H), 7.20−7.11 (m, 4H), 3.68 (d, *J* = 12.8 Hz, 1H), 3.54 (d, *J* = 12.8 Hz, 1H), 3.18 (d, *J* = 12.8 Hz, 1H), 3.02 (d, *J* = 12.8 Hz, 1H), 2.16 (d, *J* = 4.8 Hz, 1H), 1.87 (s, 1H), 1.77−1.69 (m, 1H), 1.50−1.42 (m, 1H), 1.31−1.24 (m, 1H), 0.67 (s, 3H), 0.60 (s, 3H), 0.48−0.42 (m, 1H), −0.18 (s, 3H); ^{13}C NMR *δ* 178.5, 173.0, 136.4, 135.9, 131.4, 130.7, 128.6, 127.9, 127.4, 126.6, 81.0, 69.6, 54.0, 48.5, 48.1, 47.8, 46.1, 34.6, 21.1, 19.0, 18.5, 9.2; MS *m*/*z* 387 (M$^+$, 14.6), 343 (56.1), 328 (36.4), 296 (12.3), 252 (100.0), 224 (16.1), 186 (5.1), 160 (2.6), 115 (7.2), 91 (64.6), 83 (10.1), 55 (6.7); HRMS *m*/*e* calcd for $C_{26}H_{29}NO_2$ M$^+$ 387.2205, found M$^+$ 387.2199.

(1*R*,2*S*,5*R*,8*S*)-5-Allyl-5-benzyl-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18e): 368 mg (yield 78%); $[\alpha]^{22}_D$ −15.3 (*c* = 2.13, $CHCl_3$); R_f 0.26 (hexanes/EtOAc = 10/1); IR (NaCl, $CHCl_3$) 3074 (s), 2961 (m), 1741 (s), 1702 (m) cm^{-1}; ^{1}H NMR *δ* 7.29−7.27 (m, 3H), 7.15−7.13 (m, 2H), 5.75−5.67 (m, 1H), 5.23−5.06 (m, 2H), 3.81−3.35 (d, *J* = 13.6 Hz, 1H), 3.05−2.99 (dd, *J* = 12.8, 7.6 Hz, 1H), 2.96−2.92 (d, *J* = 13.6 Hz, 1H), 2.74−2.69 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.32−2.31 (d, *J* = 4.8 Hz, 1H), 2.04 (s, 1H), 1.81−1.78 (m, 1H), 1.60−1.56 (m, 1H), 1.37−1.32 (m, 1H), 0.84 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H), 0.57−0.50 (m, 1H); ^{13}C NMR *δ* 179.1, 172.8, 135.8, 133.1, 130.4, 128.5, 127.3, 119.3, 81.0, 68.6, 53.9, 48.7, 47.8, 46.7, 45.3, 34.4, 21.0, 20.1, 19.0, 9.2; MS *m*/*z* 337 (M$^+$, 57.9), 281 (18.2), 266 (22.1), 246 (23.6), 202 (52.5), 160 (10.6), 146 (4.2), 107 (10.8), 83 (100.0), 47 (19.8); HRMS *m*/*e* calcd for $C_{22}H_{27}NO_2$ M$^+$ 337.2042, found M$^+$ 337.2034.

(1*R*,2*S*,5*S*,8*S*)-5-Allyl-5-butyl-1,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (18f): 340 mg (yield 80%); $[\alpha]^{22}_D$ −12.0 (*c* = 1.14, $CHCl_3$); IR (NaCl, $CHCl_3$) 2959 (ms), 2875 (m), 1741 (s), 1701 (m) cm^{-1}; ^{1}H NMR *δ* 5.80−5.73 (m, 1H), 5.21−5.16 (d, *J* = 17.2 Hz, 1H), 5.09−5.07 (d, *J* = 10.4 Hz, 1H), 4.36 (s, 1H), 2.88−2.83 (ddd, *J* = 13.6, 6.8, 0.8 Hz, 1H), 2.66−2.60 (ddd, *J* = 13.6, 7.2, 0.8 Hz, 1H), 2.41−2.40 (m, 1H), 2.02−1.73 (m, 3H), 1.59−1.51 (m, 2H), 1.41−1.29 (m, 4H), 1.06 (s, 3H), 0.99 (s, 1H), 0.96 (s, 3H), 0.91−0.87 (m, 3H), 0.82 (s, 3H); ^{13}C NMR *δ* 177.6, 172.2, 133.6, 118.8, 80.9, 66.5, 53.8, 49.8, 48.1, 42.9, 36.4, 34.6, 26.1, 22.8, 21.3, 20.1, 19.4, 13.8, 9.7; MS *m*/*z* 303 (M$^+$, 51.2), 275 (27.2), 247 (100.0), 216 (62.5), 202 (23.8), 190 (22.7), 164 (22.7), 152 (11.1), 107 (16.7), 83 (24.4), 55 (23.2); HRMS *m*/*e* calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2199. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62; Found: C, 75.22; H, 9.74; N, 4.6.

(1*R*,2*S*,5*R*,8*S*)-5-Allyl-1,5,11,11-tetramethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (18g): 340 mg (yield 93%); $[\alpha]^{22}_D$ −45.1 (*c* = 0.41, $CHCl_3$); R_f 0.33 (hexanes/EtOAc = 2/1); mp 76−77 °C; ^{1}H NMR NMR *δ* 5.80−5.71 (m, 1H), 5.18−5.12 (m, 2H), 4.46 (s, 1H), 2.54−2.49 (ddd, *J* = 14.0, 7.6, 0.8 Hz, H), 2.41−2.36 (dd, *J* = 13.6, 7.6 Hz, H), 2.40 (d, *J* = 4.4, 1H), 2.04−1.82 (m, 2H), 1.62−1.52 (m, 4H), 1.42−1.35 (m, 1H), 1.07 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H); ^{13}C NMR *δ* 178.2, 172.9, 131.6, 119.8, 81.6, 62.8, 53.8, 49.8, 48.1, 41.9, 34.5, 26.5, 21.4, 19.8, 19.3, 9.7; MS *m*/*z* 261 (M$^+$, 9.4), 232 (9.3), 217 (90.5), 202 (76.3), 176 (100.0), 174 (41.7), 148 (36.1), 107 (20.0), 83 (41.5), 55 (35.0), 53 (21.7); HRMS *m*/*e* calcd for $C_{16}H_{23}NO_2$ 261.1722, found 261.1728.

(1*S*,2*R*,5*S*,8*R*)-5-Benzyl-5,8,11,11-tetramethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (19a): 327 mg (yield 75%); $[\alpha]^{22}_D$ +61.7 (*c* = 1.16, $CHCl_3$); R_f 0.56 (hexanes/EtOAc = 2/1); IR (NaCl, $CHCl_3$) 3061 (s), 3028 (m), 1741 (s), 1695 (m) cm^{-1}; ^{1}HNMR *δ* 7.28−7.26 (m, 3H), 7.12−7.09 (m, 2H), 3.34−3.31 (d, *J* = 13.2 Hz, 1H), 2.96−2.92 (d, *J* = 13.2 Hz, 1H), 2.40 (s, 1H), 1.81−1.72 (m, 5H), 1.62−1.58 (m, 1H), 1.42−1.34 (m, 1H), 1.04 (s, 3H), 0.84 (s, 3H), 0.69 (s, 3H), 0.66−0.62 (m, 1H); ^{13}C NMR *δ* 179.6, 174.2, 136.2, 130.3, 128.5, 127.2, 79.5, 65.0, 52.5, 48.0, 47.3, 45.8, 29.6, 28.9, 28.8, 19.9, 19.1, 10.2; MS *m*/*z* 311 (M$^+$, 0.8), 283 (2.4), 267 (100.0), 239 (72.3), 224 (18.3), 192 (29.6), 176 (61.4), 148 (48.1), 117 (11.9), 91 (54.8), 83 (93.1), 69 (17.6); HRMS *m*/*e* calcd for $C_{20}H_{25}NO_2$ M$^+$ 311.1895, found M$^+$ 311.1885. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.15; H, 8.14; N, 4.51.

(1*S*,2*R*,5*R*,8*R*)-5-Benzyl-5,8,11,11-tetramethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (19b). 383 mg (yield 88%); $[\alpha]^{22}_D$ +48.2 (*c* = 1.30, $CHCl_3$), R_f 0.46 (hexanes/EtOAc = 2/1); mp 100−101 °C; ^{1}H NMR *δ* 7.36−7.12 (m, 5H), 4.43 (s, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 3.13 (d, *J* = 12.8 Hz, 1H), 2.04 (d, *J* = 4.8 Hz, 1H), 2.00−1.94 (m, 1H), 1.72−1.65 (m, 1H), 1.56−1.49 (m, 1H), 1.46 (s, 3H), 1.32−1.26 (m, 1H), 0.98 (s, 3H), 0.82 (s, 3H), 0.09 (s, 3H); ^{13}C NMR *δ* 177.8, 173.2, 136.9, 78.5, 63.6, 52.9, 48.2, 47.7, 46.7, 28.9, 25.8, 23.6, 20.0, 18.5, 10.0; MS *m*/*z* 311 (M$^+$, 21.9), 283 (6.9), 267 (100.0), 252 (59.2), 239 (76.2), 224 (17.0), 192 (35.7), 176 (54.9), 148 (41.2), 117 (16.7), 91 (86.3), 77 (11.4), 69 (17.9); HRMS *m*/*e* calcd for $C_{20}H_{25}NO_2$ M$^+$ 311.1895, found M$^+$ 311.1890. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.10; H, 8.24; N, 4.48.

(1*S*,2*R*,5*R*,8*R*)-5-Allyl-5-benzyl-8,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (19c): 401 mg (yield 85%); $[\alpha]^{22}_D$ +32.7 (*c* = 1.19, $CHCl_3$); R_f 0.60 (hexanes/EtOAc = 4/1); mp 62−63 °C; ^{1}H NMR *δ* 7.29−7.27 (m, 2H), 7.14−7.09 (m, 3H), 5.88−5.76 (m, 1H), 5.17−5.05 (m, 2H), 4.41 (s, 1H), 3.48−3.45 (d, *J* = 12.4 Hz, 1H), 3.11−3.08 (d, *J* = 12.4 Hz, 1H), 1.96−1.87 (m, 2H), 1.71−1.62 (m, 1H), 1.52−1.44 (m, 1H), 1.25−1.19 (m, 1H), 0.97 (s, 3H), 0.77 (s, 3H), −0.07 (s, 3H); ^{13}C NMR *δ* 178.4, 172.3, 136.6, 131.9, 131.6, 127.5, 126.4, 120.0, 79.4, 67.1, 53.0, 48.1, 47.6, 45.8, 42.9, 29.3, 26.0, 20.0, 18.2, 10.1; MS *m*/*z* 337 (M$^+$, 18.1), 293 (100.0), 265 (33.7), 246 (18.0), 202 (30.7), 174 (19.9), 150 (12.2), 120 (7.7), 91 (47.7), 69 (19.6), 55 (5.4); HRMS *m*/*e* calcd for $C_{22}H_{27}NO_2$ M$^+$ 337.2042, found M$^+$ 337.2040. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.26; H, 8.08; N, 4.23.

(1*S*,2*R*,5*S*,8*R*)-5-Allyl-5-benzyl-8,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (19d): 425 mg (yield 90%); $[\alpha]^{22}_D$ +35.5 (*c* = 1.38, $CHCl_3$); R_f 0.41 (hexanes/EtOAc = 10/1);

IR (NaCl, $CHCl_3$) 2960 (m), 2926 (m), 1741 (s), 1699 (m) cm^{-1}; ^1H NMR δ 7.29−7.25 (m, 3H), 7.13−7.11 (m, 2H), 5.72−5.68 (m, 1H), 5.21−5.16 (m, 1H), 5.07−5.03 (m, 1H), 3.38−3.34 (d, J = 13.2 Hz, 1H), 3.04−2.95 (m, 2H), 2.78−2.73 (m, 1H), 2.18 (s, 1H), 1.77−1.70 (m, 2H), 1.61−1.55 (m, 1H), 1.38−1.34 (m, 1H), 1.04 (s, 3H), 0.82 (s, 3H), 0.67 (s, 3H), 0.59−0.56 (m, 1H); ^{13}C NMR δ 180.2, 173.0, 135.9, 133.3, 130.3, 128.4, 127.2, 119.1, 79.1, 68.7, 52.7, 47.8, 47.1, 46.7, 45.2, 31.4, 28.8, 25.8, 22.5, 19.9, 19.6, 10.1; MS *m*/*z* 337 (M^+, 36.7), 293 (50.5), 265 (48.9), 252 (20.1), 202 (49.0), 174 (41.6), 150 (18.5), 120 (14.2), 91 (100.0), 83 (87.9), 69 (37.6); HRMS *m*/*e* calcd for $C_{22}H_{27}NO_2$ M^+ 337.2042, found M^+ 337.2043.

(1*S*,2*R*,5*R*,8*R*)-5-Benzyl-8,11,11-trimethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (19e): 295 mg (yield 71%); $[\alpha]^{22}_D$ +227.2 (c = 1.94, $CHCl_3$); R_f 0.49 (hexanes/EtOAc = 4/1); mp 122−124 °C; IR (NaCl, $CHCl_3$) 2961 (m), 1747 (s), 1692 (m) cm^{-1}; ^1H NMR δ 7.42−7.20 (m, 5H), 4.43 (s, 1H), 3.96−3.92 (m, 1H), 3.54−3.49 (dd, J = 14.0, 5.2 Hz, 1H), 3.32−3.26 (dd, J = 14.0, 7.6 Hz, 1H), 2.24−2.22 (d, J = 4.8 Hz, 1H), 2.10−2.03 (m, 1H), 1.78−1.70 (m, 1H), 1.59−1.52 (m, 1H), 1.35−1.28 (m, 1H), 1.04 (s, 3H), 0.95 (s, 3H), 0.71 (s, 3H); ^{13}C NMR δ 182.7, 170.7, 138.8, 130.0, 128.1, 126.3, 79.6, 62.5, 52.5, 49.1, 47.4, 37.4, 29.4, 25.3, 20.0, 19.6, 9.9; MS *m*/*z* 297 (M^+, 83.6), 269 (27.2), 253 (21.5), 225 (13.4), 206 (27.8), 178 (46.0), 162 (33.7), 148 (19.0), 105 (16.7), 91 (100.0), 69 (35.4), 55 (16.3); HRMS *m*/*e* calcd for $C_{19}H_{23}NO_2$ M^+ 297.1732, found M^+ 297.1729.

(1*S*,2*R*,5*S*,8*R*)-5-Allyl-5,8,11,11-tetramethyl-3-oxa-6-azatricyclo-[6.2.1.0^{2,7}]undec-6-en-4-one (19f): 274 mg (yield 75%); $[\alpha]^{22}_D$ +36.5 (c = 1.57, $CHCl_3$); R_f 0.42 (hexanes/EtOAc = 4/1); mp 85−86 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 5.82−5.69 (m, 1H), 5.18−5.09 (m, 2H), 4.64 (s, 1H), 2.57−2.33 (m, 2H), 2.21 (d, J = 2.6, 1H), 2.12−2.00 (m, 1H), 1.85−1.50 (m, 2H), 1.62 (s, 3H), 1.42−1.32 (m, 1H), 1.05 (s, 3H), 0.96 (s, 3H), 0.78 (s, 3H); ^{13}C NMR δ 183.5, 171.8, 131.8, 120.0, 79.7, 63.5, 56.8, 52.3, 49.1, 42.8, 29.5, 25.2, 20.0, 19.7, 17.3, 10.0; MS *m*/*z* 261 (M^+, 1.6), 217 (51.9), 202 (59.3), 192 (42.8), 189 (42.7), 176 (33.4), 148 (93.4), 124 (38.6), 107 (23.9), 91 (45.5), 69 (66.7), 53 (37.5). 41 (100); HRMS *m*/*e* calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1728. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found. C, 73.60; H, 8.88; N, 5.33.

General Procedure for Hydrolysis of α,α-Dialkylated Tricyclic Iminolactones. To a solution of **18** or **19** (0.4 mmol) in 10 mL of MeOH/acetone (v/v = 1:1) was added 2 N NaOH (0.5 mL, 1 mmol), and the mixture was stirred for 2 h at room temperature. The solution was diluted with 10 mL of water, cooled to 0 °C, and then acidified with 2 N HCl to pH 3−4. The acidic solution was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. After removal of the solvent, the residue was transferred to a sealed tube and 6 N HCl (2 mL) was added. This mixture was heated at 92 °C for 3 h and then extracted with ethyl acetate (3 × 5 mL). The aqueous layer was evaporated to dryness under reduced pressure, and the residue was dissolved in anhydrous ethanol (2 mL) followed by the addition of of propylene oxide (1.5 mL). The mixture was stirred at room temperature for 1 h (or heated at reflux for 30 min). After removal of the ethanol, the resulting white solid precipitate was washed with acetone (2 mL), collected by filtration, washed successively with acetone (3 × 2 mL), and air-dried to afford the desired α,α-dialkylated-α-amino acid.

(*S*)-2-Methylphenylalanine: 63 mg; yield 88%; mp 278−280 °C; $[\alpha]^{22}_D$ −21.6 (c = 1.04, H_2O) [lit.[24] $[\alpha]^{20}_D$ −22 (c = 1 in H_2O)]; ^1H NMR (400 MHz, D_2O) δ 7.29−7.26 (m, 3H), 7.15 (d, J = 7.0 Hz, 2H), 3.19 (d, J = 14.2 Hz, 1H), 2.87 (d, J = 14.2 Hz, 1H), 1.44 (s, 3H).

(*R*)-2-Methylphenylalanine: 62 mg; yield 86%; mp 277−279 °C; $[\alpha]^{22}_D$ +21.5 (c = 1.04, H_2O); ^1H NMR (400 MHz, D_2O) δ 7.30−7.26 (m, 3H), 7.16 (d, J = 6.2 Hz, 2H), 3.20 (d, J = 14.2 Hz, 1H), 2.88 (d, J = 14.2 Hz, 1H), 1.44 (s, 3H).

(*S*)-2-Propenyl-phenylalanine: 67 mg; yield 82%; mp > 300 °C; $[\alpha]^{22}_D$ +26.8 (c = 1.11, H_2O) [lit.[25] $[\alpha]^{20}_D$ +27.3 (c = 1 in H_2O)]; ^1H NMR (400 MHz, D_2O) δ 7.29−7.25 (m, 3H), 7.17 (d, J = 7.5 Hz, 2H), 5.75−5.65 (m, 1H), 5.23 (s, 1H), 5.20−5.18 (d, J = 6.4 Hz, 1H), 3.26 (d, J = 14.8 Hz, 1H), 2.93 (d, J = 13.7 Hz, 1H), 2.76−2.73 (dd, J = 14.6, 6.4 Hz, 1H), 2.45−2.39 (dd, J = 14.6, 8.8 Hz, 1H).

(*R*)-2-Propenylphenylalanine: 71 mg; yield 87%; mp > 300 °C; $[\alpha]^{22}_D$ −27.0 (c = 1.10, H_2O); ^1H NMR (400 MHz, D_2O) δ 7.30−7.26 (m, 3H), 7.17 (d, J = 7.4 Hz, 2H), 5.68−5.62 (m, 1H), 5.21(s, 1H), 5.17 (d, J = 6.3 Hz, 1H), 3.24 (d, J = 14.8 Hz, 1H), 2.91 (d, J = 14.2 Hz, 1H), 2.74−2.69 (dd, J = 14.6, 6.4 Hz, 1H), 2.43−2.37 (dd, J = 14.6, 8.8 Hz, 1H).

(*S*)-2-Amino-2-methyl-4-pentenoic acid: 46 mg; yield 90%; mp > 300 °C; $[\alpha]^{22}_D$ −28.0 (c = 0.88, H_2O) [lit.[26] $[\alpha]^{25}_D$ −28.5 (13 mg/dm^3, H_2O, liq, 10 cm)]; ^1H NMR (400 MHz, D_2O) δ 5.65−5.58 (m, 1H), 5.16 (s, 1H), 5.13−5.12 (d, J = 4.1 Hz, 1H), 2.56−2.51 (dd, J = 14.4, 6.5 Hz, 1H), 2.35−2.30 (dd, J = 14.4, 8.4 Hz, 1H), 1.36 (s, 3H).

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Supporting Information Available: X-ray position parameters, full bond distances and angles, and ORTEP drawings for **18b**, **18d**, **18g**, and **19e** as well as tables of total energies and Cartesian coordinates for the minimized structures by AM1 and ab initio calculations are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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