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N-Arylcarbonylpseudoprolines as Tunable Chiral Derivatizing Agents for the Determination of the Absolute Configuration of Secondary Alcohols

So-Yeong Han[a] and Kihang Choi*[a]

Keywords: Configuration determination / Chirality / Conformation analysis

New chiral derivatizing agents, 3-arylcarbonyl-2,2-dimethyloxazolidine-4-carboxylic acids (*N*-arylcarbonylpseudoprolines), were prepared through a simple, short-step synthesis. The absolute configuration of secondary alcohols can be assigned on the basis of the NMR spectroscopic chemical shift difference between diastereomeric pseudoproline esters. Preparation of more efficient agents was achieved simply by using aromatic groups with stronger anisotropic effect.

Introduction

Since the advent of asymmetric synthesis, there is a growing demand for the development of simple and efficient methods for the assignment of the absolute configuration of stereogenic centers. One of the traditional approaches especially useful for noncrystalline compounds is the NMR anisotropy method,[1] in which the chiral compound is derivatized with two enantiomers of a chiral derivatizing agent (CDA) and the NMR spectra are compared to obtain the chemical shift difference [$\Delta\delta^{RS} = \delta(R) - \delta(S)$] between the two resulting diastereomers. Proper analysis of the $\Delta\delta^{RS}$ values based on the diastereomer conformations and the anisotropic shielding effect produced by the CDA can lead to the assignment of the absolute configuration of the chiral compound.

Several CDAs have been developed for different classes of compounds, and Mosher's α-methoxytrifluoromethylphenylacetic acid (MTPA, **1**)[2] and Trost's α-methoxyphenylacetic acid (MPA, **2**)[3] are the two most widely used agents for secondary alcohols. Although successfully used for the structure determination of many chiral alcohols and natural products, these agents often produce small $\Delta\delta^{RS}$ values, because of the weak anisotropic effect of the phenyl group and the conformational flexibility of the resulting esters. There have been continuous efforts[4] to develop more efficient agents affording larger $\Delta\delta^{RS}$ values, and most of these agents are based on chiral carboxylic acids with an aromatic group directly attached to a chiral center. In a continuing effort to develop tunable CDAs,[5] we report here that *N*-arylcarbonylpseudoprolines (**3**, Figure 1) could be used as new CDAs for the determination of the absolute configuration of secondary alcohols. In our design, the aromatic group is attached to a carbonyl group, and the chiral center is derived from chiral starting materials. Because of this modular and chiral pool approach, manipulation of the anisotropic effect by switching aromatic groups could easily be accomplished.

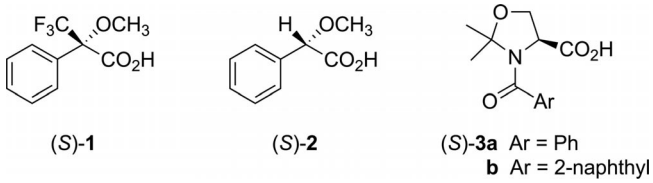

Figure 1. Structures of MTPA, MPA, and ΨPro reagents. The ΨPro amide bond is drawn in the *cis* conformation.

Results and Discussion

Pseudoprolines (ΨPros) are cyclic amino acids obtained by condensation of aldehydes or ketones with serine, threonine, and cysteine. It is well known that the incorporation of these proline surrogates into a peptide sequence induces the *cis* conformation at the amide bond *N*-terminal to the ΨPro residue.[6] The *cis*/*trans* ratio of this ΨPro amide bond is strongly affected by local structures, and it has been reported that compound **3a**, the *N*-benzoyl ΨPro derived from serine, adapts predominantly the *cis* amide conformation (Figure 1) and shows only one set of ^{1}H NMR signals in $CDCl_3$.[7] We envisioned that this conformational preference could be retained in the corresponding esters also, and, because the anisotropic aromatic group would be positioned close to the attached alcohol in the *cis* conformation, compound **3a** might be used as a new CDA for chiral alcohols.

To investigate the utility of ΨPro **3a**, we prepared the corresponding esters of α-chiral secondary alcohols of known absolute configuration. First, (*S*)- and (*R*)-**3a** were

[a] Department of Chemistry and Research Institute for Natural Sciences, Korea University,
Seoul 136-701, Republic of Korea
Fax: +82-2-3290-3121
E-mail: kchoi@korea.ac.kr

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prepared by a simple, three-step synthesis starting from L- and D-serine methyl esters, respectively, and then they were coupled with chiral alcohols. As expected, only one set of NMR signals was observed for each ester, showing that ΨPro **3a** and its esters have similar amide isomer equilibrium properties. The ^{1}H NMR signals were assigned by using the COSY and NOESY spectroscopic methods, and the chemical shifts were compared between the diastereomeric esters to obtain the $\Delta\delta^{RS}$ values (Figure 2).

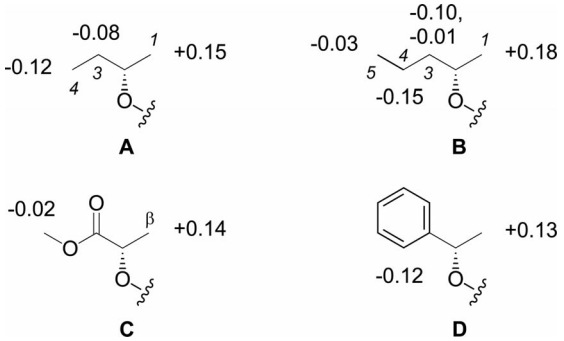

Figure 2. $\Delta\delta^{RS}$ values of ΨPro **3a** esters of chiral alcohols. ^{1}H NMR spectra were recorded in $CDCl_3$.

All the tested compounds showed the same trend in their $\Delta\delta^{RS}$ values; if structures of secondary alcohols are drawn as in Figure 2, the $\Delta\delta^{RS}$ values of the ΨPro esters are always positive for the Cα substituent on the right and negative for the substituent on the left. Although detailed studies are required to fully understand this consistent distribution of the $\Delta\delta^{RS}$ values, the result of conformational search calculations is informative.[8] In the lowest energy conformation of the (*S*)-**3a** ester of 2-propanol (Figure 3), the amide bond is in the *cis* conformation in which the steric interaction with the oxazolidine geminal dimethyl group is minimized. The (H–Cα)–(O–CO) and (Cα–O)–(C=O) bonds adopt *syn*-periplanar arrangements similar to those in the representative conformations of MTPA and MPA esters.[1a] The ΨPro Cα–N bond and the ester group C=O bond are also arranged in a *syn* relationship, presumably because this conformation can be stabilized by the intramolecular interaction between the amide carbonyl C with partial positive charge and the ester carbonyl O with partial negative charge (Figure 4). In (*S*)-ΨPro esters, the aryl group and the R^2 substituent are located on the same side of the ester carbonyl plane, so anisotropic shielding of the R^2 substituent is expected. In (*R*)-ΨPro esters, the aryl group is on the opposite side of the plane, and it is the R^1 substituent that is under the shielding effect. Thus, according to the representative conformation predicted by the modeling study, the $\Delta\delta^{RS}$ values should be positive for the R^2 substituent and negative for the R^1 substituent, and this is in good agreement with the experimental result.

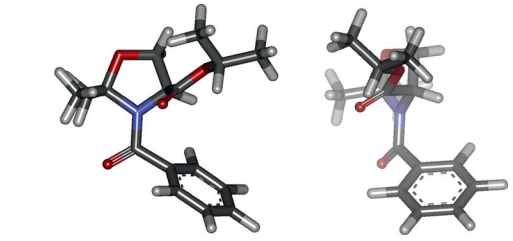

Figure 3. The calculated structure of the (*S*)-**3a** ester of 2-propanol: a front view (left) and a side view (right with depth cues) onto the oxazolidine ring (C, gray; H, light gray; O, red; N, blue).

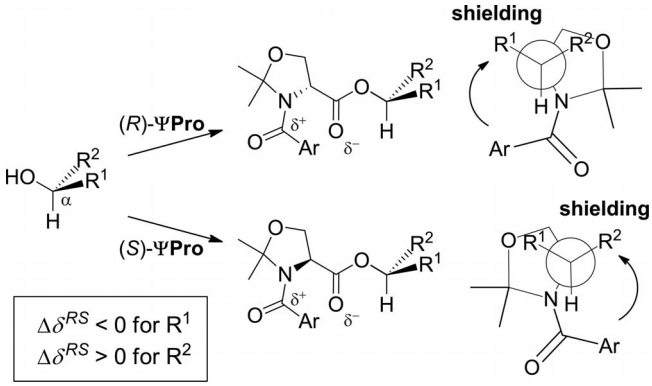

Figure 4. Representative conformations of (*R*)- and (*S*)-ΨPro esters. In the extended Newman projection, the ester group is omitted for clarity.

Because of the modular structure of *N*-arylcarbonyl ΨPro, preparation of a similar CDA with enhanced anisotropic effect was simple and straightforward. Compound **3b**, a second version of the ΨPro agent, was synthesized in a similar way by using 2-naphthoyl chloride instead of benzoyl chloride. The $\Delta\delta^{RS}$ values obtained with a new set of diastereomeric esters of ΨPro **3b** have the same signs as those obtained with ΨPro **3a** esters, suggesting that these esters have similar conformational preference. As expected, the $\Delta\delta^{RS}$ values are significantly larger for the ΨPro **3b** esters than those for the corresponding esters of MTPA, MPA, and ΨPro **3a** (Table 1). We also prepared another ΨPro agent by using 1-naphthoyl chloride, and the $\Delta\delta^{RS}$ values with this *N*-(1-naphthoyl) ΨPro turned out to be much smaller than those with ΨPro **3b** and rather close to the values observed with ΨPro **3a** (data not shown). This result suggests that the proper orientation as well as the

Table 1. $\Delta\delta^{RS}$ values of chiral alcohols **A**–**D** obtained with different CDAs in $CDCl_3$.

Alcohol		MTPA **1**[a]	MPA **2**[b]	ΨPro **3a**	ΨPro **3b**
A	1-CH_3	0.08	–0.13	0.15	0.33
	3-CH_2	–0.05/–0.04	0.11	–0.08	–0.19
	4-CH_3	–0.11	0.23	–0.12	–0.31
B	1-CH_3	0.08	–0.14	0.18	0.25
	3-CH_2	[c]	0.15	–0.10/–0.01	–0.21
	4-CH_2	[c]	0.25	–0.15	–0.40
	5-CH_3	–0.07	0.14	–0.03	–0.27
C	β-CH_3	0.07	[c]	0.14	0.36
	OCH_3	–0.04	[c]	–0.02	–0.18
D	CH_3	0.06	–0.08	0.13	0.27
	o-CH	–0.03	[c]	–0.12	–0.23

[a] From ref.[4b] and ref.[9] The originally reported values are $\Delta\delta^{SR}$ rather than $\Delta\delta^{RS}$ values. [b] From ref.[1a] and references cited therein. [c] Not available.

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size of the aromatic ring are of importance in the enhanced anisotropic effect of ΨPro **3b**.

We tested the solvent dependence of $\Delta\delta^{RS}$ values to find out whether the ΨPro agents could be used as effective CDAs in a wide range of solvents. The $\Delta\delta^{RS}$ values of ΨPro esters of (*S*)-*sec*-butyl alcohol (**A**) were compared in commonly used NMR spectroscopic solvents (Table 2). All these values have the same signs as those obtained in $CDCl_3$, which indicates that the esters retain the same conformational preference in the tested solvents. Moreover, the overall anisotropic effect increases with the solvent polarity, affording the largest $\Delta\delta^{RS}$ values in [D_4]MeOH and [D_6]-DMSO. The results obtained in [D_6]DMSO with diverse alcohols (Figure 5) show that ΨPro **3b** can be used as a reliable CDA even in polar NMR spectroscopic solvents.

Table 2. $\Delta\delta^{RS}$ values of chiral alcohol **A** obtained with ΨPro **3** in various NMR spectroscopic solvents.

Solvent	ε[a]	ΨPro **3a**		ΨPro **3b**	
		1-CH_3	4-CH_3	1-CH_3	4-CH_3
$CDCl_3$	4.8	0.15	–0.12	0.33	–0.31
[D_8]toluene	2.4	0.08	–0.08	0.28	–0.24
[D_6]acetone	20.7	0.17	–0.15	0.31	–0.38
[D_4]MeOH	32.7	0.18	–0.16	0.38	–0.46
[D_3]acetonitrile	37.5	0.16	–0.14	0.32	–0.38
[D_6]DMSO	46.7	0.18	–0.17	0.35	–0.42

[a] Solvent dielectric constant from ref.[10]

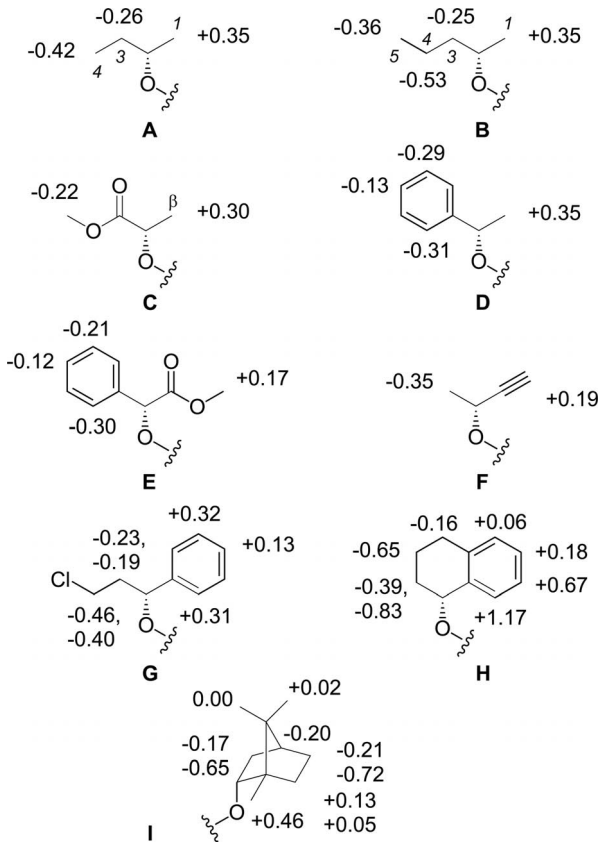

Figure 5. $\Delta\delta^{RS}$ values of ΨPro **3b** esters of chiral alcohols. ^{1}H NMR spectra were recorded in [D_6]DMSO.

Conclusions

We have presented pseudoproline-based CDAs for the determination of the absolute configuration of secondary alcohols. The agents were prepared by an efficient, short-step synthesis. Especially, manipulation of the anisotropic group was accomplished by using different arylcarbonyl halides, so that the preparation of more efficient CDAs was easy and straightforward. The esters of ΨPro **3b** showed significantly large $\Delta\delta^{RS}$ values in various solvents, suggesting that this series of compounds could provide a reliable NMR spectroscopic method to determine the absolute configuration of chiral alcohols.

Experimental Section

(*R*)-3-Benzoyl-2,2-dimethyloxazolidine-4-carboxylic Acid [(*R*)-3a]: D-Serine methyl ester hydrochloride (0.50 g, 3.2 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.1 mL, 2.0 equiv.) were dissolved in THF (10 mL), and benzoyl chloride (0.40 mL, 1.1 equiv.) was added. After stirring for 2 h, the solution was diluted with EtOAc and washed with brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography to give *N*-benzoyl-D-serine methyl ester (0.66 g, 92%). $[\alpha]_D^{22}$ = –20 (*c* = 0.4 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.83–7.86 (m, 2 H), 7.52–7.56 (m, 1 H), 7.44–7.48 (m, 2 H), 7.11 (br. s, 1 H, NH), 4.87–4.90 (m, 1 H, α-CH), 4.06–4.11 (m, 2 H, β-CH_2), 3.84 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 177.1, 167.7, 133.4, 132.0, 128.6, 127.1, 63.4, 55.1, 52.8 ppm. MS(ESI): *m*/*z* = 224.4 $[M + H]^+$.

The methyl ester (0.60 g, 2.7 mmol) was dissolved in toluene (10 mL)/$CHCl_3$ (5 mL), and *p*-toluenesulfonic acid (5 mg, 0.01 equiv.) and 2,2-dimethoxypropane (0.66 mL, 2.0 equiv.) were added. The solution was heated at reflux for 3 h to slowly remove MeOH by distillation. After cooling down to room temperature, the solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography to give (*R*)-**3a** methyl ester (0.66 g, 93%). $[\alpha]_D^{22}$ = +151 (*c* = 0.5 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.38 (m, 5 H), 4.42 (br. s, 1 H, α-CH), 4.22 [dd, ^2J(H,H) = 9.2, ^3J(H,H) = 6.7 Hz, 1 H, β-CH], 4.08–4.09 [dd, ^2J(H,H) = 9.2, ^3J(H,H) = 3.1 Hz, 1 H, β-CH], 3.59 (s, 3 H, OCH_3), 1.83 (s, 3 H, *gem*-CH_3), 1.73 (s, 3 H, *gem*-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 168.7, 137.7, 129.9, 128.7, 126.2, 97.0, 67.3, 61.4, 52.8, 24.9, 24.4 ppm. MS(ESI): *m*/*z* = 264.5 $[M + H]^+$.

The above methyl ester (0.57 g, 2.2 mmol) was added to THF (5 mL)/H_2O (5 mL), and then NaOH (0.17 g, 2.0 equiv.) was added to this mixture. After stirring for 3 h, the mixture was extracted with diethyl ether, and the aqueous layer was acidified with aqueous HCl (1 N). The resulting mixture was extracted with EtOAc, and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The mixture was concentrated to obtain (*R*)-**3a** as a white solid (0.50 g, 93%). M.p. 140–142 °C. $[\alpha]_D^{21}$ = +121 (*c* = 0.5 in MeOH). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.38–7.41 (m, 5 H), 4.47–4.46 (m, 1 H, α-CH), 4.23 [dd, ^2J(H,H) = 9.0, ^3J(H,H) = 7.0 Hz, 1 H, β-CH], 3.99 [dd, ^2J(H,H) = 9.0, ^3J(H,H) = 2.6 Hz, 1 H, β-CH], 1.67 (s, 3 H, *gem*-CH_3), 1.60 (s, 3 H, *gem*-CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 171.9, 167.6, 137.7, 129.4,

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128.2, 126.2, 95.5, 66.8, 60.6, 24.7, 23.8 ppm. HRMS(FAB): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1079; found 250.1078.

(*S*)-3-Benzoyl-2,2-dimethyloxazolidine-4-carboxylic Acid [(*S*)-3a]:[7] The procedure described for (*R*)-**3a** was followed, except that L-serine methyl ester hydrochloride was used instead of D-serine methyl ester hydrochloride. The spectroscopic data were virtually identical to those of (*R*)-**3a** except $[\alpha]_D^{21}$ = –118 (*c* = 0.5, in MeOH).

(*R*)-3-(2-Naphthoyl)-2,2-dimethyloxazolidine-4-carboxylic Acid [(*R*)-3b]: The procedure described for (*R*)-**3a** was followed except that 2-naphthoyl chloride was used instead of benzoyl chloride.

***N*-(2-Naphthoyl)-D-serine Methyl Ester:** Yield 91%. $[\alpha]_D^{23}$ = –28 (*c* = 0.5 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 7.86–7.93 (m, 4 H), 7.52–7.60 (m, 2 H), 7.29 [d, ^3J(H,H) = 6.8 Hz, 1 H], 4.93–4.96 (m, 1 H, α-CH), 4.11–4.14 (m, 2 H, β-CH_2), 3.85 (s, 3 H, OCH_3), 2.71 [t, ^3J(H,H) = 6.0 Hz, 1 H] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 167.9, 134.9, 132.4, 130.5, 129.0, 128.5, 127.9, 127.8, 127.7, 126.8, 123.5, 63.3, 55.3, 52.8 ppm. MS(ESI): *m*/*z* = 274.4 $[M + H]^+$.

(*R*)-3b Methyl Ester: Yield 85%. $[\alpha]_D^{23}$ = +159 (*c* = 0.5 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.87 (m, 4 H), 7.52–7.55 (m, 2 H), 7.45–7.47 (m, 1 H), 4.48 (br. s, 1 H, α-CH), 4.25 [dd, ^2J(H,H) = 9.2, ^3J(H,H) = 6.7 Hz, 1 H, β-CH], 4.12 [dd, ^2J(H,H) = 9.2, ^3J(H,H) = 3.0 Hz, 1 H, β-CH], 3.53 (s, 3 H, OCH_3), 1.87 (s, 3 H, *gem*-CH_3), 1.78 (s, 3 H, *gem*-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 168.6, 134.8, 133.5, 132.5, 128.5, 128.3, 127.8, 127.1, 126.8, 125.6, 123.4, 96.9, 67.0, 61.2, 52.6, 24.7, 24.1 ppm. MS(ESI): *m*/*z* = 314.5 $[M + H]^+$.

(*R*)-3b: Yield 95%; m.p. 180–184 °C. $[\alpha]_D^{22}$ = +180 (*c* = 0.5 in MeOH). ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 13.0 (br. s, 1 H), 7.93–8.00 (m, 4 H), 7.55–7.60 (m, 2 H), 7.49 [dd, ^3J(H,H) = 8.4, ^4J(H,H) = 1.5 Hz, 1 H], 4.62–4.63 (m, 1 H, α-CH), 4.28 [dd, ^2J(H,H) = 9.0, ^3J(H,H) = 7.0 Hz, 1 H, β-CH], 4.01 [dd, ^2J(H,H) = 9.0, ^3J(H,H) = 2.9 Hz, 1 H, β-CH], 1.72 (s, 3 H, *gem*-CH_3), 1.66 (s, 3 H, *gem*-CH_3) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 171.9, 167.7, 135.0, 132.9, 132.1, 128.4, 127.9, 127.7, 127.1, 126.7, 125.6, 124.1, 95.6, 66.8, 60.6, 24.7, 24.0 ppm. HRMS(FAB): calcd. for $C_{17}H_{18}NO_4$ $[M + H]^+$: 300.1236; found 300.1238.

(*S*)-3-(2-Naphthoyl)-2,2-dimethyloxazolidine-4-carboxylic Acid [(*S*)-3b]: The procedure described for (*R*)-**3a** was followed except that L-serine methyl ester hydrochloride and 2-naphthoyl chloride were used instead of D-serine methyl ester hydrochloride and benzoyl chloride, respectively. The spectroscopic data were virtually identical to those of (*R*)-**3b** except $[\alpha]_D^{22}$ = –178 (*c* = 0.5 in MeOH).

General Procedure for the Preparation of ΨPro Esters: (*S*)- or (*R*)-**3**, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl, 1.5 equiv.), and 4-(dimethylamino)pyridine (0.1 equiv.) were dissolved in DMF. To the solution was added DIEA (2.5 equiv.) followed by a secondary alcohol (1.0 equiv.). After stirring overnight, the mixture was diluted with EtOAc and washed with brine. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra and characterization data for pseudoprolines and their esters.

Acknowledgments

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