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Article

Synthesis and Catalytic Activities of 3-Decyl-β-proline for Michael Reactions in Water without an Organic Solvent

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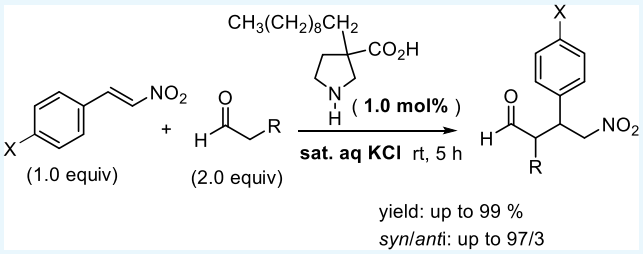
ABSTRACT: 3-Decyl-β-proline, which has a highly lipophilic substituent, was synthesized, and its catalytic activities in Michael addition using water as the solvent were investigated. The decyl substituent promoted the reaction by hydrophobic interactions to afford the Michael adduct in a high yield and with high diastereoselectivity under low catalyst loading.



INTRODUCTION

Organic reactions in water have attracted much attention because water is non-toxic, safe, and inexpensive, reduces the amount of organic solvent waste produced,[1] and is a potential solvent for stereoselective transformation.[2] Organocatalysts are metal-free and stable in moisture and air compared to metal catalysts. The ability to conduct organocatalytic reactions in water would therefore be environmentally benign and facile compared to reactions requiring the strictly anhydrous conditions necessary for traditional organic reactions and would lead to the development of truly practical synthetic reactions.[3] Our studies on the development of organocatalytic reactions showed that β-proline bearing a highly lipophilic substituent at the 3-position catalyzes Michael reactions in water with high yields at low catalyst loading. This article describes our results.

RESULTS AND DISCUSSION

We previously reported that 3-methyl-β-proline catalyzes Mannich-type reactions with high yields and high stereoselectivities at low catalyst loading.[4] We found that the solubility of β-proline in an organic solvent could be increased by introducing a methyl group to increase the lipophilicity of the catalyst and became interested in the characteristics of β-proline bearing a highly lipophilic group. Since we were especially interested in catalytic activity using water as the solvent, we examined the synthesis of 3-decyl-β-proline and its use for organic reactions in water. The synthesis of 3-decyl-β-proline (**8**) is shown in Scheme 1. Alkylation of commercially available *t*-butyl cyanoacetate (**1**) with decyl bromide under neat conditions followed by phase-transfer-catalyzed alkylation with ethyl iodoacetate afforded the dialkylated compound **3**. Treating **3** with $NaBH_4$ in the presence of $CoCl_2$ afforded lactam **4**.[5] After converting **4** to thiolactam **5** with Lawesson's reagent, hydrogenation followed by the protection of the resulting amino group with Cbz−Cl gave compound **6**.[6] Finally, sequential deprotection of the *t*-butyl and Cbz groups provided racemic 3-decyl-β-proline (**8**).With 3-decyl-β-proline (**8**) in hand, we next investigated the Michael reaction of cyclohexanone with β-nitrostyrene in water.[7] The reaction was carried out with 1.0 mol % catalyst **8** without an organic solvent, and the results are shown in Table 1. While the unsubstituted or methyl-substituted catalyst gave no product, the decyl-substituted catalyst **8** gave adduct **14** in a desirable yield with high diastereoselectivity (Table 1, entries 1, 2, and 4). The use of 2 equiv of cyclohexanone (**9**) rather than 1 equivalent improved the yield of the adduct from 46 to 65%. Since hydrophobic interactions were likely driving the reaction in water,[8] we investigated the salting-out effect using saturated aq KCl solution, and the yield increased to 79% (Table 1, entry 5). The reaction system was heterogeneous and an emulsion. Thus, the reaction was considered to take place at the interphase of the biphasic system. Saturated aqueous KCl solution, by increasing the ionic strength, facilitates the formation of the separate phase and concentrates the organic phase in which the reactants and the catalyst aggregate. These are considered to be the reason for the increase in the reaction yield. Next, we conducted the reaction using several aldehydes and saturated aq KCl solution as the solvent (Table 2).[9] The use of aldehyde rather than cyclohexanone greatly shortened

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Scheme 1. Synthesis of 3-Decyl-β-proline (8)

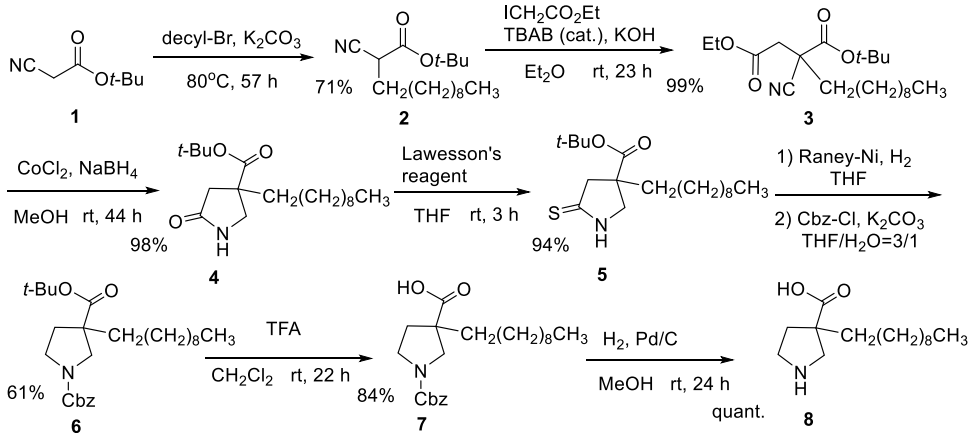
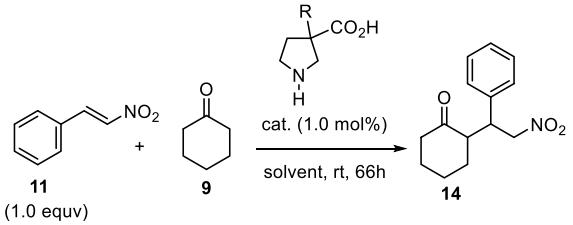


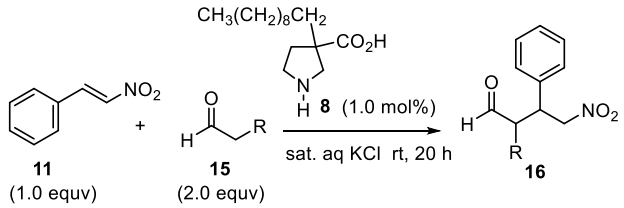
Table 1. Michael Addition of Cyclohexanone (9) to *trans*-β-Nitrostyrene (11) in Water



Entry	cat. (R)	solvent	amount of **9** (equiv)	yield of **14**[a] (%)	syn/anti[a]
1	H	H_2O	2.0	0	-
2	Me	H_2O	2.0	0	-
3	decyl	H_2O	1.0	46	96:4
4	decyl	H_2O	2.0	65	96:4
5	decyl	sat. aq KCl	2.0	79	95:5

[a]Determined by ^{1}H NMR using mesitylene as an internal standard.

Table 2. Michael Addition of Aldehydes (15) to *trans*-β-Nitrostyrene (11) in Water

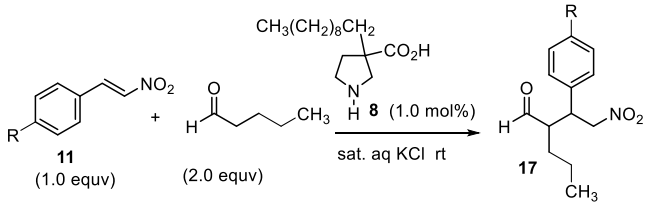


entry	R	yield of **16**[a] (%)	recovery of **11**[a] (%)	syn/anti[a]
1	Me	40	30	92:8
2	Et	74	6	94:6
3	*n*-Pr	88	0	94:6
4	*i*-Pr	76	14	97:3
5	*n*-Bu	81	2	92:8
6	*n*-hexyl	99	0	94:6

[a]Determined by ^{1}H NMR using mesitylene as an internal standard.

the reaction time. Although propanal gave a low yield, more lipophilic aldehyde gave high yields and high diastereoselectivities. Table 3 shows the results of reactions with pentanal and several β-nitrostyrenes, which have an electron-donating or electron-withdrawing substituent on the phenyl group. The electronic effect of the substituent, which changes the electron density at the reaction site, had no influence, and regardless of

Table 3. Michael Addition of Pentanal to *trans*-β-Nitrostyrene (11) in Water



entry	R	time	yield of **17**[a] (%)	recovery of **11**[a] (%)	syn/anti[a]
1	H	5	75	14	94:6
2	H	20	88	0	94:6
3	Me	5	86	3	82:18
4	Me	20	86	0	78:22
5	OMe	5	82	0	85:15
6	Cl	5	97	1	90:10
7	Br	5	88	0	87:13

[a]Determined by ^{1}H NMR using mesitylene as an internal standard.

the electronic effect, the substituted β-nitrostyrenes increased the reaction rate compared to that of the unsubstituted β-nitrostyrene and slightly decreased the diastereoselectivity. The results suggested that the substituents increase the lipophilicity of β-nitrostyrenes and made the hydrophobic interaction more effective. Diastereoselectivity also decreased when the reaction was continued for a long time, suggesting that the catalyst affects the isomerization of the adducts (Table 3, entry 4).

CONCLUSIONS

In conclusion, an organocatalyst which promotes the Michael reaction in water without an organic solvent was developed. The reaction proceeded with low catalyst loading to give high yields and high diastereoselectivities. The presence of a decyl group in the catalyst was shown to increase the reaction rate due to hydrophobic interactions. The synthesis of optically active 3-decyl-β-proline is currently under investigation to determine the enantioselectivities of the presented Michael reactions. Moreover, studies on the scope of the reactions with other Michael accepters are also underway. These results will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used without further purification.

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The organic solvents used were the commercially available dehydrated ones, and ion-exchange water was used in Michael reactions. Column chromatography was performed using silica gel (spherical, neutral, 100−200 μm) or NH silica gel (100−200 mesh). NMR spectra were recorded on 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometers using tetramethylsilane as an internal standard. IR spectra were recorded on an FT-IR spectrometer as neat or KBr. High-resolution mass spectroscopy (HRMS) spectra were recorded on an AccuTOF mass spectrometer using direct analysis in real time (DART) as an ionization method. Melting points were not corrected.

***tert*-Butyl 2-Cyanododecanoate (2).** A mixture of *t*-butyl cyanoacetate 10.0 mL (70.1 mmol), 1-bromodecane 14.5 mL (70. 1 mmol), and K_2CO_3 11.6 g (84.2 mmol) was heated at 80 °C under an Ar atmosphere for 57 h. After H_2O (80 mL) was added, the solution was neutralized with aq HCl and then extracted with AcOEt (80 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **2** (14.0 g, 49.8 mmol) in 71% yield as a colorless oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, $-CH_2CH_3$, 3H), 1.23−1.53 (m, $-CH_2(C_8H_{16})CH_3$, 16H), 1.50 (s, $-C(CH_3)_3$, 9H), 1.90 (q, J = 7.6 Hz, $-CH_2(C_8H_{16})CH_3$, 2H), 3.39 (t, J = 7.2 Hz, $=CHCH_2-$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 26.7, 27.8, 28.8, 29.18, 29.24, 29.4, 29.5, 29.9, 31.8, 38.6, 83.8, 117.0, 165.2; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{17}H_{32}N_1O_2$, 282.2433; Found, 282.2429.

1-*tert*-Butyl 4-Ethyl 2-Cyano-2-decylbutanedioate (3). To a solution of **2** (2.05 g, 7.30 mmol) in Et_2O (85 mL) were added ethyl iodoacetate (1.87 mL, 8.76 mmol), TBAB (0.070 g, 0.22 mmol), and powdered KOH (2.05 g, 36.5 mmol). The solution was stirred at room temperature (rt) for 23 h under an Ar atmosphere, and then, water was added. After Et_2O (350 mL) was added, the organic layer was washed with water (45 mL × 2) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 10/1) to give **3** (2.65 g, 7.22 mmol) in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, $-CH_2CH_2CH_3$, 3H), 1.20−1.60 (m, $-CH_2(C_8H_{16})CH_3$ and $-OCH_2CH_3$, 19H), 1.52 (s, $-C(CH_3)_3$, 9H), 1.73−1.89 (m, $-CH_2(C_8H_{16})CH_3$, 2H), 2.74 (d, J = 16.8 Hz, $-OCO-CH_aH_b-$, 1H), 2.97 (d, J = 16.8 Hz, $-OCO-CH_aH_b-$, 1H), 4.15−4.25 (m, $-OCH_2CH_3$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 24.8, 27.7, 29.10, 29.13, 29.2, 29.3, 29.4, 31.8, 37.5, 40.9, 46.5, 61.3, 84.0, 118.9, 167.2, 168.7; IR (neat) ν_{max}: 1741 (CO), 2247 (C≡N), 2928 cm^{-1} (C−H); HRMS (DART/AccuTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{38}N_1O_4$, 368.2801; Found, 368.2805.

***tert*-Butyl 3-Decyl-5-oxopyrrolidine-3-carboxylate (4).** A mixture of $NaBH_4$ (2.70 g, 72.6 mmol) and $CoCl_2$ (1.88 g, 14.5 mmol) was added to a solution of **3** (2.66 g, 7.26 mmol) in dry MeOH (38 mL) at 0 °C, and the solution was stirred at rt for 44 h under an Ar atmosphere. After 20% aqueous Rochelle salt (70 mL) was added, the mixture was stirred for 3 h and filtered. MeOH in the filtrate was evaporated, and the resulting solution was extracted with AcOEt (60 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated to give **4** (2.31 g, 7.12 mmol) in 98% yield as a solid. mp: 45−46 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, $-CH_2CH_2CH_3$, 3H), 1.26 (br s, $-CH_2(C_8H_{16})CH_3$, 16H), 1.46 (s, $-C(CH_3)_3$, 9H), 1.68−1.78 (m, $-CH_2(C_8H_{16})-CH_3$, 2H), 2.23 (d, J = 17.2 Hz, $-NHCOCH_aH_b-$, 1H), 2.82 (d, J = 17.2 Hz, $-NHCOCH_aH_b-$, 1H), 3.19 (d, J = 10.0 Hz, $-NHCH_aH_b-$, 1H), 3.73 (d, J = 10.0 Hz, $-NHCH_aH_b-$, 1H), 6.47 (br s, $-NH-$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 24.7, 27.9, 29.25, 29.28, 29.4, 29.5, 29.7, 31.8, 38.2, 39.3, 50.1, 50.3, 81.4, 173.6, 176.6; IR (KBr) ν_{max}: 1684 (C=O), 1723 (C=O), 2924 (C−H), 3383 cm^{-1} (N−H); HRMS (DART/AccuTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{36}N_1O_3$, 326.2695; Found, 326.2698.

***tert*-Butyl 3-Decyl-5-thioxopyrrolidine-3-carboxylate (5).** To a solution of **4** (0.19 g, 0.60 mmol) in THF (5 mL) was added Lawesson's reagent (0.35 g, 0.85 mmol). The solution was stirred at rt for 3 h under an Ar atmosphere. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on NH silica gel (hexane/AcOEt = 1/1) to give **5** (0.19 g, 0.56 mmol) in 94% yield. mp: 56−57 °C (hexane); ^{1}H NMR (400 Hz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, $-CH_2CH_2CH_3$, 3H), 1.20−1.35 (m, $-CH_2(C_8H_{16})CH_3$, 16H), 1.46 (s, $-C(CH_3)_3$, 9H), 1.70−1.75 (m, $-CH_2(C_8H_{16})CH_3$, 2H), 2.82 (d, J = 18.4 Hz, $-NHCSCH_aH_b-$, 1H), 3.32 (d, J = 18.4 Hz, $-NHCSCH_aH_b-$, 1H), 3.44 (d, J = 11.2 Hz, $-NHCH_aH_b-$, 1H), 4.05 (d, J = 11.2 Hz, $-NHCH_aH_b-$, 1H), 8.26 (br s, $-NH-$ 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 24.8, 27.9, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 37.8, 52.0, 52.9, 56.5, 81.8, 172.8, 203.8; IR (KBr) ν_{max}: 1307 (C=S), 1536 (C=S), 1725 (C=O), 2923 (C−H), 3197 cm^{-1} (N−H); MS: m/z $[M + H]^+$: 342; Anal. Calcd for $C_{19}H_{35}NO_2S$: C, 70.54; H, 11.44; N, 5.48; Found, C, 70.54; H, 11.48; N, 5.37.

***tert*-Butyl *N*-Cbz-3-Decylpyrrolidine-3-carboxylate (6).** In a 300 mL two-necked flask, a Raney nickel slurry in water (12 mL) was placed under an Ar atmosphere and then washed two times with H_2O (15 mL × 2), two times with MeOH (15 mL × 2), and two times with THF (15 mL × 2) consecutively by decantation. Compound **5** (1.26 g, 3.70 mmol) in THF (70 mL) was added, and the solution was stirred under a H_2 atmosphere for 22 h at rt. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated. The residue was dissolved in THF/H_2O = 3 (50 mL), and then, K_2CO_3 (1.87 g, 13.5 mmol) and *Z*-chloride (0.92 g, 5.40 mmol) were added at 0 °C. After the solution was stirred at rt for 47 h and concentrated under reduced pressure, AcOEt (100 mL) was added. The solution was washed with H_2O (10 mL × 2) and brine (5 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated, and the residue was purified by column chromatography on NH silica gel (hexane/AcOEt = 8/1) to give **6** (1.01 g, 2.27 mmol) in 61% yield as a mixture of two conformational isomers whose ratio was about 10:9. ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts in parentheses are that of a minor conformational isomer: δ 0.88 (J = 6.8 Hz, $-CH_2CH_2CH_3$, 3H), 1.09−1.17 (m, $-CH_2(C_8H_{16})CH_3$, 16H), 1.43 (s, $-C(CH_3)_3$, 9H), 1.50−1.70 (m, $-CH_2(C_8H_{16})CH_3$, 2H), 1.74 (m, $=NCH_2CH_aH_b-$ 1H), 2.31 (m, $=NCH_2CH_aH_b-$, 1H), 3.15 (3.21) (d, J = 11.2 Hz, $=NCH_aH_bC\equiv$, 1H), 3.36−3.53 (m, $=NCH_2CH_2-$, 2H), 3.88 (3.90) (d, J = 11.2 Hz, $=NCH_aH_bC\equiv$, 1H), 5.10−5.17 (m, $-OCH_2Ph$, 2H), 7.26−7.40 (m, $-OCH_2Ph$, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) chemical shifts in parentheses are that of a minor conformational isomer: δ 14.0, 22.6, 25.5, 27.9, 29.26 (29.30), 29.51(29.46), 29.9, 31.8, 33.8, 34.3, 36.7, 44.7, 45.0, 53.4 (54.0), 54.1 (53.2), 66.7 (66.6), 80.9, 127.77,

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127.82, 128.4, 137.0, 154.74 (154.68), 173.9; IR (neat) ν_{max}: 1711 (C=O), 2926 cm^{-1} (C−H); HRMS (DART/AccuTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{44}N_1O_4$, 446.3270; Found, 446.3279.

***N*-Cbz-3-Decylpyrrolidine-3-carboxylic Acid (7).** To a solution of **6** (0.12 g, 0.27 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (308 μL, 2.7 mmol), and the solution was stirred for 22 h at rt. After the solvent was evaporated, the residue was purified by column chromatography on silica gel (hexane/AcOEt/MeOH = 8/4/1) to give **7** (0.088 g, 0.23 mmol) in 85% yield as a mixture of two conformational isomers whose ratio was about 5:4. ^{1}H NMR (400 MHz, $CDCl_3$) chemical shifts in parentheses are that of a minor conformational isomer: δ 0.88 (t, J = 6.8 Hz, $-CH_2CH_2CH_3$, 3H), 1.25 (br s, $-CH_2(C_8H_{16})CH_3$, 16H), 1.62−1.73 (m, $-CH_2(C_8H_{16})CH_3$, 2H), 1.82 (m, $=NCH_2CH_aH_b-$ 1H), 2.38 (m, $=NCH_2CH_aH_b-$ 1H), 3.22 (3.27) (d, J = 11.2 Hz, $=NCH_aH_bC\equiv$, 1H), 3.40−3.58 (m, $=NCH_2CH_2-$, 2H), 3.95(3.98) (d, J = 11.2 Hz, $=NCH_aH_bC\equiv$, 1H), 5.09−5.18 (m, $-OCH_2Ph$, 2H), 7.26−7.40 (m, $-OCH_2Ph$, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) chemical shifts in parentheses are that of a minor conformational isomer: δ 14.0, 22.6, 25.6, 29.27, 29.34, 29.5, 29.9, 31.9, 33.5, 34.3, 36.5, 45.1(44.8), 53.3(53.8), 53.5(52.6), 67.0, 127.8, 127.9, 128.4, 136.7, 154.8, 180.5; IR (KBr) ν_{max}: 1672 (C=O), 1718 (C=O), 2924 (C−H), 3092 cm^{-1} (O−H); HRMS (DART/AccuTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{36}N_1O_4$, 390.2644; Found, 390.2652.

3-Decyl-β-proline (8). To a solution of **7** (60 mg, 0.15 mmol) in dry MeOH (2.5 mL) was added 10% Pd/C (31 mg, 10 mol %), and the solution was stirred under a H_2 atmosphere for 24 h at rt. The reaction mixture was filtered through a pad of celite, and the filtrate was evaporated to give **8** (38 mg, 0.15 mmol) in 95% yield. mp: 217 °C dec (MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, J = 6.8 Hz, $-CH_2CH_2CH_3$, 3H), 1.28 (br s, $-CH_2(C_8H_{16})CH_3$, 16H), 1.55 (m, $-NHCH_2CH_aH_b-$, 1H), 1.71−1.84 (m, $-CH_2(C_8H_{16})CH_3$, 2H), 2.42 (m, $-NHCH_2CH_aH_b-$, 1H), 2.82 (d, 11.2 Hz, $-NHCH_aH_bC\equiv$, 1H), 3.21−3.33 (m, $-NHCH_2CH_2-$, 2H), 3.79 (d, 11.2 Hz, $-NHCH_aH_bC\equiv$, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.4, 23.7, 27.6, 30.4, 30.59, 30.67, 30.68, 31.2, 33.0, 36.0, 38.3, 45.8, 54.4, 56.5, 180.6; IR (KBr) ν_{max}: 1390 (C−O), 1629 (C=O), 2473−2957 ($=NH_2^+$), 2920 cm^{-1}(C−H); MS: m/z $[M + H]^+$ 256.213; Anal. Calcd for $C_{15}H_{29}NO_2$, C, 70.54; H, 11.44; N, 5.48; Found, C, 70.54; H, 11.48; N, 5.37.

Typical Procedure for the Michael Reaction in Water. To a saturated KCl aqueous solution (0.75 mL) were added β-nitrostyrene (60 mg, 0.40 mmol), 3-decyl-β-proline (1.0 mg, 0.0039 mmol), and valeraldehyde (84 μL, 0.80 mmol). The suspension was stirred at rt for 20 h and then extracted with AcOEt (6 mL × 3). The combined organic layer was washed with brine (2 mL), dried over $MgSO_4$ and evaporated off to give 2-(2-nitro-1-phenylethyl) pentanal[10] as a mixture of diastereomers. The yield and diastereomeric ratio of the product were determined by ^{1}H NMR using mesitylene as an internal standard. According to the typical procedure, 2-(2-nitro-1-phenylethyl)cyclohexanone,[11] 2-methyl-4-nitro-3-phenylbutanal,[12] 2-ethyl-4-nitro-3-phenylbutanal,[12,13] 2-isopropyl-4-nitro-3-phenylbutanal,[12] 2-(2-nitro-1-phenylethyl) hexanal,[14] 2-(2-nitro-1-phenylethyl) octanal,[15] 2-[1-(4-methylphenyl)-2-nitroethyl] pentanal,[16] 2-[1-(4-methoxyphenyl)-2-nitroethyl] pentanal,[17] 2-[1-(4-chlorophenyl)-2-nitroethyl] pentanal,[18] and 2-[1-(4-bromophenyl)-2-nitroethyl] pentanal[16] were synthesized, and ^{1}H NMR spectra were in accordance with the literature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02289.

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2**−**8** and IR spectra of compounds **3**−**8** (PDF)

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Notes

The authors declare no competing financial interest.

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