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Organocatalytic Michael addition of aldehydes to trisubstituted nitroolefins

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ABSTRACT

The combination of *O*-TMS protected diphenyl-prolinol and benzoic acid was found to be effective to catalyze the Michael addition of aldehydes to 3-substituted 3-nitroacrylates. The reaction provided *syn,anti*-Michael adducts with good diastereoselectivity and excellent enantioselectivity. Some β -aryl and α -methyl substituted nitroolefins also worked under these conditions, although prolonging reaction time was required. These adducts could be used for assembling 2,3,4-trisubstituted pyrrolidines through simple hydrogenation.

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1. Introduction

Michael addition of aldehydes to nitroolefins is one of the most attractive reactions for testing organocatalysts, mainly because this reaction can proceed smoothly under catalysis by a variety of amines, particularly modified proline analogues.^{1,2} Although great progress has been achieved in this special area, limited attention has been given to exploring the reaction scope by using functionalized nitroolefins as the Michael acceptors.^{2j,3} In terms of less reactive trisubstituted nitroolefins, only 1-nitrocyclohexene,⁴ 1-nitrocyclopentene,⁵ and Cbz-protected 1-aminomethyl nitroolefins^{3f} have been reported to be suitable substrates for this reaction. Quiet recently, Wennemers and Duschmalé reported that Michael addition of β -aryl and α -methyl substituted nitroolefins with aldehydes could take place under the catalysis of some peptides.⁶

Obviously, the poor reactivity of trisubstituted nitroolefins is caused by their steric hindrance and electronic nature. We envisioned that introduction of an additional electron-withdrawing group might enhance their reactivity, and we therefore tried to use 3-substituted 3-nitroacrylates as the Michael acceptors. We were pleased to find that Michael addition of these olefins with aldehydes under the catalysis of *O*-TMS protected diphenyl-prolinol occurred to afford the corresponding Michael adducts. Further attempts revealed that some β -aryl and α -methyl substituted nitroolefins also worked under these conditions. Herein we wish to report our results.

2. Results and discussion

2.1. Michael addition of aldehydes to 3-substituted 3-nitroacrylates

The required Michael acceptors. (*E*)-ethyl-3-nitrobut-2-enoate 1a and (E)-ethyl-3-nitropent-2-enoate 1b were prepared from ethyl glyoxylate according to Stewart's⁷ and Stephens'⁸ procedures. Reaction of **1a** with pentan-1-al as a model, we explored the suitable conditions for this Michael addition. As indicated in Table 1, it was found that under the catalysis of 10 mol% O-TMS protected diphenyl-prolinol 3 and 10 mol% benzoic acid, the reaction proceeded in water at room temperature to afford the desired Michael adduct 2a, together with other diastereomers. The ratio for these isomers was about 81:2:5:13 as measured by ¹H NMR spectroscopy, and ee value of **2a** was greater than 99% (entry 1). Changing solvent from water to chloroform gave a better yield and improved diastereoselectivity (entry 2), while the best result was observed by using methylene chloride as the reaction solvent (entry 3). When less polar solvents were used, the reaction turned to be rather sluggish and unsatisfactory yields and stereochemistry were obtained (entries 4 and 5). Interestingly, Michael addition did not occur in three other commonly used solvents, methanol, acetonitrile, and THF (entries 6-8). In this case pentan-1-al might undergo some side reactions under these conditions, because the nitroolefin 1a was recovered. These results demonstrated that solvents have great influence to the present reaction, which has been seen in many organocatalytic Michael additions.^{1,2}

With the optimized conditions in hand, we explored the reaction scope by varying aldehydes and nitroolefins. As summarized



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Table 1

Effect of the solvents on the Michael addition of pentan-1-al to (E)-ethyl-3-nitrobut-2-enoate^a



Entry	Solvent	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1	H ₂ O	12	66	81:2:5:13	>99
2	CHCl ₃	24	86	~90:7:3	>99
3	CH_2Cl_2	12	86	~93:4:4	>99
4	Hexane	36	80	88:1:5:6	>99
5	Toluene	48	73	89:1:6:4	>99
6	MeOH	48	e	_	_
7	MeCN	48	e	_	_
8	THF	48	e	_	_

^a Reaction conditions: (*E*)-ethyl-3-nitrobut-2-enoate (0.2 mmol), pentan-1-al (0.4 mmol), **3** (0.02 mmol), benzoic acid (0.02 mmol), solvent (0.4 ml), rt.

^b Isolated yield for a mixture of diastereoisomers.

^c Determined by ¹H NMR spectroscopy of the crude product.

^d Determined by chiral-phase HPLC of isolated product (for major isomer).

^e No desired adducts were determined and **1a** was recovered.

in Table 2, greater than 90% diastereoselectivity was also observed when butvraldehvde. 3-methylbutanal. and 2-phenylacetaldehvde were utilized (entries 1, 3, and 4). However, when propionaldehyde was used, the reaction gave the corresponding adduct in only 37% yield with poor diastereoselectivity (entry 2), indicating that the size of the aldehydes plays an important role during the reaction course. To our delight, two functionalized aldehydes worked well, affording adducts **2f** and **2g** in good yields. Their additional functional groups would allow further manipulation for assembling more complicated molecules. The reaction of (E)-ethyl-3-nitropent-2-enoate **1b** with two aldehydes also proceeded smoothly (entries 7 and 8), illustrating that tuning the α -position of the nitroproducts is possible. Noteworthy is that recrystallization of the adduct 2i could afford a single crystal, which allowed us to determine its stereochemistry via X-ray analysis. As shown in Fig. 1, Xray analysis of 2i clearly indicated that the major isomer has a syn,anti-structure. This result implied that after Michael addition, protonation could stereoselectively occur to control the stereochemistry of the nitro group.

2.2. Michael addition of aldehydes to $\beta\text{-aryl}$ and $\alpha\text{-methyl}$ substituted nitroolefins

Further attempts revealed that some β -aryl and α -methyl substituted nitroolefins were compatible with the standard reaction conditions, providing the Michael adducts with good yields (Table 3). Their reactivity was found to be highly dependent on the electronic nature of the aromatic ring, as shown by reaction of nitro-embodied substrate being much faster that that of methoxy substituted nitroolefin (compare entries 2 and 3).

2.3. Conversion of Michael adducts to polysubstituted pyrrolidines

These Michael adducts are obviously ideal precursors for synthesizing polysubstituted pyrrolidines. To illustrate this possibility, we carried out hydrogenation of **2a** under the catalysis of $Pd(OH)_2/C$. It was found that the reaction took place in methanol, furnishing pyrrolidine **6** in 75% yield, upon treatment with TsCl/TEA. Its stereochemistry was established via NOSEY studies,

Table 2

Vichael addition of aldehydes to 3-substituted 3-nitroacrylates ^a								
E	tO ₂ C NO ₂ 10	10 mol % 3 10 mol % PhCO ₂ H		$O CO_2Et$				
	R'∖_,CHO C	H ₂ Cl ₂ , rt	→ H' Y Y Y Z					
	~		2					
Entry	Product	Yield ^b (%)	dr ^c	ee ^d (%)				
1	$H \xrightarrow{O CO_2Et}_{Et Me} NO_2$	80	90:1:4:5	>99				
2	$H \xrightarrow{O CO_2Et}_{Me Me} NO_2$	37	48:9:17:26	97				
3	H H Pr- <i>i</i> Me 2d	82	93:2:5	>99				
4	$H \xrightarrow{O CO_2Et}_{Bn Me} NO_2$	82	93:6:1	>99				
5	H CI 2f CO2Et	65	84:7:9	>99				
6	H H U ₆ CO ₂ Et NO ₂ Me	75	90:7:3	>99				
7	$H \xrightarrow{O CO_2Et}_{Pr-n Et} NO_2$	79	92:7:1	>99				
8	H CO ₂ Et Bn Ēt 2i	83	97:3	98				

^a Reaction conditions: **1** (0.2 mmol), aldehyde (0.4 mmol), **3** (0.02 mmol), benzoic acid (0.02 mmol), methylene chloride (0.4 ml), rt, 12–24 h.

^b Isolated yield for a mixture of diastereoisomers.

^c Determined by ¹H NMR spectroscopy of the crude product.

^d Determined by chiral-phase HPLC of isolated product (major isomer).

which is consistent with that observed for **2i** via X-ray analysis (Scheme 1).

3. Conclusions

In conclusion, we have demonstrated that two classes of trisubstituted nitroolefins, 3-substituted 3-nitroacrylates, and β -aryl and α -methyl substituted nitroolefins, are suitable substrates for organocatalytic Michael addition. Their reaction with aldehydes could afford *syn,anti*-products with good diastereoselectivity and excellent enantioselectivity. These products could be easily converted into polysubstituted pyrrolidines. Our result further illustrated the potential usage of this organocatalytic reaction in organic synthesis.



Fig. 1. X-ray structure of 2i.

Table 3

Michael addition of aldehydes to $\beta\text{-aryl}$ and $\alpha\text{-methyl}$ substituted nitroolefins a

Ar NO ₂ 4 Me _		10 mol % 3 10 mol % PhCO ₂ H		H NO2	
<i>n</i> -Pr>+ CHO		CH ₂ Cl ₂ , rt		Pr- <i>n</i> Me	
				5	
Entry	Ar (product)	Time (h)	Yield ^b (%)	dr ^c	ee ^d (%)
1	Ph (5a)	48	74	94:4:2	98
2	$4-NO_2C_6H_4(5b)$	10	90	92:1:2:5	>99
3	$4-MeOC_{6}H_{4}(5c)$	48	60	91:5:4	>99
4	2-Naphthyl (5d)	24	88	96:1:3	95

^a Reaction conditions: **4** (0.2 mmol), pentan-1-al (0.4 mmol), **3** (0.02 mmol), benzoic acid (0.02 mmol), methylene chloride (0.4 ml), rt.

^b Isolated yield for a mixture of diastereoisomers.

^c Determined by ¹H NMR spectroscopy of the crude product.

^d Determined by chiral-phase HPLC of isolated product (major isomer).



4. Experimental

4.1. General remarks

All solvents were purified and dried prior to use. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter in the solvent indicated. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz, and assigned in parts per million (δ). ¹H NMR chemical shifts were given on the δ scale (ppm) and were referenced to internal TMS. Reference peaks for chloroform in ¹³C NMR spectra were set at 77.0 ppm. For DMSO-*d*₆, the reference peaks in ¹H NMR and ¹³C NMR spectra were set at 2.50 and 40.0 ppm, respectively. Low-resolution mass spectra were recorded on a GILENT5973 instrument (EI) and an LCMS-2010EV instrument (ESI). High-resolution mass spectra were recorded on an IonSpec 4.7 Tesla FTMS instrument. Silica gel plate GF₂₅₄ was used for thin layer chromatography (TLC) and silica gel Silicycle (60 A, 40–63 μ m, purchased from a Canada Co. Int.) was used for flash column chromatography. Enantiomeric excesses were determined by HPLC using an IC-H column (wavelength=254 or 214 nm) with hexane/*i*-PrOH as the eluent.

4.2. General procedure for the Michael addition of aldehydes to trisubstituted nitroolefins

Aldehyde (0.4 mmol) was added to a suspension of catalyst **3** (0.02 mmol), (*E*)-ethyl-3-nitrobut-2-enoate (0.2 mmol), and benzoic acid (0.02 mmol) in methylene chloride (0.4 ml) at 0 °C. After 0.5 h at 0 °C, the reaction mixture was allowed to warm to room temperature and then stirred until the starting material was consumed as monitored by TLC. The solvent was removed at reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate) to afford the Michael adduct.

4.2.1. Ethyl (2R,3R)-3-formyl-2-((R)-1-nitroethyl)hexanoate (**2a**). Colorless oil, 42 mg (86%), $[\alpha]_D^{27}$ +40.5 (*c* 0.95, CHCl₃); IR (neat): 2983, 2854, 1727, 1556, 1462, 1396, 1386, 1204, 1019, 966, 871 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H, CHO), 4.99–4.91 (m, 1H, CHNO₂), 4.18–4.13 (m, 2H, OCH₂CH₃), 3.57–3.53 (m, 1H, CHCO₂), 2.61–2.56 (m, 1H, CHCHO), 1.69–1.64 (m, 1H, CH_aH_bCH₂), 1.61 (d, *J*=6.4 Hz, 3H, CHCH₃), 1.50–1.41 (m, 1H, CH_aH_bCH₂), 1.38–1.26 (m, 2H, CH₂CH₃), 1.23 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 0.92 (t, *J*=7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 201.1, 169.7, 81.2, 61.8, 49.4, 48.2, 27.9, 20.8, 17.8, 14.1, 14.0; HRMS (ESI) *m/z* calcd for C₁₁H₁₉NNaO₅ (M+Na)⁺ 268.1161, found: 268.1162. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=21.27 min (major), *t*_R=40.37 min (minor); ee=99%.

4.2.2. Ethyl (2R,3R)-3-formyl-2-((R)-1-nitroethyl)pentanoate (**2b**). Colorless oil, 37 mg (80%), $[\alpha]_D^{28}$ +47.28 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H, CHO), 4.99–4.92 (m, 1H, CHNO₂), 4.19–4.13 (m, 2H, –OCH₂CH₃), 3.55–3.51 (m, 1H, CHCO₂–), 2.60–2.55 (m, 1H, CHCHO), 1.74–1.66 (m, 1H, CH_aH_bCH₂), 1.61 (d, *J*=7.2 Hz, 3H, CHCH₃), 1.53–1.47 (m, 1H, CH_aH_bCH₂), 1.23 (t, *J*=6.8 Hz, 3H, OCH₂CH₃), 0.98 (t, *J*=7.2 Hz, 3H, CHC₃); ¹³C NMR (100 MHz, CDCl₃) δ 201.1, 169.7, 81.2, 61.9, 51.1, 48.1, 19.1, 17.8, 14.1, 11.9; HRMS (ESI) *m/z* calcd for C₁₀H₁₇NNaO₅ (M+Na)⁺ 254.1005, found: 254.1000. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=16.72 min (major), *t*_R=26.52 min (minor); ee=99%.

4.2.3. Ethyl (2R,3R)-3-methyl-2-((R)-1-nitroethyl)-4-oxobutanoate (**2c**). Colorless oil, 16 mg (37%), $[\alpha]_D^{29} + 32.74$ (*c* 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H, CHO), 4.98–4.94 (m, 1H, CHNO₂), 4.18–4.13 (m, 2H, OCH₂CH₃), 3.72–3.68 (m, 1H, CHCO₂), 2.64–2.61 (m, 1H, CHCHO), 1.64 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.22 (t, *J*=6.8 Hz, 3H, OCH₂CH₃), 1.09 (d, *J*=6.8 Hz, 3H, CHCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.3, 169.6, 81.2, 62.0, 48.3, 44.7, 17.8, 14.0, 9.4; HRMS (ESI) *m/z* calcd for C₉H₁₅NNaO₅ (M+Na)⁺ 240.0848, found: 240.0843. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/ min, 214 nm, *t*_R=15.32 min (major), *t*_R=20.32 min (minor); ee=97%.

4.2.4. Ethyl(2R,3R)-3-formyl-4-methyl-2-((R)-1-nitroethyl)pentanoate (**2d**). Colorless oil, 40 mg (82%), $[\alpha]_D^{28}$ +102.29 (*c* 0.50, CHCl₃); IR (neat): 2970, 2939, 1736, 1555, 1446, 1365, 1227, 1216, 1021, 865 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.90 (d, *J*=1.2 Hz, 1H, CHO), 4.92–4.85 (m, 1H, CHNO₂), 4.21–4.16 (q, *J*=7.6 Hz, 2H, OCH₂CH₃), 3.33–3.30 (m, 1H, CHCO₂), 3.05–3.01 (m, 1H, CHCHO), 1.98–1.90 (m, 1H, CH(CH₃)₂), 1.55 (d, *J*=6.4 Hz, 3H, CHCH₃), 1.26 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 1.19 (d, *J*=7.2 Hz, 3H, CHMe_aMe_b), 0.93 (d, *J*=6.8 Hz, 3H,

CHMe_a*Me*_b); ¹³C NMR (100 MHz, CDCl₃) δ 202.9, 169.8, 80.5, 61.7, 55.0, 48.1, 29.0, 21.7, 18.0, 17.3, 14.1; HRMS (ESI) *m/z* calcd for C₁₁H₁₉NNaO₅ (M+Na)⁺ 268.1161, found: 268.1157. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=11.57 min (major), *t*_R=16.77 min (minor); ee=99%.

4.2.5. Ethyl (2R,3R)-3-benzyl-2-((R)-1-nitroethyl)-4-oxobutanoate (**2e**). Colorless oil, 48 mg (82%), $[\alpha]_D^{30}$ –4.13 (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H, CHO), 7.31 (t, *J*=7.2 Hz, 2H, CH=C), 7.26 (d, *J*=7.2 Hz, 1H, CH=C), 7.16 (d, *J*=7.2 Hz, 2H, CH=C), 4.86–4.79 (m, 1H, CHNO₂), 4.22–4.15 (m, 2H, OCH₂CH₃), 3.65–3.62 (m, 1H, CHCO₂), 3.13 (dd, *J*=8.0, 14.4 Hz, 1H, CH_aH_bPh), 2.98–2.94 (m, 1H, CHCHO), 2.64 (dd, *J*=6.0, 14.4 Hz, 1H, CH_aH_bPh), 1.48 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.25 (t, *J*=7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.4, 169.6, 137.7, 129.1, 129.0 (2C), 127.3 (2C), 80.9, 62.1, 51.5, 48.6, 32.1, 17.8, 14.1; HRMS (ESI) *m/z* calcd for C₁₅H₁₉NNaO₅ (M+Na)⁺ 316.1161, found: 316.1165. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=19.17 min (major), *t*_R=33.77 min (minor); ee=99%.

4.2.6. *Ethyl* (2*R*,3*R*)-6-*chloro*-3-*formyl*-2-((*R*)-1-*nitroethyl*)*hexanoate* (**2***f*). Colorless oil, 36 mg (65%), $[\alpha]_D^{29} + 15.95$ (*c* 1.05, CHCl₃); IR (neat): 2962, 2928, 2853, 1732, 1555, 1447, 1392, 1360, 1197, 1019, 868 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H, *CHO*), 5.01–4.94 (m, 1H, *CHNO*₂), 4.21–4.11 (m, 2H, OCH₂CH₃), 3.62–3.58 (m, 1H, *CHCO*₂), 3.53 (t, *J*=6.4 Hz, 2H, *CH*₂Cl), 2.65–2.61 (m, 1H, *CHCHO*), 2.01–1.92 (m, 1H, *CH*₄H_bCH₂), 1.79–1.71 (m, 2H, *CH*₂CH₂), 1.65 (d, *J*=7.2 Hz, 3H, CHCH₃), 1.63–1.56 (m, 1H, *CH*₄H_bCH₂), 1.23 (t, *J*=7.6 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.2, 169.5, 81.1, 62.1, 49.0, 48.0, 44.4, 33.1, 22.7, 17.9, 14.0; HRMS (ESI) *m/z* calcd for C₁₁H₁₈ClNNaO₅ (M+Na)⁺ 302.0772, found: 302.0769. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=12.37 min (major), *t*_R=19.67 min (minor); ee=99%.

4.2.7. *Ethyl* (2*R*,3*R*)-3-formyl-2-((*R*)-1-nitroethyl)dodec-11-enoate (**2g**). Colorless oil, 49 mg (75%), $[\alpha]_D^{28}$ +29.17 (*c* 1.35, CHCl₃); IR (neat): 3075, 2998, 2927, 2855, 1736, 1720, 1556, 1442, 1364, 1217, 908 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H, *CHO*), 5.83–5.76 (m, 1H, CH₂=CH), 5.00–4.91 (m, 3H, CHNO₂, CH₂=CH), 4.18–4.13 (m, 2H, OCH₂CH₃), 3.55–3.52 (m, 1H, CHCO₂), 2.59–2.57 (m, 1H, CHCHO), 2.05–2.00 (m, 2H, CH₂CH=CH₂), 1.61 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.39–1.36 (m, 4H, CH₂CH₂), 1.27–1.21 (m, 11H, (CH₂)₄, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 201.2, 169.8, 139.1, 114.4, 81.2, 62.0, 49.7, 48.3, 33.8, 29.7, 29.3, 29.1, 28.9, 27.6, 26.0, 17.9, 14.1; HRMS (ESI) *m/z* calcd for C₁₇H₂₉NNaO₅ (M+Na)⁺ 350.1944, found: 350.1951. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=17.35 min (major), *t*_R=31.78 min (minor); ee=99%.

4.2.8. Ethyl (2R,3R)-3-formyl-2-((R)-1-nitropropyl)hexanoate (**2h**). Colorless oil, 41 mg (79%), $[\alpha]_D^{28}$ +45.70 (*c* 1.05, CHCl₃); IR (neat): 2964, 2938, 2867, 1739, 1556, 1463, 1375, 1192, 1028, 811 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H, CHO), 4.84–4.79 (m, 1H, CHNO₂), 4.18–4.13 (m, 2H, OCH₂CH₃), 3.58–3.55 (m, 1H, CHCO₂), 2.58–2.54 (m, 1H, CHCHO), 1.99–1.88 (m, 2H, CH₂CH₃), 1.71–1.61 (m, 1H, CH_aH_bCH₂), 1.51–1.42 (m, 1H, CH_aH_bCH₂), 1.38–1.31 (m, 2H, CH₂CH₃), 1.23 (t, *J*=7.2 Hz, 3H, OCH₂CH₃), 1.00 (t, *J*=8.0 Hz, 3H, CH₂CH₃), 0.92 (t, *J*=7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 201.2, 169.7, 87.0, 61.9, 49.4, 46.8, 28.1, 24.6, 20.8, 14.2, 14.1, 9.6; HRMS (ESI) *m/z* calcd for C₁₂H₂₁NNaO₅ (M+Na)⁺ 282.1318, found: 282.1313. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=17.45 min (major), *t*_R=23.41 min (minor); ee=99%.

4.2.9. *Ethyl* (2*R*,3*R*)-3-*nitro*-2-((*R*)-1-oxo-3-*phenylpropan*-2-*yl*)*pentanoate* (**2i**). Colorless oil, 51 mg (83%), [α]_D²⁸ +1.57 (*c* 1.05, CHCl₃); IR (neat): 3085, 3064, 3027, 2982, 2943, 2885, 1735, 1553, 1455, 1378, 1246, 1200, 1012, 893, 859, 804, 744, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H, CHO), 7.32 (t, *J*=6.8 Hz, 2H, CH=C), 7.26 (m, 1H, CH=C), 7.16 (d, *J*=7.2 Hz, 2H, CH=C), 4.69–4.64 (m, 1H, CHNO₂), 4.22–4.16 (m, 2H, OCH₂CH₃), 3.68–3.65 (m, 1H, CHCO₂), 3.13 (dd, *J*=8.0, 14.4 Hz, 1H, CH_aH_bPh), 2.96–2.91 (m, 1H, CHCHO), 2.65 (dd, *J*=6.0, 14.4 Hz, 1H, CH_aH_bPh), 1.85–1.77 (m, 2H, CH₂CH₃), 1.27 (t, *J*=6.8 Hz, 3H, OCH₂CH₃), 0.86 (t, *J*=7.6 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 200.4, 169.6, 137.7, 129.1 (2C), 129.0 (2C), 127.3, 86.8, 62.1, 51.4, 47.1, 32.2, 24.6, 14.1, 9.5; HRMS (ESI) *m/z* calcd for C₁₆H₂₁NNaO₅ (M+Na)⁺ 330.1318, found: 330.1323. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=20.72 min (major), *t*_R=24.07 min (minor); ee=98%.

4.2.10. (2R,3S,4R)-4-Nitro-3-phenyl-2-propylpentanal (**5a**). Colorless oil, 37 mg (74%), $[\alpha]_D^{28}$ +62.03 (*c* 0.95, CHCl₃); IR (neat): 3086, 3065, 2958, 2932, 2872, 1722, 1545, 1454, 1389, 1361, 852, 736, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.83 (d, *J*=1.6 Hz, 1H, *CHO*), 7.32–7.30 (m, 3H, *CH*=C), 7.06–7.04 (m, 2H, *CH*=C), 5.06–4.99 (m, 1H, *CH*NO₂), 3.43–3.11 (m, 1H, *CHP*h), 3.16–3.11 (m, 1H, *CHCHO*), 1.42 (d, *J*=6.8 Hz, 3H, *CHCH*₃), 1.40–1.35 (m, 2H, *CH*₂CH₃), 1.31–1.23 (m, 1H, *CH*₂*CH*₃), 1.20–1.10 (m, 1H, *CH*₂*H*_b*CH*₂), 0.77 (t, *J*=7.2 Hz, 3H, *CH*₂*CH*₃); ¹³C NMR (100 MHz, CDCl₃) δ 204.2, 135.2, 129.0 (2C), 128.9 (2C), 128.3, 83.8, 51.9, 49.2, 30.0, 19.6, 17.6, 14.2; HRMS (ESI) *m/z* calcd for C₁₄H₁₉NNaO₃ (M+Na)⁺ 272.1263, found: 272.1265. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=13.44 min (major), *t*_R=15.71 min (minor); ee=98%.

4.2.11. (2R,3S,4R)-4-Nitro-3-(4-nitrophenyl)-2-propylpentanal (**5b**). Colorless oil, 53 mg (90%), $[\alpha]_D^{29}$ +62.03 (*c* 0.95, CHCl₃); IR (neat): 3230, 3086, 2969, 2873, 1736, 1723, 1551, 1522, 1455, 1363, 1349, 1228, 1216, 854 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.86 (d, *J*=1.2 Hz, 1H, CHO), 8.20 (d, *J*=8.4 Hz, 2H, CH=C), 7.26 (d, *J*=8.8 Hz, 2H, CH=C), 5.11–5.05 (m, 1H, CHNO₂), 3.58–3.54 (m, 1H, CHC₆H₄NO₂), 3.22–3.16 (m, 1H, CHCHO), 1.43 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.39–1.33 (m, 2H, CH₂CH₃), 1.31–1.25 (m, 1H, CH_aH_bCH₂), 1.22–1.15 (m, 1H, CHa_H_bCH₂), 0.78 (t, *J*=7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 203.0, 147.9, 142.8, 130.2 (2C), 124.0 (2C), 83.4, 51.4, 48.6, 30.0, 19.4, 17.6, 14.1; HRMS (ESI) *m/z* calcd for C₁₄H₁₉N₂O₅ (M+H)⁺ 295.1294, found: 295.1293. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=43.12 min (major), *t*_R=46.52 min (minor); ee=99%.

4.2.12. (2R,3S,4R)-3-(4-Methoxyphenyl)-4-nitro-2-propylpentanal (**5c**). Colorless oil, 33 mg (60%), $[\alpha]_{D}^{29}$ +71.36 (*c* 0.55, CHCl₃); IR (neat): 3001, 2969, 2956, 2929, 1723, 1549, 1514, 1456, 1364, 1253, 1228, 1217, 1033, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.81 (d, *J*=2.0 Hz, 1H, CHO), 6.96 (d, *J*=8.4 Hz, 2H, CH=C), 6.83 (d, *J*=8.8 Hz, 2H, CH=C), 5.01–4.95 (m, 1H, CHNO₂), 3.78 (s, 3H, OCH₃), 3.37–3.33 (m, 1H, CHC₆H₄OMe), 3.11–3.05 (m, 1H, CHCHO), 1.40 (d, *J*=6.8 Hz, 3H, CHCH₃), 1.38–1.32 (m, 2H, CH₂CH₃), 1.30–1.23 (m, 1H, CH₄H_bCH₂), 1.18–1.11 (m, 1H, CH₄H_bCH₂), 0.77 (t, *J*=7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 204.4, 159.5, 130.0 (2C), 127.0, 114.2 (2C), 84.0, 55.3, 52.0, 48.5, 30.0, 19.6, 17.6, 14.2; HRMS (ESI) *m/z* calcd for C₁₅H₂₁NNaO₄ (M+Na)⁺ 302.1369, found: 302.1373. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/ min, 214 nm, *t*_R=25.57 min (major), *t*_R=30.82 min (minor); ee=99%.

4.2.13. (2R,3S,4R)-3-(Naphthalen-2-yl)-4-nitro-2-propylpentanal (**5d**). Colorless oil, 53 mg (88%), $[\alpha]_D^{28}$ +76.53 (*c* 1.00, CHCl₃); IR (neat): 3060, 2957, 2940, 2870, 1723, 1541, 1463, 1389, 1352, 1127, 995, 867, 851, 826, 813, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.89 (d, J=1.6 Hz, 1H, CHO), 7.84–7.79 (m, 3H, CH=C), 7.54–7.48 (m, 3H, CH=C), 7.15 (d, J=9.2 Hz, 1H, CH=C), 5.14–5.08 (m, 1H, CHNO₂), 3.60–3.56 (m, 1H, CHnaphthyl), 3.28–3.23 (m, 1H, CHCHO), 1.46 (d, J=6.8 Hz, 3H, CHCH₃), 1.43–1.38 (m, 2H, CH₂CH₃), 1.33–1.25 (m, 1H, CH_aH_bCH₂), 1.22–1.13 (m, 1H, CH_aH_bCH₂), 0.74 (t, *J*=7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 204.3, 133.3, 133.2, 132.7, 128.7, 128.7, 128.0, 127.8, 126.6, 126.5, 126.1, 83.8, 51.93, 49.3, 30.3, 19.6, 17.7, 14.2; HRMS (ESI) *m/z* calcd for C₁₈H₂₁NNaO₃ (M+Na)⁺ 322.1419, found: 322.1424. HPLC: IC column, hexane/*i*-PrOH=95:5, flow rate 0.7 ml/min, 214 nm, *t*_R=20.57 min (major), *t*_R=25.32 min (minor); ee=95%.

4.3. Ethyl (2*R*,3*R*,4*R*)-2-methyl-4-propyl-1-tosylpyrrolidine-3-carboxylate (6)

To a solution of 2a (145 mg, 0.6 mmol) in MeOH (18 ml) was added 10% Pd(OH)₂/C (30 mg). The resultant mixture was stirred under hydrogen at 5 atm for 24 h. After the catalyst was filtered off, the filtrate was concentrated and the residue was dissolved in CH₂Cl₂ (15 ml). To this solution were added TsCl (126 mg, 0.66 mmol) and TEA (0.13 ml, 0.9 mmol) at 0 °C. The mixture was stirred at room temperature overnight and quenched by adding 1 M HCl. The mixture was extracted with CH₂Cl₂, washed with brine, and dried over Na₂SO₄. Concentration and flash chromatography (1:50 to 1:20 EtOAc/hexanes as elute) afforded 6 (155 mg, 73%) as a colorless oil. $[\alpha]_D^{29}$ +2.99 (c 0.95, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J*=8.0 Hz, 2H, CH=C), 7.33 (d, *J*=8.0 Hz, 2H, CH=C), 4.16-4.10 (m, 2H, OCH2CH3), 4.08-4.03 (m, 1H, CHCH3), 3.68-3.64 (m, 1H, -NCHaHb-), 2.71-2.66 (m, 1H, -NCH_aH_b), 2.63-2.56 (m, 1H, CHCOOEt), 2.44 (s, 3H, -C₆H₄CH₃), 2.32-2.27 (m, 1H, CHCH₂), 1.46-1.38 (m, 1H, CH_aH_bCH₂CH₃), 1.26-1.22 (m, 2H, CH₂CH₃), 1.26 (t, J=7.2 Hz, 3H, OCH₂CH₃), 1.19 (d, J=6.4 Hz, 3H, CHCH₃), 1.02–1.92 (m, 1H, CH_aH_bCH₂CH₃), 0.86 (t, J=7.2 Hz, 3H, CH_aH_bCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.5, 143.7, 134.7, 129.9 (2C), 127.6 (2C), 60.9, 57.1, 53.5, 52.8, 38.6, 34.6, 21.7, 21.2, 19.2, 14.3, 14.2; HRMS (ESI) *m*/*z* calcd for C₁₈H₂₇NNaO₄S (M+Na)⁺ 376.1559, found: 376.1554.

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