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A domino reaction of a β-ketoester, phenylethylamine and ethyl glyoxylate: leading to chiral tricarboxylate containing multiple stereocenters

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ABSTRACT

A new type of chiral tricarboxylate containing multiple stereocenters was synthesized via the one-pot reaction of a β-ketoester, (*S*)-phenylethylamine, and ethyl glyoxylate. High yields and diastereoselectivities (up to 96:4 dr) were obtained under optimal conditions. The reaction of the chiral tricarboxylate with $Zn(BH_4)_2$ gave chiral γ-lactones in good yields with up to 92:8 dr. The structures and configurations of the new chiral tricarboxylates were characterized by X-ray diffraction analysis.

1. Introduction

The development of efficient methods to access complex molecules with multiple stereocenters continues to be a substantial challenge in both academic research and industrial applications.[1] Many methods have been developed for the synthesis of chiral complex molecules over the past decades. In recent years much attention is being paid to the Mannich reaction, which is one of the classical methods for the preparation of β-amino carbonyl compounds. This is mainly because nitrogen atoms exist in many drugs and natural products, as well as due to the potential of this multi-component reaction to generate molecular diversity in medicinal chemistry and evolutionary chemistry.[2] Furthermore, the asymmetric Mannich reaction of β-ketoesters with imines is one of the most efficient methods for constructing vicinal quaternary carbon stereocenters.[3] In 2003, Jørgensen et al. [4] reported the first asymmetric Mannich-type addition of unmodified β-ketosters to activated *N*-tosyl-α-imino esters catalyzed by chiral $Cu(OTf)_2$/BOX complexes to give excellent enantio- and diastereoselectivities. Subsequently, Sodeoka[5] reported the direct Mannich-type reaction of β-ketoesters with various imines catalyzed with chiral Palladium complex. Schaus et al.[6] developed cinchona alkaloid catalysts for indirect Mannich reactions of β-ketoesters with acyl imines. In addition, Deng et al. reported the indirect Mannich-type reaction of β-ketoesters and Boc-protected imines with bifunctional cinchona alkaloids as a catalyst,[7a] as well as the reaction with the in situ generation of carbamate-protected imines, catalyzed by a bifunctional thiourea cinchona alkaloid.[7b] On the other hand, the asymmetric Michael reaction is one of the most important strategies for constructing chiral 1,5-dicarbonyl skeletons in organic synthesis.[8] A great deal of chiral catalysts and methods have been developed in recent decades.[9] Among them, Koga and co-workers developed an asymmetric Michael reaction via chiral α,β-unsaturated aldimines,[10a] and studied the reaction using a chiral amine as the ligand and a ketone as the Michael donor.[10b,c] They also reported the Michael reaction of L-valine-based chiral lithioenamine of ethyl acetoacetate and alkylidene malonates.[10d–g] Christoffers et al. made extensive investigations on chiral auxiliaries and active metals for the Michael addition of 1,3-dicarbonyl compounds with vinyl ketones, especially, with valine diethylamide as the chiral auxiliary, with up to 99% ee being obtained at ambient temperature.[11] Herein, we report a domino reaction of a β-ketoester, phenylethylamine, and ethyl glyoxylate to produce a chiral tricarboxylate containing multi-functional groups and stereocenters under catalyst-free conditions.

2. Results and discussion

Usually, there are two general approaches to prepare chiral molecules, one is catalytic enantioselective reactions while the other is asymmetric inducement with a chiral auxiliary. Although asymmetric catalytic reactions have emerged as powerful tools for the preparation of enantiopure compounds in recent years, it is also necessary to use an inexpensive chiral auxiliary for the synthesis of complex molecules as an alternative method, especially for those with multiple stereogenic centers. Among the various chiral auxiliaries, α-phenylethylamine (α-PEA) is well known as a simple and powerful chiral adjuvant. Both enantiomers of α-PEA are readily available. Therefore, their recovery may not be critical even when used on a large scale. With this in mind, we began our investigation with methyl acetoacetate and the imine derived from ethyl glyoxylate and (*S*)-phenylethylamine, to obtain a multi-functional compound **1**. In addition to the anticipated Mannich addition product **1** (38% yield), a double β-ketoesters addition

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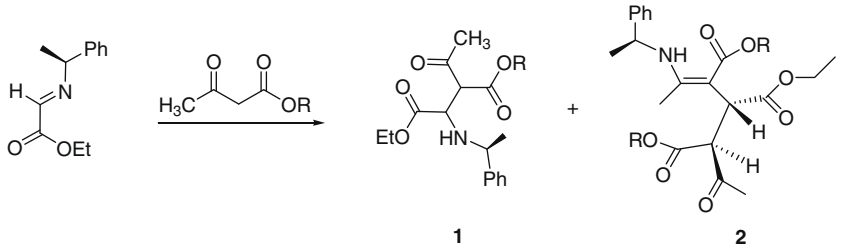


Scheme 1. The reaction of an imine with β-ketoesters.

product **2** (26%) was also obtained. Compound **2** was very stable in the work-up process. The other way round, compound **1** was partly converted to its diastereoisomer when purified with silica gel (see Scheme 1).

We then carried out a one-pot reaction using ethyl glyoxylate, (*S*)-phenylethylamine, and ethyl acetoacetate as the starting materials. Higher yields of compound **2** were obtained than those with imines as substrates. The results indicated that free amine and carbonyl compounds were favorable to form compound **2**. When the molecular ratio of β-ketoesters, ethyl glyoxylate, and (*S*)-phenylethylamine was changed to 2:1:1, we obtained compound **2** as the only product.

The single crystal of compound **2** was obtained, and the structure was characterized by X-ray diffraction analysis (Fig. 1). The (*S*)-configuration of C1 hails from (*S*)-phenylethylamine which induces another two new stereocenters at C14 (*R*) and C17 (*S*).

A possible mechanism of the reaction is shown in Scheme 2. Firstly, ethyl glyoxylate and (*S*)-phenylethylamine react with methyl acetoacetate to give the Knoevenagel product **5** and the enamine **4**. The Michael addition of **5** and **4** forms the chiral tricarboxylate derivative **2**.

On the other hand, the Mannich reaction product **1** also undergoes elimination to form compound **5** and phenylethylamine, which resulted in a mixture of products **1** and **2** when the imine and methyl acetoacetate were used as the starting materials (see Scheme 3).

The yields of the domino reaction of the β-ketoester, (*S*)-phenylethylamine, and ethyl glyoxylate were found to be sensitive to the choice of solvents. The use of dichloromethane, toluene, tetrahydrofuran, and acetonitrile gave yields ranging from 69% to 96% (Table 1, entries 1, 2 and 8, 9). Acetonitrile was found to be the best solvent for the reaction at room temperature (96% yields). Mixed solvents were found to be unfavorable to the reaction. For example, the yields slightly decreased when the mixture of the two solvents was used (Table 1, entry 3, Tol/DCM = 1:2, 65% yield; entry 4, Tol/DCM = 9:1, 67% yield). We studied this reaction further by using different β-ketoesters, such as methyl acetoacetate, ethyl acetoacetate, and *t*-butyl acetoacetate; among them methyl acetoacetate had shown a greater effect in the yields as well as in diastereoselectivity (Table 1, entries 9–11).

Other amines, such as (*S*)-1-naphthylethylamine, (*S*)-2-naphthylethylamine, and the ester of amino acids, were also tested for the reaction with β-ketoester and ethyl glyoxylate, and the results are listed in Table 2. The use of naphthylethylamine gave the normal domino reactions similar to that of phenylethylamine (Table 2, entries 1 and 2: 77% yields with 80:20 dr for (*S*)-1-naphthylethylamine, and 85% yields with 82:18 dr for (*S*)-2-naphthylethylamine were obtained, respectively). On the other hand, the reaction of the β-ketoester, ethyl glyoxylate, and the esters of amino acids gave only the enamine under the same reaction conditions (Table 2, entries 3–5). The stereo effect of the β-ketoester was very important for the reaction. For example, the reaction of methyl acetoacetate with ethyl glyoxylate and amines gave good to excellent chemical yields (Table 1, entry 9, 96% yield for phenylethylamine; Table 2, entries 1 and 2, 77% and 85% yields for 1- and 2-naphthylethylamine); however, under the same reaction conditions, the reaction of methyl 3-oxopentanoate provided lower yields (Table 2, entries 6–8, 73% yield for phenylethylamine, 61% and 65% for 1- and 2-naphthylethylamine, respectively). Methyl 4-methyl-3-oxopentanoate and ethyl 3-oxo-3-phenylpropanoate, which bear more hindered groups, only gave aldol reaction (Table 2, entries 9 and 10).

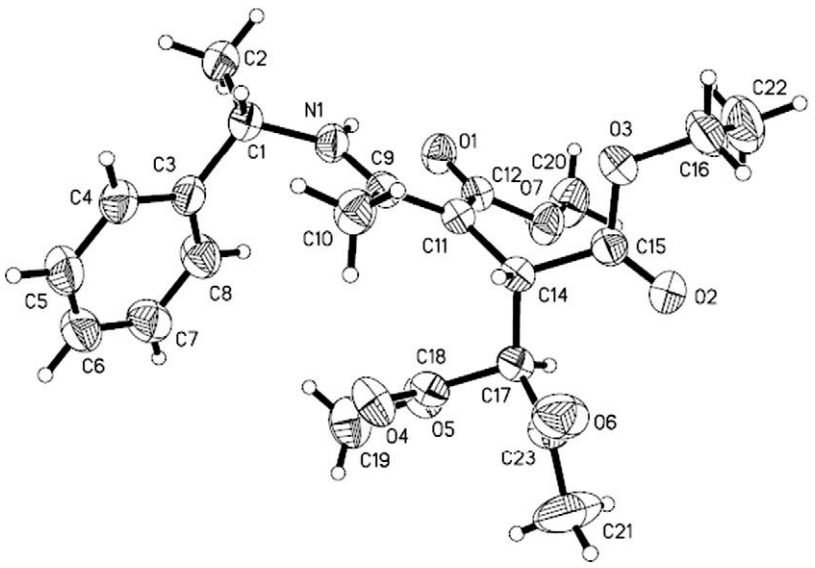
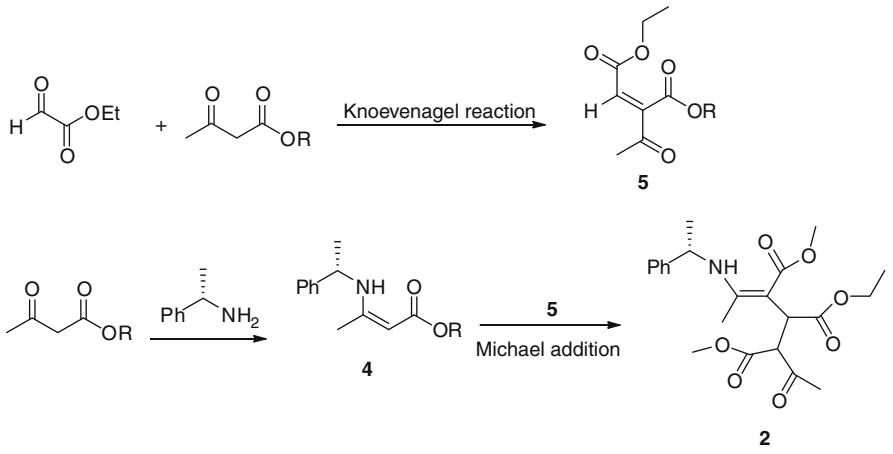
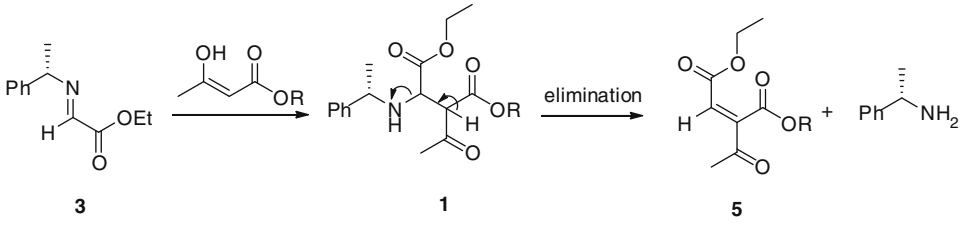


Figure 1. ORTEP of the molecule of chiral tricarboxylate bearing multi-functional groups and stereocenters at 50% probability (CCDC 696159).

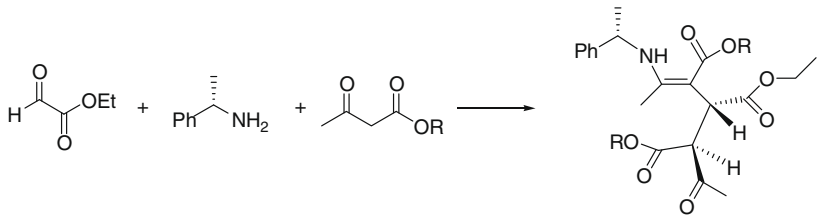


Scheme 2. The possible reaction mechanism.



Scheme 3. The other route to intermediate **5**.

Table 1
Optimization of the double β-ketoester addition conditions[a]



Entry	R	Solvent	Time (h)	Yields of **2**[c] (%)	dr[d] (major:others)
1(D)[b]	Me	Toluene	48	76	95:5
2(D)	Me	DCM	48	69	90:10
3(D)	Me	Tol/DCM = 1:2	48	65	96:4
4(D)	Me	Tol/DCM = 9:1	72	67	95:5
5(I)[b]	Me	Toluene	48	72	93:7
6(I)	Me	DCM	60	62	84:16
7(I)	Me	Tol/DCM = 5:1	48	74	95:5
8(D)	Me	THF	48	85	94:6
9(D)	Me	CH_3CN	40	96	96:4
10(D)	Et	CH_3CN	40	90	70:30
11(D)	*t*-Bu	CH_3CN	40	87	65:35

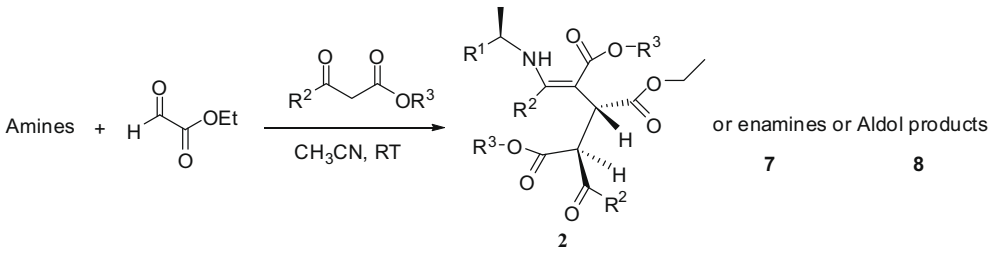
[a] All reactions were performed on a 0.8 mmol scale and the ratio of substrates was 1:1:2 (phenylethylamine–ethyl glyoxylate–β-ketoester).
[b] D: direct reaction (one-pot reaction of amine, ethyl glyoxylate, and β-ketoester); I: indirect reaction (the reaction of imine with β-ketoester).
[c] Isolated yield.
[d] Determined by ^1H NMR analysis of the flash chromatography purified product.

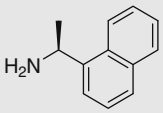
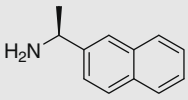
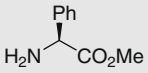
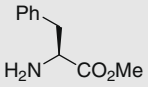
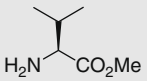
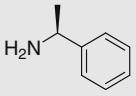
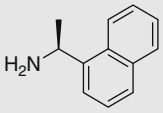
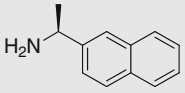
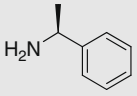
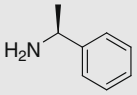
We also screened a simple aldehyde, such as benzaldehyde or propionaldehyde, and reacted it with an amine and β-ketoesters (Scheme 4). The results indicate that these simple aldehydes also gave aldol reactions under the same reaction conditions.

The chiral tricarboxylate derivative could be converted to other useful chiral compounds. For example, on reacting with zinc borohydride,[12] the chiral tricarboxylate derivative **2** was converted into the corresponding γ-lactone in high yield and stereoselectivity (up to 92:8 dr) (see Scheme 5).

In conclusion, we have found an unexpected domino reaction of β-ketoesters, amines, and ethyl glyoxylates, which gave a chiral tricarboxylate containing multi-functional groups and multi-stereocenters. The reaction could be carried out under very mild conditions without any catalyst or additives with high yields and

Table 2
The reaction of different amines, β-ketoesters, and ethyl glyoxylates[a]



Entry	Amines	R_2	R_3	Products	Times (h)	Yields[b] (%)	dr[c] (major:others)
1		Me	Me	**2d**	40	77	80:20
2		Me	Me	**2e**	40	85	82:18
3		Me	Me	**7a**	40	83	—
4		Me	Me	**7b**	40	86	—
5		Me	Me	**7c**	40	81	—
6		Et	Me	**2f**	40	73	50:50
7		Et	Me	**2g**	40	61	61:39
8		Et	Me	**2h**	40	65	71:29
9[d]		*i*-Prop	Me	**8a**	65	82	—
10		Ph	Et	**8b**	90	87	—

[a] All reactions were performed on a 0.8 mmol scale and the ratio of substrates was 1:1:2 (amine–ethyl glyoxylate–β-ketoester).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis of the flash chromatography purified product.
[d] Reactions of entries 9 and 10 were carried out at 40 °C.

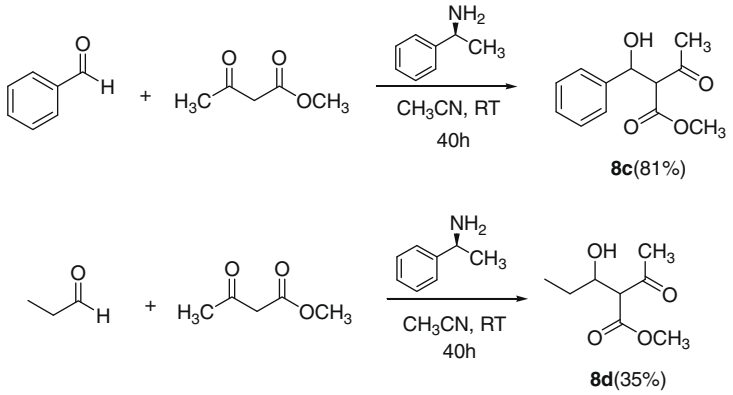
diasteroselectivities. Further studies on the scope and application of this reaction are currently underway.

3. Experimental

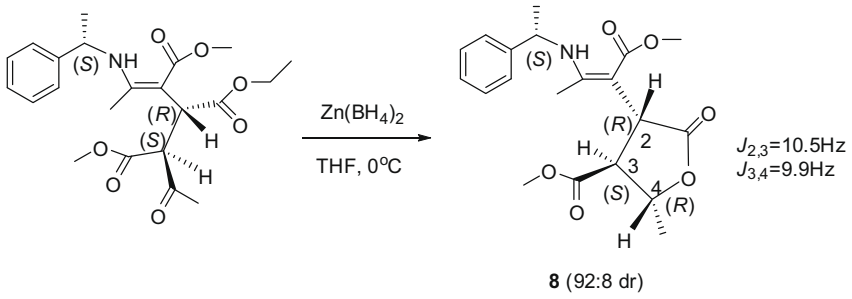
All reagents were purchased from either Acros or Aldrich Company and were used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-Plus 300 spectrometer. HRMS spectra were obtained on a VG-ZAB-HS mass spectrometer with EI resource.

3.1. The preparation of (*Z*)-4-ethyl 3,5-dimethyl 6-oxo-2-((*S*)-1-phenylethylamino)hept-2-ene-3,4,5-tricarboxylate 2a

To a dried flask containing (*S*)-phenylethylamine (0.100 g, 0.825 mmol) in 1 ml CH_3CN was added ethyl glyoxylate (0.169 g, 0.825 mmol, 50% solution in toluene) and stirred for 10 min at 0 °C, methyl acetoacetate (0.192 g, 1.650 mmol) in 0.8 ml CH_3CN was added in one portion. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 38 h. The solvent was removed under reduced pressure and the residue was purified



Scheme 4. The reaction of a simple aldehyde with an amine and β-ketoester.



Scheme 5. The reduction of chiral tricarboxylate derivative **2** with zinc borohydride.

by column chromatography to give the desired product (0.332 g, 0.792 mmol, 96% yield) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.02–10.00 (d, J = 6.0 Hz, 1H), 7.31–7.29 (t, J = 6.6 Hz, 2H), 7.21–7.16 (t, J = 8.1 Hz, 3H), 4.67 (dq, J = 6.6 Hz, J' = 6.9 Hz, 1H), 4.47 (d, J = 10.5 Hz, 1H), 4.26 (d, J = 10.5 Hz, 1H), 4.16–4.06 (m, 2H), 3.66 (s, 3H), 3.30 (s, 3H), 2.30 (s, 3H), 1.95 (s, 3H), 1.64 (d, J = 6.9 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 173.5, 170.2, 167.9, 162.7, 145.2, 129.0, 127.3, 125.6, 89.5, 61.2, 61.1, 53.8, 52.3, 50.6, 43.9, 30.5, 25.3, 16.3, and 14.6; HRMS (EI): m/z $[M]^+$ calcd for $C_{22}H_{29}NO_7$: 419.1944; found: 419.1939.

3.2. (*Z*)-Triethyl 6-oxo-2-((*S*)-1-phenylethylamino)hept-2-ene-3,4,5-tricarboxylate 2b

The preparation of **2b** was carried out in the same way as described for **2a**. Colorless solid, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (d, J = 6.9 Hz, 1H), 7.32 (t, J = 4.5 Hz, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 7.20 (t, J = 7.5 Hz, 2H), 4.67 (dq, J = 6.6 Hz, J' = 6.9 Hz, 1H), 4.50 (d, J = 10.2 Hz, 1H), 4.25 (d, J = 10.2 Hz, 1H), 4.18–4.00 (m, 6H), 2.30 (s, 3H), 1.98 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 1.28 (t, J = 6.9 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 173.6, 169.8, 167.7, 162.5, 145.3, 128.9, 127.3, 125.7, 89.5, 61.5, 61.2, 59.2, 53.8, 43.9, 30.4, 25.4, 16.4, 14.8, 14.5, and 14.3; HRMS (EI): m/z $[M]^+$ calcd for $C_{24}H_{33}NO_7$: 447.2257; found: 447.2252.

3.3. (*Z*)-3,5-Di-*tert*-butyl 4-ethyl 6-oxo-2-((*S*)-1-phenylethylamino)hept-2-ene-3,4,5-tricarboxylate 2c

The preparation of **2c** was carried out in the same way as described for **2a**. Colorless solid, 87% yield (both diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97–9.87 (m, 1H), 7.33 (d, J = 4.5 Hz, 2H), 7.27–7.21 (m, 3H), 4.63 (dq, J = 6.3 Hz, J' = 6.6 Hz, 1H), 4.45–4.30 (m, 1H), 4.17 (d, J = 10.5 Hz, 1H), 4.09–4.02 (m, 2H), 2.29 (s, 3H), 2.00 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 5.1 Hz, 3H), 1.49 (s, 9H), 1.40 (t, J = 6.6 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 201.7, 173.9, 169.5, 169.4, 167.0, 161.9, 152.5, 145.4, 128.8, 127.2, 127.0, 125.9, 110.0, 90.2, 81.7, 79.4, 69.9, 62.2, 62.1, 61.1, 53.9, 44.3, 35.8, 35.7, 33.3, 30.4, 30.3, 28.9, 28.2, 27.1, 25.5, 24.1, 23.3, 23.2, 20.5, 20.3, 20.1, 16.5, 16.4, 14.6, and 14.5; HRMS (EI): m/z $[M]^+$ calcd for $C_{28}H_{41}NO_7$: 503.2883; found: 503.2878.

3.4. The preparation of (*Z*)-4-ethyl 3,5-dimethyl 6-oxo-2-((*S*)-1-(1-naphthalen)-ethylamino)hept-2-ene-3,4,5-tricarboxylate 2d

The preparation of **2d** was carried out in the same way as described for **2a**. Colorless solid, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 8.4, 2H), 7.41 (t, J = 5.6 Hz, J' = 7.2 Hz, 1H), 7.34 (d, J = 6.0 Hz, 1H), 5.49 (dq, J = 6.6 Hz, J' = 6.9 Hz, 1H), 4.51 (d, J = 11.2, 1H), 4.27 (d, J = 10.4, 1H), 4.14–4.04 (m, 2H), 3.71 (s, 3H), 3.34 (s, 3H), 2.31 (s, 3H), 1.89 (s, 3H), 1.66 (d, J = 6.6 Hz, 3H), 1.19 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 173.4, 170.2, 167.8, 162.6, 140.7, 133.9, 129.8, 129.2, 127.8, 126.5, 125.8, 125.7, 122.4, 122.0, 89.5, 61.0, 60.8, 52.1, 50.3, 49.7, 43.6, 30.2, 23.8, 15.9 and 14.2; HRMS(EI): m/z $[M]^+$ calcd for $C_{26}H_{31}NO_7$: 469.2101; found: 469.2097.

3.5. The preparation of (*Z*)-4-ethyl-3,5-dimethyl 6-oxo-2-((*S*)-1-(2-naphthalen)-ethylamino)hept-2-ene-3,4,5-tricarboxylate 2e

The preparation of **2e** was carried out in the same way as described for **2a**. Colorless solid, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (d, J = 5.6 Hz, 1H), 7.80 (s, 4H), 7.45 (s, 2H), 7.34 (d, J = 8.8 Hz, 1H), 4.85 (dq, J = 6.4 Hz, J' = 6.6 Hz, 1H), 4.49 (d, J = 10.4 Hz, 1H), 4.27 (d, J = 10.4 Hz, 1H), 4.18–4.01 (m, 2H), 3.70 (s, 3H), 3.22 (s, 3H), 2.30 (s, 3H), 1.99 (s, 3H), 1.61 (d, J = 6.4 Hz,

3H), 1.18 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 173.4, 170.2, 167.8, 162.7, 152.6, 142.5, 133.5, 132.7, 128.8, 127.7, 127.6, 126.4, 125.9, 123.9, 123.8, 89.3, 61.0, 53.7, 52.0, 50.3, 43.6, 30.2, 24.9, 16.0 and 14.2; HRMS(EI): m/z $[M]^+$ calcd for $C_{26}H_{31}NO_7$: 469.2101; found: 469.2097.

3.6. Enamine 7a (Table 2, entry 3)

Colorless oil, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 7.2 Hz, 1H), 7.41–7.32 (m, 5H), 5.20 (d, J = 8.0 Hz, 1H), 4.58 (s, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 159.5, 137.4, 129.1, 128.5, 126.8, 85.0, 60.0, 53.0, 50.2, 29.7 and 19.6; HRMS(EI): m/z $[M]^+$ calcd for $C_{14}H_{17}NO_4$: 263.1158; found: 263.1155.

3.7. Enamine 7b (Table 2, entry 4)

Colorless oil, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 7.20 (d, J = 6.8 Hz, 2H), 4.45 (s, 1H), 4.32–4.26 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.16 (dd, J = 5.2 Hz, J' = 13.6 Hz, 1H), 2.98 (dd, J = 8.8 Hz, J' = 13.6 Hz), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 168.7, 158.1, 134.4, 127.5, 126.8, 125.3, 82.5, 56.1, 50.6, 48.3, 38.5 and 17.4; HRMS(EI): m/z $[M]^+$ calcd for $C_{15}H_{19}NO_4$: 277.1314; found: 277.1311.

3.8. Enamine 7c (Table 2, entry 5)

Colorless oil, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 8.8 Hz, 1H), 4.54 (s, 1H), 3.91 (dd, J = 6.0 Hz, J' = 10.0 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.23–2.15 (m, J = 6.4 Hz, 1H), 1.87 (s, 3H), 1.02 (d, J = 5.2 Hz, 3H), 1.00 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.9, 158.7, 82.3, 59.9, 50.3, 48.3, 30.0, 17.7, 17.4 and 16.1; HRMS(EI): m/z $[M]^+$ calcd for $C_{11}H_{19}NO_4$: 229.1314; found: 229.1311.

3.9. (*Z*)-5-Ethyl 4,6-dimethyl 7-oxo-3-((*S*)-1-phenylethylamino)non-3-ene-4,5,6-tricarboxylate 2f

The preparation of **2f** was carried out in the same way as described for **2a**. Colorless solid, 73% yield (both diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08–9.92 (m, 1H), 7.29 (t, J = 7.2 Hz, 3H), 7.19 (d, J = 7.2 Hz, 2H), 7.14 (d, J = 7.2 Hz, 1H), 4.64 (dq, J = 6.0 Hz, J' = 6.6 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.26 (d, J = 10.4 Hz, 1H), 4.12–4.05 (m, 2H), 3.67 (s, 3H), 3.26 (s, 3H), 2.75–2.22 (m, 3H), 2.15–2.06 (m, 1H), 1.53 (d, J = 6.4 Hz, 3H), 1.19 (t, J = 7.2 Hz, 6H), 1.07 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 202.4, 171.8, 168.7, 168.6, 167.6, 166.4, 166.2, 165.7, 143.8, 143.3, 127.1, 127.0, 125.4, 123.9, 123.6, 123.4, 86.7, 85.4, 59.2, 58.4, 56.5, 51.2, 51.1, 50.6, 50.1, 48.5, 41.6, 41.5, 37.0, 34.7, 23.3, 20.4, 20.2, 12.4, 10.8, 10.6, 5.9 and 5.4; HRMS(EI): m/z $[M]^+$ calcd for $C_{24}H_{33}NO_7$: 447.2257; found: 447.2253.

3.10. (*Z*)-5-Ethyl 4,6-dimethyl 7-oxo-3-((*S*)-1-(1-naphthalen)-ethylamino)non-3-ene-4,5,6-tricarboxylate 2g

The preparation of **2g** was carried out in the same way as described for **2a**. Colorless solid, 61% yield (both diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29–10.11 (m, 1H), 8.03 (t, J = 6.0 Hz, 1H), 7.87 (s, 1H), 7.73 (t, J = 6.4 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 9.6 Hz, 1H), 7.40 (d, J = 6.8 Hz, 1H), 5.47 (q, J = 6.6 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.26 (d, J = 10.8 Hz, 1H), 4.14–4.03 (m, 2H), 3.72 (s, 3H), 3.26 (s, 3H), 2.76–2.29 (m, 4H), 1.66 (d, J = 5.2 Hz, 3H), 1.26–1.19 (m, 6H), 1.07 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 204.7, 204.1, 203.8, 173.6, 170.6, 168.2, 167.9, 167.4, 163.3, 152.7, 141.3, 140.9, 138.3, 134.0, 133.9, 130.6, 129.8, 129.2, 129.0, 128.1, 127.7, 126.5, 126.3, 125.8, 125.7, 125.6, 124.4, 123.1, 122.3, 121.9, 88.8, 87.6, 70.0, 69.4, 64.3, 62.2, 61.8, 61.0, 60.8, 60.1, 58.3, 52.4, 52.0, 50.4, 49.1, 43.4, 43.3, 38.7, 36.4, 36.2, 29.7, 24.0, 23.0, 22.1, 14.2, 14.1, 14.0, 12.7, 12.5, 7.6, 7.4 and 7.2; HRMS(EI): m/z $[M]^+$ calcd for $C_{28}H_{35}NO_7$: 497.2414; found: 497.2410.

3.11. (*Z*)-5-Ethyl 4,6-dimethyl 7-oxo-3-((*S*)-1-(2-naphthalen)-ethylamino)non-3-ene-4,5,6-tricarboxylate 2h

The preparation of **2h** was carried out in the same way as described for **2a**. Colorless solid, 65% yield (both diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17–10.03 (m, 1H), 7.79 (s, 4H), 7.60 (d, J = 11.6 Hz, 1H), 7.45 (s, 2H), 4.78 (q, J = 6.6 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 10.4 Hz, 1H), 4.13–4.02 (m, 2H), 3.71 (s, 3H), 3.16 (s, 3H), 2.73–2.15 (m, 4H), 1.61 (d, J = 6.0 Hz, 3H), 1.26–1.18 (m, 6H), 1.08 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 204.7, 204.1, 203.8, 173.6, 170.6, 168.0, 167.5, 163.2, 152.6, 142.9, 140.1, 133.4, 132.8, 132.7, 132.6, 128.7, 128.4, 127.9, 127.8, 127.7, 127.6, 126.3, 126.2, 125.9, 125.8, 125.5, 125.0, 123.7, 123.5, 88.6, 87.3, 70.0, 69.7, 69.4, 62.2, 61.8, 61.2, 61.0, 60.8, 60.1, 58.3, 53.0, 51.9, 50.3, 43.3, 38.6, 36.4, 36.2, 29.7, 25.0, 23.7, 22.0, 14.2, 14.0, 12.6, 12.4, 12.0, 11.8, 7.6, 7.4 and 7.3; HRMS(EI): m/z $[M]^+$ calcd for $C_{28}H_{35}NO_7$: 497.2414; found: 497.2410.

3.12. Aldol product 8a (Table 2, entry 9)

Colorless oil, 82% yield (both diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 4.23 (q, J = 6.8 Hz, 2H), 3.83 (s, 3H), 2.89 (m, 1H), 2.03 (d, J = 12.8 Hz, 1H), 1.31–1.26 (m, 4H), 1.20 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 200.1, 164.1, 163.5, 146.5, 144.0, 129.5, 128.2, 61.8, 61.7, 53.0, 52.8, 41.1, 37.0, 29.7, 18.5, 17.7 and 14.0; HRMS(EI): m/z $[M]^+$ calcd for $C_{11}H_{18}O_6$: 246.1103; found: 246.1100.

3.13. Aldol product 8b (Table 2, entry 10)

Colorless oil, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 6.8 Hz, 2H), 7.07 (s, 1H), 4.25 (q, J = 6.0 Hz, 2H), 4.06 (q, J = 5.6 Hz, 2H), 1.60 (s, 1H), 1.26 (s, 1H), 1.21 (t, J = 6.8 Hz, 3H), 1.07 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 163.8, 163.2, 145.2, 135.8, 133.8, 130.7, 128.8, 128.7, 62.5, 61.7, 29.7, 13.9 and 13.6; HRMS(EI): m/z $[M]^+$ calcd for $C_{15}H_{18}O_6$: 294.1103; found: 294.1100.

3.14. Aldol product 8c

Colorless oil, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.35 (t, J = 2.8 Hz, 2H), 7.34 (t, J = 1.6 Hz, 2H), 7.32 (d, J = 3.2 Hz, 1H), 7.19 (s, 1H), 3.78 (s, 3H), 2.36 (s, 3H), 1.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 166.4, 139.8, 132.5, 131.0, 129.0, 127.6, 127.1, 50.7, 27.8 and 24.7; HRMS(EI): m/z $[M]^+$ calcd for $C_{12}H_{14}O_4$: 222.0892; found: 222.0889.

3.15. Aldol product 8d

Colorless oil, 35% yield (both diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 5.89 (dq, J = 1.6 Hz, J' = 1.2 Hz, 1H), 3.70 (s, 3H), 3.08 (d, J = 6.8 Hz, 1H), 2.54 (d, J = 4.4 Hz, 1H), 2.10 (d, J = 8.4 Hz, 1H), 1.91–1.88 (m, 3H), 1.46–1.36 (m, 2H), 1.35–1.25 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 198.0, 172.5, 170.7, 156.4, 155.5, 128.6, 128.2, 52.3, 52.1, 50.7, 39.9, 39.2, 39.1, 38.8, 29.7, 29.3, 26.6, 26.3, 23.3,

22.9, 11.4 and 11.0; HRMS(EI): *m/z* $[M]^+$ calcd for $C_8H_{14}O_4$: 174.0892; found: 174.0889.

3.16. Procedure for the reduction of 2a by zinc borohydride leading to: (2*R*,3*S*,4*R*)-methyl-4-((*Z*)-1-methoxy-1-oxo-3-((*S*)-1-phenylethylamino)but-2-en-2-yl)-2-methyl-5-oxo-tetrahydrofuran-3-carboxylate

To a dried flask containing $NaBH_4$ (0.235 g, 6.220 mmol) and freshly fused $ZnCl_2$ (0.424 g, 3.110 mmol) was added 5 ml of dry tetrahydrofuran at 0 °C. The mixture was stirred at room temperature for 24 h under an Ar atmosphere and then filtered by suction. The filtrate was cooled to 0 °C, after which compound **2a** (0.100 g, 0.238 mmol) in 1 ml of THF was added. After it was stirred at the same temperature for 24 h, the mixture was cooled with ice water and ethyl acetate (20 ml), and saturated NH_4Cl solution (20 ml) was added carefully for quenching the reaction. The organic layers were separated and the aqueous phase was extracted with ethyl acetate (20 ml × 2). The combined organic phase was washed (brine) and dried (magnesium sulfate). The removal of the solvent under reduced pressure gave the crude product which was purified by chromatography to give the reduced product **6** as a colorless oil (0.085 g, 0.226 mmol, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.31 (d, J = 7.2 Hz, 2H), 7.23 (t, J = 6.3 Hz, 3H), 4.67 (dq, J = 6.3 Hz, J' = 6.6 Hz, 1H), 4.49 (dq, J = 6.0 Hz, J' = 6.6 Hz, 1H), 3.90 (d, J = 10.5 Hz, 1H), 3.70 (s, 3H), 3.57 (s, 3H), 3.18 (t, J = 9.9 Hz, 1H), 1.90 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 172.5, 169.2, 162.6, 144.9, 129.0, 127.4, 125.6, 88.4, 75.7, 54.7, 53.9, 52.6, 50.7, 45.6, 25.4, 21.2, and 16.1; HRMS(EI): *m/z* $[M]^+$ calcd for $C_{20}H_{25}NO_6$: 375.1682; found: 375.1678.

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