JOC The Journal of Organic Chemistry

Brief Communication

pubs.acs.org/joc

Organocatalytic Kinetic Resolution of Racemic Secondary Nitroallylic Alcohols Combined with Simultaneous Desymmetrization of Prochiral Cyclic Anhydrides

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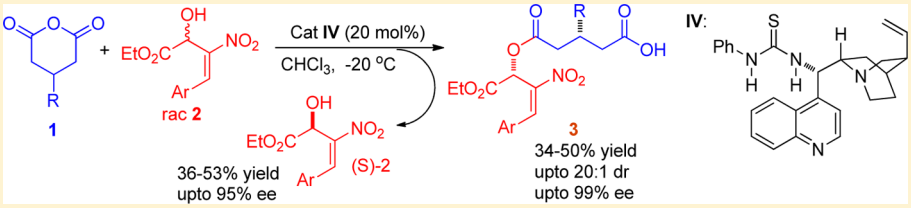
Supporting Information



ABSTRACT: This study describes an organocatalytic kinetic resolution of racemic secondary nitroallylic alcohols (**2**) combined with simultaneous desymmetrization of prochiral cyclic anhydrides (**1**). The experimental results revealed that enantioselective alcoholysis of 3-substituted glutaric anhydrides afforded hemiesters (**3**) with high levels of enantioselectivities (up to 99% ee) in the presence of cinchonidine-derived thiourea catalyst (**IV**). The highly optical enrichment (up to 95% ee) of (*S*)-nitroallylic alcohols (**2**) was recovered.

Preparing chiral nonracemic molecules with multiple stereogenic centers has long been a synthetic challenge in organic synthesis.[1] Many efficient synthetic protocols have been developed through either metal-mediated[2] or metal-free processes.[3] The conventional kinetic resolution (KR) that incorporates a chiral catalyst to promote enantioselective transformations remains a highly useful method for preparing optically enriched materials from their racemates.[4] The kinetic resolution of racemic secondary alcohols has received considerable attention because of functional group demonstrates considerable synthetic value. Enantioselective acylation has been extensively adopted in the kinetic resolution of racemic secondary alcohols.[5] The use of a small organic catalyst in kinetic resolution has been developed recently.[6] On the other hand, asymmetric desymmetrization is a valuable protocol in which a simple symmetry-breaking operation is performed for accessing chiral nonracemic molecules.[7] This operation enables establishing multiple stereogenic centers in the final products when *meso* compounds were used.[8] Desymmetrizing cyclic anhydrides generates dense functionalized and synthetically useful hemiesters with multiple chiral centers. Kinetic resolution processes are effective for the enantioselective ring opening of prochiral cyclic anhydrides.[7a,9]

Enantioselective syntheses have been recognized as a powerful strategy for asymmetric synthesis.[10] An interesting concept that combines kinetic resolution with asymmetric desymmetrization to prepare optically enriched substances has been demonstrated.[11] To our knowledge, functionalized racemic secondary alcohols have not been used for enantioselective alcoholysis of prochiral cyclic anhydrides. To extend our previous investigation on organocatalytic kinetic resolution,[12] we describe herein the desymmetrization of prochiral cyclic anhydrides by the use of racemic secondary nitroallylic alcohols.

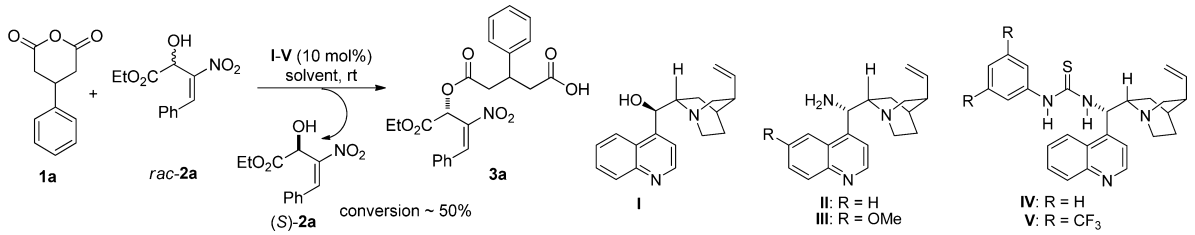
Initially, we attempted to desymmetrize 3-phenylglutaric anhydride (**1a**) with racemic 1-phenylethanol in the presence of various cinchona alkaloid derived organocatalysts. However, many attempts failed to obtain promising results. We then turned to the use of (±)-ethyl 2-hydroxy-3-nitro-4-phenylbut-3(*E*)-enoate (**2a**).[13] Cinchona alkaloid-based catalysts were used in the catalysis protocol, which involved a "general base catalysis mechanism".[7a,14] Our initial attempt to use cinchonidine (**I**) as the catalyst was not successful regarding the ee of both the product and recovered starting substrate (Table 1, entry 1). Thus, primary amine derivatives of cinchona alkaloids (**II** and **III**) were used. However, these catalysts were not effective because both the product and starting material were obtained with inferior results (Table 1, entries 2 and 3). In contrast, cinchonidine-derived thiourea catalysts (**IV** and **V**) were found to be promising and equally efficient. We thus used catalyst **IV** in subsequent experiments. The reaction between 3-phenylglutaric anhydride (**1a**) and racemic nitroallyic alcohol (**2a**) in dichloromethane (DCM) at ambient temperature afforded the corresponding desired hemiester **3a** with a chemical yield of 44%, ee of 88%, and a diastereomeric ratio of 14:1 at a conversion rate of approximately 50% (Table 1, entry 4). The less reactive nitroallylic alcohol (*S*)-**2a** was recovered with a high enantiomeric purity (93% ee).[15]

Various solvents were screened for the kinetic resolution/desymmetrization reaction (Table 1, entries 6−12). Comparable

Received: August 14, 2014
Published: September 11, 2014

dx.doi.org/10.1021/jo501882q | J. Org. Chem. 2014, 79, 8955−8959

Table 1. Optimization of the Organocatalytic Kinetic Resolution/Desymmetrization Process[a]



				recovered **2a**	product **3a**		
entry	cat.	solvent	time (h)	ee[b] (%)	yield[c] (%)	dr[d]	ee[b] (%)
1	**I**	CH_2Cl_2	20	−9	45	3:1	−9
2	**II**	CH_2Cl_2	48	20	15	15:1	32
3	**III**	CH_2Cl_2	48	24	14	13:1	28
4	**IV**	CH_2Cl_2	4	93	44	14:1	88
5	**V**	CH_2Cl_2	4	92	42	10:1	90
6	**IV**	hexanes	48		nd		
7	**IV**	toluene	4	96	41	16:1	90
8	**IV**	$CHCl_3$	4	96	37	>20:1	90
9	**IV**	EtOAc	5	94	35	12:1	92
10	**IV**	THF	5	94	40	14:1	90
11	**IV**	MeCN	5	92	28	7:1	88
12	**IV**	DMF	48		nd		
13[e]	**IV**	$CHCl_3$	4	90	32	>20:1	90
14[f]	**IV**	$CHCl_3$	5	74	42	>20:1	88

[a]The reaction was performed using **1a** (0.1 mmol, 19 mg) and **2a** (0.1 mmol, 25 mg) in the presence of cat. **I**−**V** (10 mol %) in the solvent indicated (0.2 mL) at ambient temperature (25 °C). The reaction was stopped at ∼50% conversion based on the ^{1}H NMR spectra of the crude reaction mixtures using CH_2Br_2 as an internal standard. [b]Determined by HPLC analysis. [c]Isolated yield of the product **3a**. [d]Determined from ^{1}H NMR spectra of the crude reaction mixtures. [e]The reaction was performed with 0.8 equiv of **1a** (0.08 mmol, 15.2 mg) under the same reaction conditions. [f]The reaction was carried out with 5 mol % catalyst.

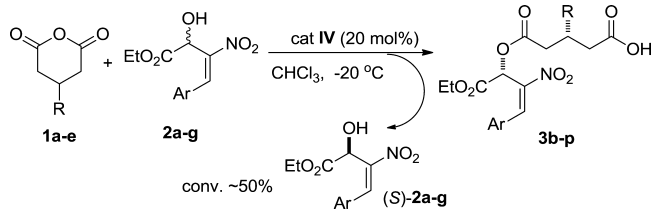
results were observed regarding the enantioselectivities of the product and recovered substrates when using various solvents (CH_2Cl_2, $CHCl_3$, EtOAc, THF, and MeCN). However, both DMF (polar) and hexanes (nonpolar) were found to be infeasible for the reaction, probably because of the low solubility of the substrates in hexanes and the interruption of H-bond formation in DMF. The most appropriate solvent was $CHCl_3$ because the product was obtained with a high enantioselectivity (90%) and diastereoselectivity (>20:1), exhibiting an excellent enantioselectivity of the recovered alcohol (96% ee, Table 1, entry 8). Furthermore, our results demonstrated that a low catalyst loading (5 mol %) decreased the enantioselectivity of the recovered alcohol to 74% ee (Table 1, entry 14).

Thus, we generalized the kinetic resolution/desymmetrization reaction. Various racemic nitroallylic alcohols (**2a**−**g**) were used for the enantioselective desymmetrization of 3-substituted cyclic anhydrides. Although the optimal ambient temperature was applied, the enantioselective alcoholysis of 3-phenylglutaric anhydride (**1a**) using a 4-methylphenyl-substituted nitroallylic alcohol (**2b**) yielded the hemiester (**3b**) only with a moderately high enantioselectivity (83%) at approximately 50% conversion (Table 2, entry 1). The stereoselectivity was substantially increased to 99% when the reaction temperature was lowered to −20 °C under a prolonged reaction time (Table 2, entry 2). Moreover, 0.6 equiv of cyclic anhydride was determined to be sufficient for the reaction to proceed. The desymmetrization of **1a** was performed using 4-halophenyl-substituted nitroallylic alcohols (**2c** and **2d**), and the hemiesters **3c** and **3d** were obtained with high enantiomeric purities (>99% and 96% ee, respectively), along with a considerably high ee of the unreacted alcohols at −20 °C (Table 2, entries 3 and 4). When a 2-bromophenyl-derived nitroallylic alcohol was used, the product was obtained with a high enantioselectivity (90%), but the recovered alcohol was obtained with a moderate ee (Table 2, entry 5). Using a 3-bromophenyl-substituted nitroallylic alcohol yielded the recovered alcohol with promising results (95% ee) at ambient temperature (Table 2, entry 6). The heteroaryl substituent in **2g** also worked efficiently for the enantioselective alcoholysis (hemiester with 92% ee and recovered alcohol with 74% ee) (Table 2, entry 7). Furthermore, various prochiral cyclic anhydrides **1b**−**e** were subject to the desymmetrization process. Several 4-aryl-substituted cyclic anhydrides (**1b**−**d**) were desymmetrized with various racemic nitroallylic alcohols producing the desired hemiesters with high to excellent stereoselectivites (Table 2, entries 8−13).

The less reactive (*S*)-substrates were consistently obtained with acceptable to high ee. When a 4-methoxyphenyl-derived anhydride (**1b**) was coupled with a 3-bromophenyl-derived nitroallylic alcohol (**2f**), both the hemiester and recovered alcohol were obtained with 92% ee (Table 2, entry 9). In addition, the reaction between a 4-bromophenyl-derived anhydride (**1c**) and a secondary alcohol (**2d**) yielded the product, and the less reactive substrate of the secondary alcohols were recovered with 92% and 94% ee, respectively (Table 2, entry 12). The current protocol proceeded smoothly when a 3-methylglutaric anhydride was used (Table 2, entries 14−16). The reaction was intermittently performed at ambient temperature to optimize the organocatalytic kinetic resolution/desymmetrization process (Table 2, entries 6−7 and 14). All of the products were obtained with high levels of diastereoselectivity (7:1 to >20:1).

dx.doi.org/10.1021/jo501882q | J. Org. Chem. 2014, 79, 8955−8959

Table 2. Substrate Scope of Desymmetrization/Kinetic Resolution Process[a]



				recov sub (*S*)-**2a**–**g**		products **3b**–**p**			
entry	R (**1a**–**e**)	Ar (**2a**–**g**)	time (days)	yield[b] (%)	ee[c] (%)		yield[b] (%)	dr[d]	ee[c] (%)
1[e]	Ph (**1a**)	4-MeC_6H_4 (**2b**)	4 h	44	86	**3b**	37	>20:1	83
2	Ph (**1a**)	4-MeC_6H_4 (**2b**)	5	47	86	**3b**	42	>20:1	99
3	Ph (**1a**)	4-ClC_6H_4 (**2c**)	6	49	82	**3c**	43	13:1	>99
4	Ph (**1a**)	4-BrC_6H_4 (**2d**)	5	42	79	**3d**	51	8:1	96
5	Ph (**1a**)	2-BrC_6H_4 (**2e**)	5	52	61	**3e**	34	7:1	90
6[e]	Ph (**1a**)	3-BrC_6H_4 (**2f**)	4 h	53	95	**3f**	43	11:1	84
7[e]	Ph (**1a**)	2-thienyl (**2g**)	4 h	37	74	**3g**	39	10:1	92
8	4-OMeC_6H_4 (**1b**)	Ph (**2a**)	3	49	79	**3h**	39	20:1	94
9	4-OMeC_6H_4 (**1b**)	3-BrC_6H_4 (**2f**)	5	45	92	**3i**	42	10:1	92
10	4-OMeC_6H_4 (**1b**)	4-MeC_6H_4 (**2b**)	5	49	82	**3j**	40	>20:1	96
11	4-BrC_6H_4 (**1c**)	Ph (**2a**)	4	40	87	**3k**	53	15:1	93
12	4-BrC_6H_4 (**1c**)	4-BrC_6H_4 (**2d**)	5	36	94	**3l**	54	9:1	92
13	4-MeC_6H_4 (**1d**)	4-Br C_6H_4 (**2d**)	5	41	84	**3m**	50	10:1	95
14[e]	Me (**1e**)	Ph (**2a**)	6 h	49	94	**3n**	39	9:1	92
15	Me (**1e**)	4-MeC_6H_4 (**2b**)	4	45	88	**3o**	47	11:1	83
16	Me (**1e**)	2-thienyl (**2g**)	3	55	83	**3p**	36	>20:1	82

[a]The reaction was performed using **1a**–**e** (0.12 mmol) and **2a**–**g** (0.2 mmol) in the presence of cat. **IV** (20 mol %, 17.1 mg) in $CHCl_3$ (0.4 mL) at −20 °C. The reaction was stopped at ∼50% conversion from ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as an internal standard. For absolute stereochemistry determination of the products, see the Supporting Information. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Determined from ^{1}H NMR spectra of the crude reaction mixtures. [e]Reaction performed at ambient temperature (25 °C) with 10 mol % of organocatalyst **IV**.

It is widely assumed that the reaction proceeds through an acid/base catalysis mechanism and that the bifunctional organocatalyst **IV** simultaneously activates the nucleophile and electrophile.[16,17] The tertiary amine moiety of the organocatalyst **IV** deprotonates alcohol, whereas the appropriately seated thiourea moiety activates the cyclic anhydride through H-bond formation. Thus, the kinetic resolution of the nucleophile and desymmetrization of the electrophilic component occurs concomitantly in a stereocontrolled manner.

In conclusion, we demonstrated an example that combine the kinetic resolution of functionalized nitroallylic secondary alcohols with desymmetrization of cyclic anhydrides. The synthesis is interesting that no reactive chemistry is involved at either of the resulting stereogenic centers in the product. The hemiesters were obtained with high diastereoselectivities and enantioselectivities (up to >20:1 dr and 99% ee). The less reactive nucleophilic (*S*)-nitroallylic alcohols were resolved with high levels of enantioselectivity (up to 95% ee). The protocol tolerates various starting substrates including cyclic anhydrides and nitroallylic alcohols. The bifunctional behavior of the cinchonidine-derived thiourea catalyst has proven to be useful in organocatalysis and further studies are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Procedure. To a solution of cyclic anhydrides (**1a**–**e**, 0.12 mmol) in $CHCl_3$ was added sequentially racemic nitroallylic alcohols (**2a**–**g**, 0.2 mmol) and organocatalyst (**IV**, 20 mol %, 17.1 mg) at −20 °C. The reaction mixture was stirred at the same temperature for the reaction period indicated in Table 2. The reaction was monitored at ∼50% conversion by using ^{1}H NMR data analyses of the crude reaction mixture using CH_2Br_2 as an internal standard. Then, the reaction mixture was subjected directly to flash column chromatography (silica gel with ethyl acetate/hexanes = 1:3) to afford the unreacted substrates **2a**–**g** first and then the hemiesters of **3a**–**p**. Racemic products of **3a**–**p** were prepared following the general procedure using DABCO (30 mol %) as a catalyst.

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-phenylbut-3-en-2-yl)oxy)-5-oxo-3-phenylpentanoic Acid (**3a**).* Reaction time: 4 h. Yield: 37% (33 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.49–7.40 (m, 3H), 7.29–7.23 (m, 4H), 7.21–7.15 (m, 3H), 6.46 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.70–3.62 (m, 1H), 2.97–2.66 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 169.6, 165.7, 144.6, 141.7, 140.6, 131.3, 130.2, 129.6, 129.2, 128.7, 127.2, 127.1, 65.5, 62.6, 40.1, 39.8, 37.6, 13.8 ppm. IR (ν/cm^{-1}): 2977, 2924, 1745, 1730, 1649, 1531, 1295. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{23}NO_8Na$ [M + Na]$^+$ 464.1321, found 464.1317; ee 90%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 20/80, 0.2 mL/min, λ = 254 nm, retention time 66.2 min (major), 86.0 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(p-tolyl)but-3-en-2-yl)oxy)-5-oxo-3-phenylpentanoic Acid (**3b**).* Reaction time: 5 d. Yield: 42% (38 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.27–7.25 (m, 2H), 7.23–7.20 (m, 5H), 7.19–7.17 (m, 2H), 6.50 (s, 1H), 4.18–4.12 (m, 2H), 3.70–3.62 (m, 1H), 2.96–2.66 (m, 4H), 2.39 (s, 3H), 1.16 (t, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 169.7, 165.8, 143.9, 142.3, 141.8, 140.8, 130.1, 129.9, 128.7, 127.4, 127.2 (×2), 65.7, 62.6, 40.0, 39.9, 37.7, 21.6, 13.9 ppm. IR (ν/cm^{-1}): 2924, 1764, 1741, 1710, 1527, 1367, 1333, 1295. HRMS: (ESI-TOF) m/z calcd for $C_{24}H_{25}NO_8Na$ [M + Na]$^+$ 478.1478, found 478.1476; ee 99%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 22/78, 0.2 mL/min, λ = 254 nm, retention time 47.1 min (major), 50.9 min (minor)].

*5-(((E)-4-(4-Chlorophenyl)-1-ethoxy-3-nitro-1-oxobut-3-en-2-yl)-oxy)-5-oxo-3-phenylpentanoic Acid (**3c**).* Reaction time: 6 d. Yield: 43% (41 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s,

dx.doi.org/10.1021/jo501882q | J. Org. Chem. 2014, 79, 8955–8959

1H), 7.38 (d, J = 8.4 Hz, 2H), 7.28−7.24 (m, 3H), 7.21−7.18 (m, 4H), 6.40 (s, 1H), 4.19−4.13 (m, 2H), 3.67−3.63 (m, 1H), 2.97−2.66 (m, 4H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 169.6, 165.6, 145.0, 141.7, 139.2, 137.8, 130.9, 129.6, 128.7, 128.6, 127.3, 127.2, 65.3, 62.7, 40.0, 39.8, 37.7, 13.8 ppm. FTIR (ν/cm^{-1}): 2924, 1768, 1745, 1714, 1528, 1333, 1229. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{22}ClNO_8Na$ [M + Na]$^+$ 498.0932, found 498.0936; ee >99%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 25/75, 0.2 mL/min, λ = 254 nm, retention time 46.3 min (major).

*5-(((E)-4-(4-bromophenyl)-1-ethoxy-3-nitro-1-oxobut-3-en-2-yl)-oxy)-5-oxo-3-phenylpentanoic acid (**3d**).* Reaction time: 5 d; Yield: 51% (53 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.25−7.22 (m, 2H), 7.19−7.17 (m, 3H), 7.12 (d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 4.18−4.13 (m, 2H), 3.67−3.60 (m, 1H), 2.96−2.64 (m, 4H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 169.6, 165.5, 144.9, 141.6, 139.2, 132.5, 130.9, 129.0, 128.7, 127.1, 126.1, 65.2, 62.7, 40.2, 39.7, 37.5, 13.8 ppm; IR (ν/cm^{-1}): 2977, 1730, 1710, 1535, 1371, 1280, 1215. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{22}BrNO_8Na$ [M + Na]$^+$ 542.0426, found 542.0425; ee 96%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 0.5 mL/min, λ = 254 nm, retention time: 62.8 min (major), 68.8 min (minor)].

*5-(((E)-4-(2-Bromophenyl)-1-ethoxy-3-nitro-1-oxobut-3-en-2-yl)-oxy)-5-oxo-3-phenylpentanoic Acid (**3e**).* Reaction time: 5 d. Yield: 34% (35 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.66−7.64 (m, 1H), 7.31−7.25 (m, 5H), 7.23−7.18 (m, 3H), 7.06−7.03 (m, 1H), 6.26 (s, 1H), 4.17−4.10 (m, 2H), 3.67−3.60 (m, 1H), 2.94−2.63 (m, 4H), 1,18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 169.4, 165.5, 145.8, 141.7, 139.7, 133.2, 132.2, 131.3, 130.1, 128.7, 127.9, 127.2 (×2), 124.3, 65.3, 62.7, 40.1, 39.8, 37.6, 13.8 ppm; IR (ν/cm^{-1}): 2916, 1744, 1729, 1710, 1535, 1340, 1280, 1223. HRMS (EI-ion trap): m/z calcd for $C_{23}H_{23}BrNO_8$ [M + H]$^+$ 520.0607, found 520.0602; ee 90%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 25/75, 0.2 mL/min, λ = 254 nm, retention time 38.1 min (major), 52.4 min (minor)].

*5-(((E)-4-(3-Bromophenyl)-1-ethoxy-3-nitro-1-oxobut-3-en-2-yl)-oxy)-5-oxo-3-phenylpentanoic Acid (**3f**).* Reaction time: 4 h. Yield: 43% (44 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.29−7.28 (m, 2H), 7.25−7.23 (m, 2H), 7.21−7.17 (m, 3H), 6.38 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.68−3.61 (m, 1H), 2.98−2.64 (m, 4H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 169.5, 165.5, 145.7, 141.7, 138.6, 134.1, 132.3, 132.2, 130.7, 128.8, 128.6, 127.8, 127.2, 123.2, 65.2, 62.8, 40.0, 39.8, 37.7, 13.9 ppm. IR (ν/cm^{-1}): 2985, 1741, 1730, 1710, 1539, 1531, 1337, 1227. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{22}BrNO_8Na$ [M + Na]$^+$ 542.0426, found 542.0428; ee 84%. HPLC [Chiralcel AD-H, 2-propanol/hexanes =25/75, 0.2 mL/min, λ = 254 nm, retention time 51.7 min (major), 72.3 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(thiophen-2-yl)but-3-en-2-yl)-oxy)-5-oxo-3-phenylpentanoic Acid (**3g**).* Reaction time: 4 h. Yield: 39% (32 mg). Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.47 (d, J = 3.7 Hz, 1H), 7.26−7.22 (m, 1H), 7.21−7.19 (m, 4H), 7.18−7.16 (m, 1H), 6.72 (s, 1H), 4.23−4.15 (m, 2H), 3.70−3.62 (m, 1H), 2.96−2.63 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 170.1, 165.4, 141.7, 140.8, 136.8, 134.4, 133.1, 132.5, 128.8, 128.6, 127.1, 127.0, 65.7, 62.6, 40.0, 39.9, 37.6, 13.8 ppm. FTIR (ν/cm^{-1}): 2977, 1764, 1737, 1710, 1634, 1524, 1333, 1310, 1215. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{21}NO_8SNa$ [M + Na]$^+$ 470.0886, found 470.0884; ee 92%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 22/78, 0.2 mL/min, λ = 254 nm, retention time 78.5 min (major), 88.8 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(phenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-methoxyphenyl)pentanoic Acid (**3h**).* Reaction time: 3 d. Yield: 39% (37 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.44−7.37 (m, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.46 (s, 1H), 4.23−4.13 (m, 2H), 3.70 (s, 3H), 3.69−3.55 (m, 1H), 2.92 (dd, J = 18.0 and 7.2 Hz, 1H), 2.89−2.72 (m, 2H), 2.65 (dd, J = 16.0 and 8.4 Hz, 1H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 169.6, 165.8, 158.6, 144.7, 140.6, 133.7, 131.3, 130.2, 129.7, 129.3, 128.2, 114.1, 65.5, 62.6, 55.1, 40.2, 40.1, 37.0, 13.8 ppm. IR (ν/cm^{-1}): 2931, 1760, 1736, 1710, 1524, 1249. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{25}NO_9Na$ [M + Na]$^+$ 494.1427, found 494.1418; ee 94%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 35.9 min (major), 46.0 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(3-bromophenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-methoxyphenyl)pentanoic Acid (**3i**).* Reaction time: 5 d. Yield: 42% (46 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.32−7.24 (m, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 3.67−3.53 (m, 1H), 2.92 (dd, J = 16.0 and 6.8 Hz, 1H), 2.81 (dd, J = 14.4 and 8.4 Hz, 1H), 2.75 (dd, J = 14.8 and 6.8 Hz, 1H), 2.64 (dd, J = 16.0 and 8.0 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 169.6, 165.5, 158.6, 145.7, 138.7, 134.1, 133.7, 132.4, 132.2, 130.7, 128.2, 127.8, 123.2, 114.1, 65.2, 62.8, 55.2, 40.3, 40.0, 36.9, 13.9 ppm. IR (ν/cm^{-1}): 2933, 1763, 1743, 1714, 1514, 1249. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{24}NO_9BrNa$ [M + Na]$^+$ 572.0532, found 572.0532; ee 92%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 48.4 min (major), 74.5 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(4-methylphenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-methoxyphenyl)pentanoic Acid (**3j**).* Reaction time: 5 d. Yield: 40% (39 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.23−7.15 (m, 4H), 7.11 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 4.21−4.10 (m, 2H), 3.70 (s, 3H), 3.66−3.55 (m, 1H), 2.91 (dd, J = 15.6 and 7.2 Hz, 1H), 2.86−2.73 (m, 2H), 2.64 (dd, J = 10.0 and 8.4 Hz, 1H), 2.38 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 169.8, 165.8, 158.5, 143.8, 142.3, 140.8, 133.7, 130.0, 129.9, 128.2, 127.3, 114.1, 65.6, 62.6, 55.1, 40.3, 40.1, 37.0, 21.5, 13.8 ppm. IR (ν/cm^{-1}): 2931, 1763, 1742, 1710, 1514, 1249. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{27}NO_9Na$ [M + Na]$^+$ 508.1584, found 508.1577; ee 96%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 33.7 min (major), 40.8 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(phenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-bromophenyl)pentanoic Acid (**3k**).* Reaction time: 4 d. Yield: 53% (55 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.55−7.35 (m, 5H), 7.30 (d, J = 7.6 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.47 (s, 1H), 4.22−4.10 (m, 2H), 3.70−3.52 (m, 1H), 2.99−2.53 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 169.4, 165.7, 144.6, 140.7, 140.6, 131.8, 131.4, 130.2, 129.6, 129.3, 129.1, 121.1, 65.6, 62.7, 39.8, 39.7, 37.2, 13.8 ppm; IR (ν/cm^{-1}): 2977, 1760, 1743, 1714, 1530, 1222. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{22}NO_8BrNa$ [M + Na]$^+$ 542.0426, found 542.0417; ee 93%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time: 35.3 min (major), 45.7 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(4-bromophenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-bromophenyl)pentanoic Acid (**3l**).* Reaction time: 5 d. Yield: 54% (65 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 4.24−4.10 (m, 2H), 3.69−3.51 (m, 1H), 3.20−2.87 (m, 1H), 2.86−2.70 (m, 2H), 2.69−2.56 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 169.3, 165.5, 144.8, 140.6, 139.3, 132.7, 131.8, 131.7, 131.0, 129.0, 126.4, 121.1, 65.3, 62.8, 39.9, 39.6, 37.1, 13.8 ppm. IR (ν/cm^{-1}): 2931, 1767, 1743, 1714, 1535, 1224. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{21}NO_8Br_2Na$ [M + Na]$^+$ 619.9536, found 619.9532; ee 92%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 38.8 min (major), 44.4 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(4-bromophenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-methylphenyl)pentanoic Acid (**3m**).* Reaction time: 5 d. Yield: 50% (53 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.14−7.01 (m, 6H), 6.37 (s, 1H), 4.25−4.10 (m, 2H), 3.70−3.55 (m, 1H), 2.94 (dd, J = 16.0 and 6.8 Hz, 1H), 2.83 (dd, J = 15.6 and 8.8 Hz, 1H), 2.76 (dd, J = 16.0 and 6.8 Hz, 1H), 2.67 (dd, J = 16.0 and 8.0 Hz, 1H), 2.24 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 169.6, 165.6, 144.9, 139.2, 138.6, 136.8, 132.5, 131.0, 129.4, 129.0, 127.1, 126.1, 65.3, 62.7, 40.3, 39.9, 37.3, 20.9, 13.8 ppm. IR (ν/cm^{-1}): 2925, 1763, 1741, 1714, 1535, 1223. HRMS (ESI-TOF): m/z calcd for $C_{24}H_{24}NO_8BrNa$ [M + Na]$^+$ 556.0583, found 556.0592; ee 95%. HPLC [Chiralcel AS-H,

dx.doi.org/10.1021/jo501882q | J. Org. Chem. 2014, 79, 8955−8959

2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 23.0 min (major), 30.1 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(4-phenyl-2-yl)but-3-en-2-yl)-oxy)-5-oxo-3-(4-methyl)pentanoic Acid (**3n**).* Reaction time: 6 h. Yield: 39% (30 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.55−7.43 (m, 5H), 6.60 (s, 1H), 4.30−4.10 (m, 2H), 2.65−2.40 (m, 4H), 2.39−2.20 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 170.5, 165.8, 144.8, 140.5, 131.4, 130.3, 129.7, 129.3, 65.5, 62.7, 40.1, 40.0, 27.1, 19.6, 13.9 ppm. IR (ν/cm^{-1}): 2970, 1763, 1744, 1710, 1532, 1339, 1214. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{21}NO_8Na$ $[M + Na]^+$ 402.1165, found 402.1174; ee 92%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 0.5 mL/min, λ = 220 nm, retention time: 34.2 min (major), 39.8 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(4-methylphenyl-2-yl)but-3-en-2-yl)oxy)-5-oxo-3-(4-methyl)pentanoic Acid (**3o**).* Reaction time: 4 d. Yield: 47% (37 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.62 (s, 1H), 4.30−4.10 (m, 2H), 2.62−2.45 (m, 4H), 2.41 (s, 3H), 2.40−2.30 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 170.7, 165.9, 144.0, 142.4, 140.8, 130.1, 130.0, 127.5, 65.7, 62.7, 40.1, 39.9, 27.2, 21.6, 19.6, 13.9 ppm. IR (ν/cm^{-1}): 2968, 1767, 1742, 1710, 1532, 1335, 1219. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{23}NO_8Na$ $[M + Na]^+$ 416.1321, found 416.1328; ee 83%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 12.2 min (major), 14.1 min (minor)].

*5-(((E)-1-Ethoxy-3-nitro-1-oxo-4-(2-thienyl-2-yl)but-3-en-2-yl)-oxy)-5-oxo-3-(4-methyl)pentanoic Acid (**3p**).* Reaction time: 3 d. Yield: 36% (28 mg). Viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.58 (d, J = 3.6 Hz, 1H), 7.25−7.20 (m, 1H), 6.84 (s, 1H), 4.39−4.13 (m, 2H), 2.70−2.41 (m, 4H), 2.40−2.25 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 171.0, 165.6, 141.1, 137.0, 134.4, 133.1, 132.5, 129.0, 65.8, 62.7, 40.1, 40.1, 27.1, 19.6, 13.9 ppm. IR (ν/cm^{-1}): 2968, 1767, 1744, 1706, 1636, 1524, 1312, 1220. HRMS (ESI-TOF): m/z calcd for $C_{16}H_{19}NO_8SNa$ $[M + Na]^+$ 408.0729, found 408.0736; ee 82%. HPLC [Chiralcel AD-H, 2-propanol/hexanes = 10/90, 1 mL/min, λ = 220 nm, retention time 24.0 min (major), 27.8 min (minor)].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology of the Republic of China (MOST 102-2113-M-003-005-MY3) for financial support of our work.

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■ NOTE ADDED AFTER ASAP PUBLICATION

An author (R.G.) was inadvertently omitted from the original author list. The correct version reposted September 16, 2014.