Thiol-Free Synthesis of Oseltamivir and Its Analogues via Organocatalytic Michael Additions of Oxyacetaldehydes to 2-Acylaminonitroalkenes

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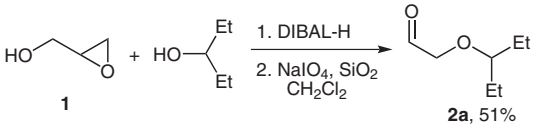
Abstract: The organocatalytic addition of substituted oxyacetaldehydes to 2-acylaminonitroethenes proceeded with good to high diastereoselectivities and enantioselectivities. The resulting adducts reacted with ethyl 2-(diethoxyphosphoryl) acrylate to afford highly functionalized cyclohexenes. A thiol-free protocol for cyclization has been developed that leads to a separable mixture of two diastereoisomers. The unwanted diastereoisomer can be efficiently epimerized. The resulting cyclohexenes are precursors to oseltamivir and its analogues. The synthesis of the key reagent, 3-pentyloxyaldehyde, was also improved.

Key words: enantioselectivity, Michael addition, cyclization, aminonitroethene, organocatalysis

Asymmetric organocatalytic Michael addition is one of the most versatile transformations for enantioselective formation of C–C and C–heteroatom bonds.[1] Organocatalysts has proved to be useful for additions of a range of donors such as enolizable aldehydes and ketones, diketones, ketoesters, and nitroalkanes. In addition, a large variety of Michael acceptors have been utilized such as unsaturated ketones, aldehydes, esters or sulfones.[2] Particular attention has been devoted to nitroalkenes, because the resulting functionalized nitro-derivatives are useful building blocks for the synthesis of many biologically relevant compounds. Successful additions of both aldehydes[3] and ketones[4] to nitroalkenes have already been demonstrated. Interestingly, the simplest enolizable aldehyde, acetaldehyde, poses a special challenge because of its high reactivity. List and co-workers solved the problem by slow addition of an acetaldehyde solution to nitroalkenes.[3a,5] On the other hand, Michael additions of functionalized aldehydes are also challenging. Although, functional groups within the aldehyde offer interesting possibilities for subsequent target-oriented synthesis, only a few examples of functionalized aldehyde additions are known.[6] We showed that alkoxy and aryloxyacetaldehydes can be enantioselectively added to a range of nitroalkenes.[7]

The organocatalytic Michael addition also serves as an initiating reaction for domino transformations, which lead to a number of structurally or functionally interesting molecules.[8] Already a large number of bioactive compounds have been synthesized through the use of organocatalytic reactions.[9] It was recognized that conjugate addition is also a useful transformation in the synthesis of the antiviral agent oseltamivir.[10] Hayashi and co-workers used the addition of pentyloxyacetaldehyde to *tert*-butyl nitroacrylate as the key step in a one-pot synthesis of oseltamivir.[11] We envisaged a more direct approach based on the use of 2-acylaminonitroethenes. Recently, Ma and co-workers demonstrated the viability of this approach.[12] In this paper, we present results of our studies on Michael additions of a range of oxyacetaldehydes to 2-acylaminonitroethenes. This reaction is the first step in an organocatalytic synthesis of oseltamivir. Access to its analogues, through structural variations of reaction partners, may become important in view of emerging resistance towards oseltamivir itself.[13]

First, we investigated the possibility of an organocatalytic Michael addition of oxyacetaldehydes to N-protected 2-aminonitroethenes. As the second partner for the Michael addition we chose 3-pentyloxyacetaldehyde (**2a**), because a 3-pentyloxy group is present in oseltamivir. The starting material **2a** can be prepared by Hayashi's procedure based on osmium tetraoxide cleavage of an alkene. We have developed an alternative method involving sodium periodate cleavage of a protected diol, which results from an opening of glycidol **1** (Scheme 1). The resulting aldehyde **2a** is unstable and decomposes rapidly within a few hours, however, this decomposition can be slowed down by addition of 1% hydroquinone. *N*-Acyl nitroalkene derivatives **3**, which are readily available by a two-step procedure,[14] were selected as suitable candidates for Michael addition. An interesting feature is their propensity to form *Z*-configured double bonds, due to intramolecular hydrogen bonding.



Scheme 1

The Michael addition of **2a** with **3a** and **3b** afforded compounds **4a** and **4b**, respectively (Scheme 2). The former

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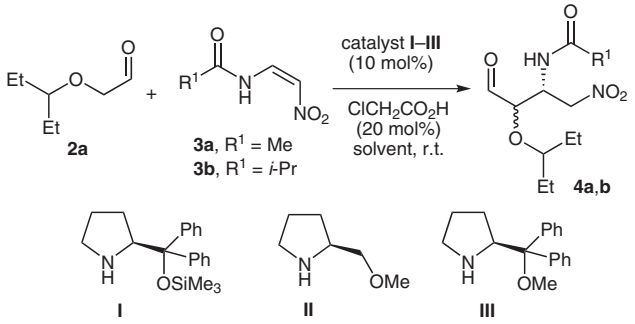
product **4a**, as a key intermediate for oseltamivir synthesis, has also been prepared by Ma,[12] and, using an alternative route from diethyl tartrate, by Lu.[15]

Catalyst screening in the reaction of nitroalkenes **3** with aldehyde **2a** revealed that Jørgensen–Hayashi catalyst **I**[16] was the most selective. Similarly to Ma's work,[12] we have found that **4a** can be obtained in high enantiomeric purity through the use of **I** (97% ee). Ma and co-workers used benzoic acid as an additive in chloroform, but we obtained the best results with chloroacetic acid in a mixture of chloroform and water. At 0 °C, the product **4a** was obtained in 88% yield and in high enantiomeric purity [98% ee (*syn*)]. The results of catalyst and initial conditions screening are collected in Table 1.



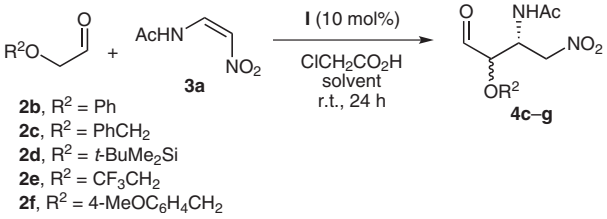
Scheme 2

Table 1 Addition of Aldehyde **2a** to 2-Aminonitroethenes **3b** and **3b**[a]

R^1	Catalyst	Solvent	Yield (%)	*syn* /*anti*[b]	ee *syn* /*anti*[c]
Me	**I**	MeOH	95	45:55	12/9
Me	**I**	DMSO	38	35:65	17/21
Me	**I**	THF–brine	38	56:44	53/24
Me	**I**	CH_2Cl_2/brine	53	73:27	86/55
Me	**I**	$CHCl_3$/brine	75	76:23	92/38
Me	**I**	$CHCl_3/H_2O$	77	74:26	91/58
Me	**I**	$CHCl_3/H_2O$[d]	88	81:19	97/56
Me	**II**	$CHCl_3/H_2O$	30	81:19	46/65
Me	**III**	$CHCl_3/H_2O$	76	70:30	86/77
i-Pr	**I**	$CHCl_3/H_2O$	77	76:24	71/22

[a] Reaction conditions: aldehyde **2a** (3 mmol), catalyst (0.2 mmol), alkene **3** (2 mmol), $ClCH_2CO_2H$ (0.4 mmol), $CHCl_3$–H_2O (1:1, 32 mL).
[b] Determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by enantioselective HPLC after derivatization with 9-fluorenylidenetriphenylphosphorane.
[d] The reaction was performed at 0 °C for 5 h.

In order to prepare analogues of oseltamivir, we have further explored the scope of this transformation by evaluating a range of alkyloxyacetaldehydes **2** in the addition to alkene **3a** (Scheme 3). Interestingly, the best solvent for the addition of aldehyde **2a** was not the most suitable for addition of other aldehydes. After testing the addition of aldehyde **2c** in several solvents and solvent mixtures, we established that DMSO was effective; the results are summarized in Table 2.



Scheme 3

Table 2 Addition of Aldehydes **2** to 2-Aminonitroethenes **3a**

R^2	Product	Solvent	Yield (%)	*syn* /*anti*[a]	ee *syn* /*anti*[b]
Ph	**4c**	DMSO	70	61:39	74/30
$PhCH_2$	**4d**	NMP	55	56:44	45/45
$PhCH_2$	**4d**	MeOH	38	53:47	30/29
$PhCH_2$	**4d**	DMSO	81	56:44	53/58
$PhCH_2$	**4d**	DMSO–H_2O	68	56:44	53/56
$PhCH_2$	**4d**	$CHCl_3$	50	56:44	53/63
$PhCH_2$	**4d**	$CHCl_3/H_2O$	40	53:47	20/21
$PhCH_2$	**4d**	THF–H_2O	55	50:50	55/35
t-$BuMe_2Si$	**4e**	CH_2Cl_2	60[c]	60:40	75/76
CF_3CH_2	**4f**	DMSO	48	67:33	31/30
4-$MeOC_6H_4CH_2$	**4g**	DMSO	80	50:50	58/39

[a] Determined by ^{1}H NMR spectroscopic analysis.
[b] Determined by enantioselective HPLC after derivatization with 9-fluorenylidenetriphenylphosphorane.
[c] Reaction time: 72 h.

Based on the model of Seebach and Golinski,[17] the proposition of Ma,[12] and on our own recent calculations[7] of enamines formed from oxyacetaldehydes, the formation of product **4** can be explained by the transition state model depicted on Figure 1. Here the *anti*-product (*R,R*)-**4** results from the *E*-enamine and the *syn*-product (*S,R*)-**4** results from the *Z*-enamine, as a result of *Si*-attack of the *Z*-configured alkene **3a**.

The usefulness of the described conjugate addition products **4** was shown by synthesizing oseltamivir and its analogues. Cyclization was performed by modifying Hayashi's procedure.[11] Hayashi used *p*-toluenethiol with Cs_2CO_3 to obtain the desired diastereoisomer. The thiol is required for efficient epimerization of predominantly formed *R,R,R*-isomer to the desired *R,R,S*-isomer, on the other hand, use of stoichiometric amounts of thiol makes

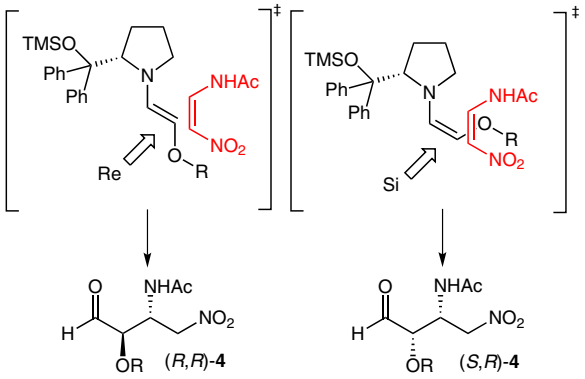
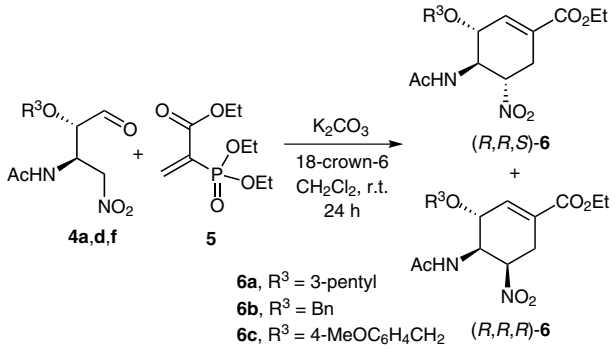


Figure 1

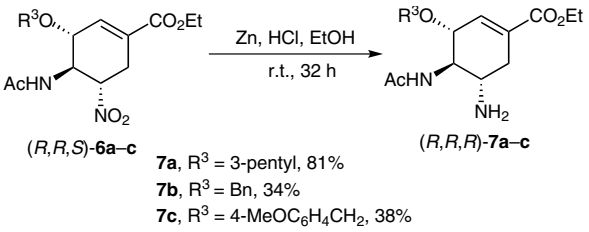
the synthesis problematic from a practical point of view. We have performed this reaction without intermediate addition of the thiol (Scheme 4). From the diastereoisomeric mixture, the required diastereomer for oseltamivir synthesis, (*R*,*R*,*S*)-**6a**, can be isolated in pure form. The best conditions for cyclization of **4a** were found to be four hours heating under microwave irradiation in the presence of 18-crown-6 and K_2CO_3, which afforded **6a** in 66% yield for both diastereoisomers. Again, these conditions were not ideal for cyclization of **4d** and **4f**, for which the use of Cs_2CO_3 in DMSO gave better yields (Table 3).



Scheme 4

Although diastereoselectivities of the cyclization are low, the diastereoisomers can be efficiently separated by column chromatography. The isomer (*R*,*R*,*R*)-**6a** can be epimerized to the desired isomer (*R*,*R*,*S*)-**6a** by treatment with K_2CO_3 followed by crystallization, resulting in an enrichment of (*R*,*R*,*S*)-**6a**/(*R*,*R*,*R*)-**6a** to between 96:4 and 98:2 (96% yield). Relative configurations of (*R*,*R*,*S*) and (*R*,*R*,*R*)-**6a** and **6b** were confirmed by 2D NMR experiments.

The synthesis of oseltamivir (**7a**) was then finished by reduction of the nitro group by treatment with zinc in acetic acid.[18] Two derivatives (**7b** and **7c**) were synthesized in a similar way (Scheme 5).



Scheme 5

The presented synthesis of oseltamivir can also be performed on a gram scale. Organocatalytic Michael addition was realized with 4.5 grams of aldehyde **2a** and 3.0 grams of alkene **3a**, giving 3.2 grams of pure *syn*-**4a**. The limiting step in terms of scale was cyclization in the microwave reactor, which, with our apparatus, could be performed in up to 0.5 gram batches.

In summary, organocatalyzed Michael addition of substituted oxyacetaldehydes to 2-aminonitroethenes lead to useful α-hydroxy-β-amino-γ-nitrocarbonyl structural motifs. These compounds are obtained in good yields, moderate diastereoselectivity and good to high enantioselectivities (up to 97% ee). Such compounds are useful building blocks for the synthesis of oseltamivir and its analogues. Cyclization can be performed without a thiol by using microwave irradiation. The minor diastereoisomer was efficiently epimerized to the desired isomer by using K_2CO_3 followed by crystallization.

Table 3 Cyclization of Aldahydes **4** to Cyclohexenes **6**

R^3	Base	Solvent, conditions	dr (*R*,*R*,*S*)/(*R*,*R*,*R*)	Yield (%)
3-pentyl	K_2CO_3, 18-crown-6	CH_2Cl_2, 70 °C	1:1.8	56
3-pentyl	K_2CO_3, 18-crown-6	CH_2Cl_2, 70 °C, MW	1:1.5	66
3-pentyl	DBU, LiCl	MeCN	1.5:1	61
Bn	K_2CO_3, 18-crown-6	CH_2Cl_2	1:1.4	20
Bn	DBU, LiCl	MeCN	1:2.4	22
Bn	Cs_2CO_3	DMSO	1:1	48
4-$MeOC_6H_4CH_2$	Cs_2CO_3	DMSO	1.2:1	27

Solvents were dried and purified by standard methods before use. NMR spectra were recorded with a Varian NMR System 300 instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Flash chromatography was performed with Merck silica gel 60. Thin-layer chromatography was performed with Merck TLC plates (silica gel 60, F-254). Enantiomeric excesses were determined by HPLC analysis on Chiralpak AD-H, AS-H, IC and Chiralcel OD-H (Daicel Chemical Industries) columns using hexane–*i*-PrOH as a mobile phase and by UV detection. HRMS analyses were performed with a LC-IT-TOF MS (Shimadzu, Kyoto, Japan) using an Ascentis C18 column with gradient H_2O–MeCN elution over 33 min. Racemic mixtures of all the products were prepared according to the general procedure using morpholine as catalyst.

Alkyloxyacetaldehydes 2

Aldehydes **2c** and **2d** are commercially available. Aldehydes **2b**,[19] **2e** and **2f**[20] were prepared according to literature procedures.

2-(Pentan-3-yloxy)acetaldehyde (2a)

Pentan-3-ol (59 mL, 555 mmol) was added to anhydrous CH_2Cl_2 (270 mL) under an inert atmosphere and the resulting solution was cooled in an ice bath. DIBAL-H (20% in toluene, 402 mL, 481 mmol) was added dropwise over 2 h, and the mixture was then stirred for 30 min. Epoxide **1** (24.5 mL, 370 mmol) was added at 20 °C over 30 min and the reaction mixture was then stirred at r.t. for 72 h. The reaction mixture was slowly added to a mixture of crushed ice (500 mL) and concd HCl (100 mL) and the product was extracted with EtOAc (3 × 100 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated. Vacuum distillation (bp 79 °C, 56 Pa) of the residue provided 3-(pentan-3-yloxy)propane-1,2-diol.

Yield: 12 g (20%); colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (ddd, *J* = 4.0, 5.6, 8.0 Hz, 1 H), 3.68 (m, 2 H), 3.53 (m, 2 H), 3.17 (quint, *J* = 5.8 Hz, 1 H), 2.79 (br s, 2 H), 1.51 (m, 4 H), 0.90 (t, *J* = 7.4 Hz, 6 H).

A solution of $NaIO_4$ (11.6 g, 54.6 mmol) in H_2O (79 mL) was added to a suspension of silica gel (90 g) in CH_2Cl_2 (640 mL) over 15 min, then a solution of 3-(pentan-3-yloxy)propane-1,2-diol (6.5 g, 42 mmol) in CH_2Cl_2 (80 mL) was added over 20 min. After 3 h, the silica gel was filtered off and washed with CH_2Cl_2 (3 × 100 mL). The organic phase was extracted with a solution of $Na_2S_2O_4$ (6 g, 34.5 mmol) in H_2O (150 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product **2a** was purified by distillation (bp 42 °C, 1.2 kPa) to provide pure aldehyde **2a**.

Yield: 3.9 g (72%); colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 1.1 Hz, 1 H), 4.06 (d, *J* = 1.1 Hz, 2 H), 3.23 (quint, *J* = 5.8 Hz, 1 H), 1.56 (dq, *J* = 3.3, 7.6 Hz, 4 H), 0.93 (t, *J* = 7.4 Hz, 6 H). Spectral data in agreement with the literature.[11b]

Preparation of Acylaminonitroethenes 3; Typical Procedure

Acetic anhydride (3.7 mL) was added to a solution of 2-nitroethenylamine (1.76 g, 20 mmol) in pyridine (24 mL) at 0–5 °C during 5 min, then the reaction mixture was stirred at r.t. for 28 h. The reaction mixture was added to aq sat. $CuSO_4$ (200 mL) and the obtained mixture was extracted with Et_2O (5 × 80 mL). The organic layers were dried with Na_2SO_4 and concentrated. Column chromatography of the residue (SiO_2; EtOAc–hexane, 1:1) afforded pure **3**.

***N*-[(*Z*)-2-Nitroethenyl]acetamide (3a)**

Yield: 2.22 g (85%); white crystals; mp 117–119 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40 (br s, 1 H), 7.59 (dd, *J* = 7.0, 12.3 Hz, 1 H), 6.61 (d, *J* = 6.7 Hz, 1 H), 2.28 (s, 3 H).

MS: *m*/*z* [MH^+] calcd for $C_4H_7N_2O_3$: 131.11; found: 131.04.

2-Methyl-*N*-[(*E*)-2-nitroethenyl]propanamide (3b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 11.2, 12.1 Hz, 1 H), 7.71 (d, *J* = 11.2 Hz, 1 H), 7.42 (d, *J* = 12.1 Hz, 1 H), 2.57 (sept, *J* = 7.0 Hz, 1 H), 1.25 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 136.6, 125.0, 35.9, 18.9.

HRMS: *m*/*z* [$MH]^+$ calcd for $C_6H_{11}N_2O_3$: 159.076; found: 159.075.

Michael Addition of Alkyloxyacetaldehydes to 3; General Procedure

To a solution of (*Z*)-*N*-(2-nitrovinyl)acetamide (**3a**; 70 mg, 0.538 mmol) in DMSO (1 mL) was added alkyloxyacetaldehyde **2** (0.807 mmol). To the stirred solution was added (*S*)-**I** dissolved in DMSO (0.5 mL) and chloroacetic acid (10.3 mg, 0.107 mmol). The mixture was stirred under a nitrogen atmosphere for 24–48 h (reaction was monitored by TLC). Upon completion, the reaction mixture was poured into H_2O and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to leave a yellow oil, which was purified by column chromatography on silica (hexane–EtOAc, 3:1→1:1) to give the corresponding Michael adduct **4c**–**g**.

Derivatization of Michael Adducts for HPLC Analysis; General Procedure

The Michael adduct was dissolved in toluene (1 mL) and 9-fluorenylidenetriphenylphosphorane (139 mg, 0.324 mmol) was added. The reaction mixture was heated under reflux in an atmosphere of nitrogen for 1 h. After cooling to r.t. the toluene was evaporated under reduced pressure and the residue was purified by column chromatography on silica (hexane–EtOAc, 3:1→1:1).

***N*-[1-Nitro-4-oxo-3-(pentan-3-yloxy)butan-2-yl]acetamide (4a)**

Yield: 920 mg (88%); colorless oil.

HPLC for triphenylphosphoranylidene derivative (Chiralcel OD-H; *i*-PrOH–hexane, 20:80; 0.75 mL/min; λ = 259 nm): t_R = 8.31 (*anti*-**4a**, major), 9.65 (*anti*-**4a**, minor), 12.04 (*syn*-**4a**, major), 19.31 (*syn*-**4a**, minor) min.

***syn*-4a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (t, *J* = 0.6 Hz, 1 H), 6.04 (br d, *J* = 8.5 Hz, 1 H), 5.11–5.02 (m, 1 H), 4.58 (d, *J* = 6.5, 2 H), 4.08 (dd, *J* = 0.3, 3.3 Hz, 1 H), 3.41 (quint, *J* = 5.8 Hz, 1 H), 1.99 (s, 3 H), 1.62–1.49 (m, 4 H), 0.98–0.87 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0, 170.6, 83.5, 79.7, 74.2, 48.1, 25.9, 24.9, 22.8.

HRMS: *m*/*z* [$MH]^+$ calcd for $C_{11}H_{21}N_2O_5$: 261.144; found: 261.145.

***anti*-4a**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.61 (d, *J* = 3.1 Hz, 1 H), 6.11 (br d, *J* = 8.8 Hz, 1 H), 4.85–4.50 (m, 3 H), 3.95 (dd, *J* = 3.1, 8.0 Hz, 1 H), 3.27 (quint, *J* = 5.5 Hz, 1 H), 2.00 (s, 3 H), 1.57–1.42 (m, 4 H), 0.95–0.84 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 170.5, 83.2, 80.4, 74.1, 47.2, 26.0, 24.8, 23.0.

HRMS: *m*/*z* [$MH]^+$ calcd for $C_{11}H_{21}N_2O_5$: 261.144; found: 261.144.

***N*-[1-Nitro-4-oxo-3-(pentan-3-yloxy)butan-2-yl]isobutyramide (4b)**

Yield: 290 mg (77%); colorless oil.

HPLC for triphenylphosphoranylidene derivative (Chiralcel OD-H; *i*-PrOH–hexane, 15:85; 0.75 mL/min; λ = 259 nm): t_R = 7.43 (*anti*-**4b**, minor), 10.26 (*anti*-**4b**, major), 10.05 (*syn*-**4b**, minor), 31.92 (*syn*-**4b**, major) min.

***syn*-4b**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.64 (t, *J* = 0.5 Hz, 1 H), 6.06 (br d, *J* = 8.5 Hz, 1 H), 5.11–5.01 (m, 1 H), 4.60 (d, *J* = 1.1 Hz, 1 H), 4.57 (d, *J* = 1.7 Hz, 1 H), 4.10 (dd, *J* = 0.3, 3.1 Hz, 1 H), 3.41

(quint, J = 5.7 Hz, 1 H), 2.38–2.36 (m, 1 H), 1.64–1.45 (m, 4 H), 1.16–1.01 (m, 6 H), 0.98–0.87 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8, 176.8, 83.4, 79.5, 74.1, 47.7, 35.4, 26.0, 25.0, 19.4, 19.3, 9.4, 9.3.

HRMS: m/z $[MH]^+$ calcd for $C_{13}H_{25}N_2O_5$: 289.176; found: 289.166.

***anti*-4b**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.60 (d, J = 3.1 Hz, 1 H), 6.09 (br d, J = 8.7 Hz, 1 H), 4.82 (dd, J = 5.3, 13.3 Hz, 1 H), 4.76–4.68 (m, 1 H), 4.56 (dd, J = 3.6, 13.3 Hz, 1 H), 3.94 (dd, J = 3.1, 8.2 Hz, 1 H), 3.26 (quint, J = 5.7 Hz, 1 H), 2.38–2.36 (m, 1 H), 1.61–1.46 (m, 4 H), 1.16–1.11 (m, 6 H), 0.94–0.84 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9, 177.2, 83.2, 80.4, 74.2, 46.9, 35.5, 26.1, 24.9, 19.4, 19.3, 9.5, 9.1.

HRMS: m/z $[MH]^+$ calcd for $C_{13}H_{25}N_2O_5$: 289.176; found: 289.167.

***N*-(1-Nitro-4-oxo-3-phenoxybutan-2-yl)acetamide (Mixture of *syn* and *anti*-4c)**

Yield: 106 mg (70%); colorless oil.

HPLC (Chiralpak IC; *i*-PrOH–hexane, 18:82; 0.8 mL/min; λ = 254 nm): t_R = 18.87 (*anti*-**4c**, major), 28.8 (*anti*-**4c**, minor), 25.13 (*syn*-**4c**, minor), 48.0 (*syn*-**4c**, major) min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 and 2.05 (s, 3 H), 4.64–4.79 (m, 2 H), 4.87–4.94 (m, 1 H), 5.28–5.36 (m, 1 H), 6.21 (m, 1 H), 6.87–7.01 (m, 2 H), 7.28–7.36 (m, 3 H), 9.65 (d, J = 2.5 Hz) and 9.73 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 47.4, 73.9 and 74.2, 79.9 and 80.0, 115.3, 123.2, 130.0, 156.6, 170.3 and 170.7, 198.3 and 198.8.

HRMS: m/z $[MH]^+$ calcd for $C_{12}H_{15}N_2O_5$: 267.098; found: 267.096.

***N*-[3-(Benzyloxy)-1-nitro-4-oxobutan-2-yl]acetamide (4d)**

Yield: 140 mg (81%); colorless oil.

HPLC (Chiralpak IC; *i*-PrOH–hexane, 18:82; 1.2 mL/min; λ = 254 nm): t_R = 21.77 (*anti*-**4d**, major), 34.80 (*anti*-**4d**, minor), 29.5 (*syn*-**4d**, major), 54.7 (*syn*-**4d**, minor) min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 and 1.96 (s, 3 H), 3.93 (dd, J = 2.6, 7.6 Hz, 1 H), 4.10–4.18 (m, 1 H), 4.48–4.60 (m, 2 H), 4.70–4.90 (m, 2 H), 5.18–5.22 and 5.98–6.02 (m, 1 H), 7.40–7.20 (m, 5 H), 9.56 (d, J = 2.5 Hz) and 9.60 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 45.9, 72.7, 73.0 and 73.3, 80.0–80.6, 127.5, 127.7, 127.8, 134.8, 169.1 and 169.3, 198.0 and 198.7.

HRMS: m/z $[MH]^+$ calcd for $C_{13}H_{17}N_2O_5$: 281.114; found: 281.114.

***N*-{3-[(*tert*-Butyldimethylsilyl)oxy]-1-nitro-4-oxobutan-2-yl}acetamide (4e)**

Yield: 97 mg (60%); colorless oil.

HPLC (Chiralpak IC; *i*-PrOH–hexane, 9:91; 0.7 mL/min; λ = 226 nm): t_R = 17.20 (*anti*-**4e**, major), 30.00 (*anti*-**4e**, minor), 25.6 (*syn*-**4e**, major), 53.3 (*syn*-**4e**, minor) min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 6 H), 0.95 (s, 9 H), 1.99 and 2.01 (s, 3 H), 4.21 (dd, J = 2.0, 6.9 Hz) and 4.35 (d, J = 3.2 Hz, 1 H), 4.49–4.57 (m, 1 H), 4.67–4.76 (m, 1 H), 5.03–5.11 (m, 1 H), 5.97 (d, J = 8.5 Hz) and 6.21 (d, J = 8.0 Hz, 1 H), 9.56 (s) and 9.58 (d, J = 2.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 23.3, 26.0, 30.6, 46.0, 75.3 and 75.8, 79.3 and 79.6, 169.9 and 170.1, 201.2 and 202.6.

HRMS: m/z $[MH]^+$ calcd for $C_{12}H_{24}N_2O_5Si$: 305.153; found: 305.148.

***N*-[1-Nitro-4-oxo-3-(2,2,2-trifluoroethoxy)butan-2-yl]acetamide (4f)**

Yield: 70 mg (48%); colorless oil.

HPLC (Chiralpak IB; *i*-PrOH–hexane, 10:90; 1 mL/min; λ = 254 nm): t_R = 17.18 (*anti*-**4f**, major), 24.4 (*anti*-**4f**, minor), 31.29 (*syn*-**4f**, major), 46.68 (*syn*-**4f**, minor) min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.0 (s, 3 H), 3.81–3.91 (m, 1 H), 4.18–4.35 (m, 2 H), 4.55 (dd, J = 3.4, 13.9 Hz, 1 H), 4.62 (d, J = 6.7 Hz, 1 H), 4.77 (dd, J = 8.8, 13.9 Hz, 1 H, CH_2NO_2), 5.28–5.37 (m, 1 H, CHCHO), 5.91 (d, J = 8.9 Hz) and 6.18 (d, J = 7.6 Hz, 1 H), 9.61 (s) and 9.65 (d, J = 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 46.5, 68.1 and 68.6, 73.5 and 73.7, 83.8 and 83.9, 125.0 and 126.5, 170.0 and 171.2, 196.5 and 197.3.

HRMS: m/z $[MH]^+$ calcd for $C_8H_{12}F_3N_2O_5$: 273.070; found: 273.069.

***N*-{3-[(4-Methoxybenzyl)oxy]-1-nitro-4-oxobutan-2-yl}acetamide (4g)**

Yield: 135 mg (80%); colorless oil.

HPLC (Chiralpak IC; *i*-PrOH–hexane, 18:82; 0.6 mL/min; λ = 254 nm): t_R = 49.8 (*anti*-**4g**, minor), 70.83 (*anti*-**4g**, major), 65.7 (*syn*-**4g**, minor), 121.2 (*syn*-**4g**, major) min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.92 and 1.95 (s, 3 H), 3.81 (s, 3 H), 4.48 (m, 1 H), 4.52–4.54 (m, 1 H), 4.60–4.78 (m, 2 H), 4.82 (m, 1 H), 5.17 (m, 1 H), 6.09 (d, J = 8.9 Hz) and 6.20 (d, J = 8.8 Hz, 1 H), 6.90 (m, 2 H), 7.25 (m, 2 H), 9.54 (d, J = 2.5 Hz) and 9.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 47.0, 55.3, 73.3, 74.1 and 74.3, 80.6 and 81.2, 114.2, 127.9, 130.4, 160.0, 170.0 and 170.2, 199.2 and 199.8.

HRMS: m/z $[MH]^+$ calcd for $C_{14}H_{19}N_2O_6$: 311.124; found: 311.143.

Ethyl 4-Acetamido-5-nitro-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (6a)

18-Crown-6 (33 mg, 0.124 mmol) and K_2CO_3 (373 mg, 2.70 mmol) were added to a solution of **4a** (293 mg, 1.13 mmol) and 2-(diethoxyphosphoryl)acrylate (**5**; 266 mg, 1.13 mmol) in CH_2Cl_2 (15 mL) at 0 °C under an Ar atmosphere. The reaction mixture was then heated for 4 h at 70 °C in a microwave reactor before being quenched with sat. aq NH_4Cl (13 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography (SiO_2; hexane–EtOAc, 2:1) provided (*R*,*R*,*S*)-**6a** (153 mg, 40%) and (*R*,*R*,*R*)-**6a** (102 mg, 26%) as white solids.

Compound (*R*,*R*,*S*)-6a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84–6.82 (m, 1 H), 5.80 (d, J = 6.4 Hz, 1 H), 5.62 (ddd, J = 6.0, 10.6, 11.1 Hz, 1 H), 4.85–4.81 (m, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 3.77–3.68 (m, 1 H), 3.34 (quint, J = 5.8 Hz, 1 H), 3.16–3.08 (m, 1 H), 2.91–2.81 (m, 1 H), 1.97 (s, 3 H), 1.56–1.46 (m, 4 H), 1.30 (t, J = 7.2 Hz, 3 H), 0.94–0.86 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 165.2, 137.9, 126.8, 82.2, 81.8, 71.5, 61.3, 56.3, 29.6, 26.2, 25.5, 23.6, 14.2, 9.6, 9.3.

HRMS: m/z $[MH]^+$ calcd for $C_{16}H_{27}N_2O_6$: 343.186; found: 343.186.

Compound (*R*,*R*,*R*)-6a

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.90–6.87 (m, 1 H), 5.63 (br d, J = 8.8 Hz, 1 H), 5.0 (dt, J = 3.3, 6.6 Hz, 1 H), 4.77 (ddd, J = 3.3, 5.1, 8.4 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 4.13–4.10 (m, 1 H), 3.51 (quint, J = 5.8 Hz, 1 H), 3.04 (td, J = 7.0, 1.8 Hz, 2 H), 1.99 (s, 3 H), 1.64–1.45 (m, 4 H), 1.32 (t, J = 7.1 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H), 0.91 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 165.3, 135.3, 128.5, 82.7, 80.1, 72.3, 61.5, 50.1, 26.4, 26.3, 25.6, 23.3, 14.2, 9.9, 9.3.

HRMS: m/z $[MH]^+$ calcd for $C_{16}H_{27}N_2O_6$: 343.186; found: 343.186.

Cyclization of 4d and 4f; General Procedure
To a solution of Michael adduct **4d** or **4f** (0.285 mmol) dissolved in DMSO (1.5 mL) under a nitrogen atmosphere was added ethyl 2-(diethoxyphosphoryl)acrylate (**5**; 87.6 mg, 0.371 mmol). A solution of Cs_2CO_3 (279 mg, 0.855 mmol) in H_2O (0.5 mL) was added at r.t. within 2 h by using a syringe pump. The reaction mixture was stirred for an additional 1 h, quenched with sat. NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a yellow oil that was purified by column chromatography on silica (hexane–EtOAc, 3:1→1:1) to give the corresponding cyclohexene derivative **6b** or **6c** as pale-yellow viscous oils.

Ethyl 4-Acetamido-3-benzyloxy-5-nitrocyclohex-1-enecarboxylate (6b)
Yield: 50 mg (48%); pale-yellow oil.

Compound (*R*,*R*,*R*)-6b
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.28–7.42 (m, 5 H, 5 × HPh), 7.00 [m, 1 H, H-C(2)], 5.83 (d, $J_{NH,4}$ = 8.8 Hz, 1 H, NH), 4.92 [ddd, $J_{4,5}$ = 10.7 Hz, $J_{5,6}$ = 8.8 Hz, $J_{5,6}$ = 6.3 Hz, 1 H, H-C(5)], 4.73–4.83 [m, 1 H, H-C(4)], 4.71 [d, *J* = 11.5 Hz, 1 H, PhCHO-], 4.53 (d, *J* = 11.5 Hz, 1 H, PhCHO-), 4.25 (q, *J* = 7.2 Hz, 2 H, $COOCH_2$), 4.17 [dd, $J_{3,4}$ = 6.3 Hz, $J_{2,3}$ = 4.1 Hz, 1 H, H-C(3)], 3.11 [dd, *J* = 17.9 Hz, $J_{5,6}$ = 5.8 Hz, 1 H, H-C(6)], 3.06 [ddd, *J* = 17.9 Hz, $J_{5,6}$ = 9.2 Hz, $J_{2,6}$ = 1.6 Hz, 1 H, H-C(6)], 1.91 (s, 3 H, CH_3CON), 1.32 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 169.9 (CON), 165.0 (COOEt), 136.9 (C1), 133.6 (C2), 130.1, 128.8, 128.1, 127.7 (6 × CPh), 81.5 (C5), 72.3 ($PhCH_2$), 70.9 (C3), 61.5 ($COOCH_2$), 49.7 (C4), 28.9 (C6), 23.1 (CH_3CON), 14.1 (OCH_2CH_3).

Compound (*R*,*R*,*S*)-6b
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.28–7.41 (m, 5 H, HPh), 6.92 [ddd, *J* = 2.7, 2.6, 0.9 Hz, 1 H, H-C(2)], 5.91 (d, $J_{NH,4}$ = 8.9 Hz, 1 H, NH), 5.41 [ddd, $J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = 10.4 Hz, *J* = 5.9 Hz, 1 H, H-C(5)], 4.74–4.77 [m, 1 H, H-C(3)], 4.72 (d, *J* = 11.7 Hz, 1 H, PhCHO), 4.55 (d, *J* = 11.7 Hz, 1 H, PhCHO), 4.24 (q, *J* = 7.1 Hz, 2 H, $COOCH_2$), 4.05 [ddd, $J_{4,5}$ = 11.0 Hz, $J_{NH,4}$ = 8.3 Hz, $J_{3,4}$ = 7.6 Hz, 1 H, H-C(4)], 3.05–3.13 [m, 1 H, H-C(6)], 2.92 [dddd, *J* = 17.5 Hz, $J_{5,6}$ = 10.1 Hz, *J* = 3.0 Hz, *J* = 3.0 Hz, 1 H, H-C(6)], 1.88 (s, 3 H, CH_3CON), 1.31 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.9 (CON), 165.0 (COOEt), 137.3 (C1), 136.4 (C2), 128.6, 128.5, 128.3, 128.2 (6 × CPh), 82.0 (C5), 73.6 (C3), 72.0 ($PhCH_2$), 61.4 ($COOCH_2$), 54.5 (C4), 29.3 (C6), 23.4 (CH_3CON), 14.2 (OCH_2CH_3).

HRMS: *m*/*z* $[MH]^+$ calcd for $C_{18}H_{23}N_2O_6$: 363.156; found: 363.156.

(3*R*, 4*R*, 5*S*)-Ethyl 4-Acetamido-3-[(4-methoxybenzyl)oxy]-5-nitrocyclohex-1-enecarboxylate [(*R*,*R*,*S*) and (*R*,*R*,*R*)-6c, Mixture of Isomers]
Yield: 230 mg (27%); pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.89, 1.91 and 1.95 (s, 3 H), 2.86–3.50 (m, 2 H), 3.80 and 3.81 (s, 3 H), 4.20–4.28 (m, 2 H), 4.50–4.96 (m, 2 H), 4.85–4.94 (m), 5.04 (dt, *J* = 3.5, 5.9, 5.9 Hz) and 5.41 (dt, *J* = 6.0, 10.4 Hz, 1 H), 5.57 (d, *J* = 7.8 Hz), 5.71 (d, *J* = 7.2 Hz) and 5.85 (d, *J* = 8.7 Hz, 1 H), 6.87–6.97 (m, 3 H), 7.19–7.30 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.0, 23.2, 49.6, 55.3, 61.4, 71.2, 71.9 and 72.4, 80.8, 81.6, 114.1, 129.3, 129.8, 129.9, 133.8, 135.0, 159.6, 165.1, 169.9 and 170.3.

HRMS: *m*/*z* $[M - H^-]$ calcd for $C_{19}H_{23}N_2O_7$: 391.151; found: 391.174.

Reduction of Nitrocyclohexene Derivatives to the Corresponding Amines
To a solution of **6** (0.131 mmol) in EtOH (2 mL) under a nitrogen atmosphere was added activated Zn powder (257 mg, 3.93 mmol). 2 M HCl (2 mL) was added within 2 h using syringe pump. The reaction mixture was stirred for an additional 32 h at r.t., then quenched by addition of 10% NH_4OH (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a yellow oil that was purified by column chromatography on silica ($CHCl_3$–MeOH, 15:1→10:1) to give the corresponding amine **7** as pale-yellow viscous oils.

(3*R*,4*R*,5*S*)-Ethyl 4-Acetamido-5-amino-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (7a)
Acetic acid was used instead of HCl/EtOH.

Yield: 170 mg (81%); pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (t, *J* = 2.0 Hz, 1 H), 5.50 (d, *J* = 7.9 Hz, 1 H), 4.22 (q, *J* = 7.3 Hz, 2 H), 4.20–4.15 (m, 1 H), 3.51 (q, *J* = 8.8 Hz, 1 H), 3.35 (quint, *J* = 5.8 Hz, 1 H), 3.24 (m, 1 H), 2.75 (dd, *J* = 5.5, 5.2 Hz, 1 H), 2.15 (m, 1 H), 2.04 (s, 3 H), 1.60–1.40 (m, 4 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.5 Hz, 3 H). ^{1}H NMR data agree with those reported in the literature.[8a]

Ethyl 4-Acetamido-5-amino-3-(benzyloxy)cyclohex-1-enecarboxylate (7b; Mixture of Isomers)
Yield: 15 mg (34%); pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.97, 1.98 and 2.01 (s, 3 H), 2.26 (m), 2.66 (m) and 2.88 (dd, *J* = 5.2, 18.3 Hz, 2 H), 3.14 and 3.47 (m, 1 H), 3.95 and 4.28 (m, 2 H), 4.21 (q, *J* = 7.14 Hz, 2 H), 4.28 and 4.50 (m, 1 H), 4.70 (m, 4 H), 5.51 (br s, 2 H), 5.75 (d, *J* = 7.36 Hz) and 6.02 (t, *J* = 9.8, 9.8 Hz, 1 H), 6.87 and 6.97 (m, 1 H), 7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 23.7, 28.9, 46.6, 61.2, 65.3, 71.7, 77.2, 126.9, 127.8, 128.1, 128.4, 128.7, 137.8, 166.2, 172.3.

HRMS: *m*/*z* $[MH]^+$ calcd for $C_{18}H_{25}N_2O_4$: 333.181; found: 333.185.

Ethyl 4-Acetamido-5-amino-3-[(4-methoxybenzyl)oxy]cyclohex-1-enecarboxylate (7c; Mixture of Isomers)
Yield: 42 mg (38%); pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.89, 2.02 and 2.17 (s, 3 H), 2.64 (m, 2 H), 3.17 and 3.40 (m, 1 H), 3.80 and 3.15 (s, 3 H), 4.05 (m, 2 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 4.37 and 4.49 (m, 1 H), 4.65 (m, 2 H), 5.45 (br s, 2 H), 5.64 (d, *J* = 7.36 Hz) and 5.95 (dd, *J* = 7.9, 14.1 Hz, 1 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 6.84 and 6.94 (m, 1 H), 7.28 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 23.5, 30.8 and 33.7, 46.2 and 47.1, 55.2, 60.9, 68.3, 70.8, 73.3, 113.9, 129.7, 134.8, 159.4, 166.3, 170.8.

HRMS: *m*/*z* $[MH]^+$ calcd for $C_{19}H_{27}N_2O_5$: 363.192; found: 393.197.

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