DOI: 10.1002/adsc.201200093

Asymmetric Domino Nitro-Michael/Horner–Wadsworth–Emmons Reaction for Disubstituted Cyclohexenecarboxylate Annulation: Efficient Synthesis of Dipeptidyl Peptidase IV Inhibitor ABT-341 and Influenza Neuraminidase Inhibitor

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Received: February 4, 2012; Revised: April 18, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200093.

Abstract: An asymmetric domino nitro-Michael/Horner–Wadsworth–Emmons (HWE) reaction involving α,β-unsaturated aldehydes and nitro phosphonates has been developed, which gave 4,5-disubstituted cyclohexenecarboxylates with high stereoselectivities (*dr* up to >20:1, *ee* 83–92%) in good yields (44–76%). Furthermore, using this methodology as a key step, a short and practical synthesis of pharmaceutically useful compounds (such as the dipeptidyl peptidase IV inhibitor ABT-341 and an influenza neuraminidase inhibitor) has also been accomplished.

Keywords: asymmetric synthesis; domino reactions; Michael addition; organocatalysis

Introduction

In the past decade organocatalytic domino reactions have attracted increasing attention and become a powerful tool for the efficient and stereoselective construction of complex molecules.[1,2] These reactions allow the formation of multiple new bonds and stereocenters in a single operation under mild conditions, thereby minimizing the time- and cost-consuming purification steps and reducing the generation of wastes. They also offer the opportunity to access complex organic molecules which are difficult to assemble by traditional chemical synthesis.

Highly functional cyclohexene groups are privileged structural motifs of many natural products and pharmaceutical molecules, such as the neuraminidase (NA) inhibitors tamiflu (oseltamivir phosphate)[3] and tamiphosphor,[4] the dipeptidyl peptidase IV (DPP-4) inhibitor ABT-341[5] (Figure 1). Consequently, asymmetric reactions involved in the synthesis of cyclohexene scaffolds have attracted considerable interest from the organic synthesis community.[6] Following the pioneering work of Enders and co-workers in 2006,[7] different types of organocatalytic domino annulation reactions have been explored.[8] However, the development of conceptually different and target-oriented synthetic alternatives is still in the nascent stage.

ABT-341 is a highly potent, selective and orally efficacious third-generation DPP-4 inhibitor developed by Abbott laboratories in 2006.[5] In Abbott's synthesis, the chiral ABT-341 was obtained after 11 steps

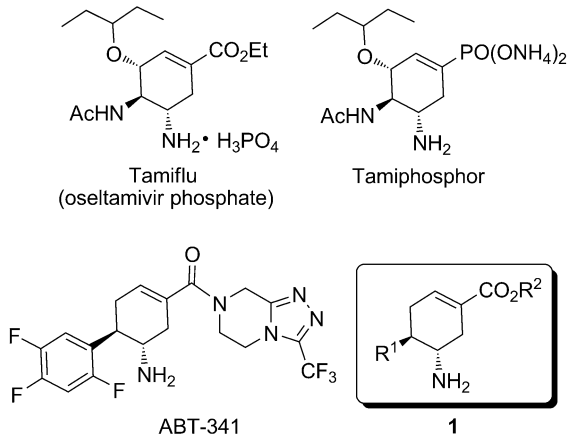
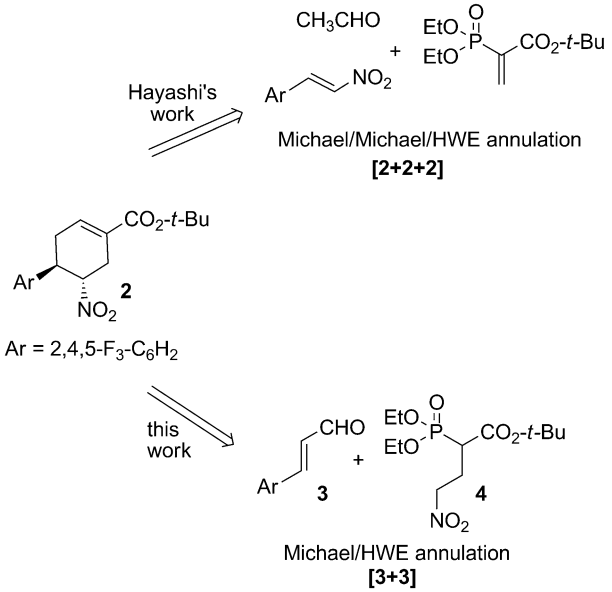


Figure 1. Representative chiral drugs containing a highly functional cyclohexene scaffold.

with very low yield. Moreover, chiral high-performance liquid chromatography (HPLC) separation of the key intermediate aminocyclohexenecarboxylate (**1**, Figure 1) was needed for obtaining the optically pure inhibitor. Furthermore, substituted cyclohexenecarboxylate **1** could also serve as the precursor for oseltamivir and tamiphosphor. Therefore development of an efficient and general enantioselective synthetic approach for obtaining the building block **1** is highly desirable.

As a part of our ongoing research on organocatalysis[9] and drug synthesis,[10] we set out to develop a general organocatalytic approach for the asymmetric synthesis of 4,5-disubstituted cyclohexenecarboxylate (**1**), and then apply the method for the synthesis of ABT-341 and oseltamivir analogues.[11] In the meantime, Hayashi and co-workers have recently developed a one-pot, high-yielding synthesis of ABT-341, in which the asymmetric domino Michael/Michael/Horner–Wadsworth–Emmons (HWE) reaction of acetaldehyde, nitroalkene and vinyl phosphonate was used as the key step (Scheme 1).[12] Differently, herein we envisioned that the key intermediate **2** in Hayashi's route towards ABT-341 could also be assembled from an α,β-unsaturated aldehyde (**3**) and a nitro phosphonate (**4**) through a secondary amine-catalyzed domino nitro-Michael/HWE reaction.

The racemic version of this reaction has been carried out by Kraus using stoichiometric 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), although generally low to moderate yields (seven examples, 26–74% yields) have been obtained.[13] However, for our newly designed asymmetric reaction, some challenges needed to be considered. (i) The addition of nitroalkane to α,β-unsaturated aldehyde is the initial step of the cascade reaction, but the diastereoselectivity was moderate (usually 1:1) in most cases when long-chain nitroalkanes were used as substrates.[14] (ii) The HWE reaction, as an important olefin-formation reaction, has been reported to a lesser extent in organocatalytic domino annulation reactions compared with the Wittig reaction,[15] ring-closing metathesis reaction,[6b] aldol reaction,[7,8h,i,16] and other reactions, mainly because of the need to use large amount of bases. Hence, the basicity and quantity of the base used should be compatible with the initial Michael reaction. (iii) The sequence of the domino reaction should be a Michael reaction, followed by the HWE reaction. If the HWE reaction takes place first, then the enantioselectivity will be decreased because the aldehyde will be consumed and the chiral iminium intermediate cannot be formed.



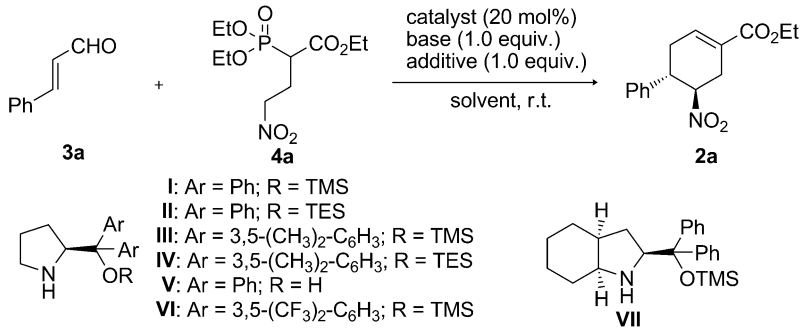
Scheme 1. Domino Michael/Michael/HWE and Michael/HWE annulation for the synthesis of the ABT-341 intermediate **2**.

Results and Discussion

Screening of Organocatalysts and Optimization of Reaction Conditions for the Domino Reaction

Based on these considerations, the domino reaction between cinnamaldehyde (**3a**) and nitro phosphonate (**4a**) was selected as a model reaction. We first studied the domino reaction catalyzed by diphenyl prolinol silyl ether **I** (20 mol%) in the presence of Et_3N and LiCl in chloroform at ambient temperature. To our delight, the reaction proceeded smoothly to furnish the desired product **2a** with modest stereoselectivity (72% *ee*, 2:1 *dr*); however, the yield was low (Table 1, entry 1). Then several organic and inorganic bases were screened (Table 1, entries 2–7), a higher yield was obtained when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used, and the diastereo- and enantioselectivity were also improved (entry 4). Considering the positive role of lithium salt additives in HWE reactions, other lithium salts ($LiClO_4$ and LiBr) were also examined, higher yield and diastereoselectivity were obtained when the additive was $LiClO_4$ (entry 8). Next, a range of solvents was explored, and the highest *ee* value was achieved in CH_2Cl_2 (entry 10).[17] Subsequently, other secondary amine organocatalysts **II–VII** were screened to improve the enantioselectivity (entries 11–16) and catalyst **III** was found to be the most promising candidate for this transformation (entry 12).

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Base	Lithium salt	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**I**	$CHCl_3$	Et_3N	LiCl	35	2:1	72
2	**I**	$CHCl_3$	DIPEA	LiCl	54	2:1	41
3	**I**	$CHCl_3$	DBU	LiCl	70	3:1	27
4	**I**	$CHCl_3$	DABCO	LiCl	54	6:1	86
5	**I**	$CHCl_3$	NaOAc	LiCl	68	3:1	78
6	**I**	$CHCl_3$	Cs_2CO_3	LiCl	52	1.5:1	70
7	**I**	$CHCl_3$	K_2CO_3	LiCl	36	2:1	85
8	**I**	$CHCl_3$	DABCO	$LiClO_4$	68	20:1	86
9	**I**	$CHCl_3$	DABCO	LiBr	46	5:1	70
10	**I**	CH_2Cl_2	DABCO	$LiClO_4$	70	>20:1	88
11	**II**	CH_2Cl_2	DABCO	$LiClO_4$	48	10:1	90
12	**III**	CH_2Cl_2	DABCO	$LiClO_4$	75	>20:1	92
13	**IV**	CH_2Cl_2	DABCO	$LiClO_4$	53	>20:1	89
14	**V**	CH_2Cl_2	DABCO	$LiClO_4$	36	>20:1	24
15	**VI**	CH_2Cl_2	DABCO	$LiClO_4$	30	5:1	38
16	**VII**	CH_2Cl_2	DABCO	$LiClO_4$	50	6:1	70

[a] Reactions were performed with cinnamaldehyde **3a** (0.3 mmol), nitro phosphonate **4a** (0.36 mmol), base (0.3 mmol) and lithium salt (0.3 mmol) with a secondary amine (0.06 mmol) as catalyst in solvent (1.5 mL) at room temperature for 60 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the crude products.
[d] Determined by chiral HPLC analysis.

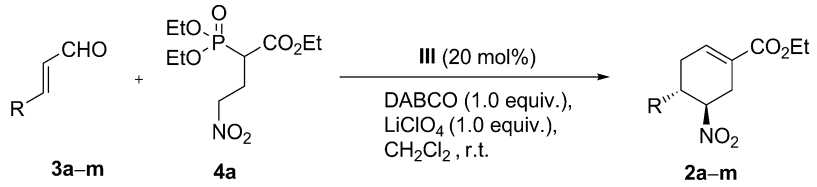
Domino Nitro-Michael/HWE Reactions of Various α,β-Unsaturated Aldehydes and Nitro Phosphonate

With the optimized reaction conditions in hand, various α,β-unsaturated aldehydes were examined and the results are summarized in Table 2. In most cases, the annulation products were obtained in good yields with high *dr* and *ee* values. For aryl-substituted unsaturated aldehydes, the steric hindrance of the aryl group showed some influence on the diastereoselectivities (entries 2, 3, 5–7), while the electronic properties of the aryl groups have limited effects, both electron-deficient (Cl, F) and electron-rich (OMe, Me) aryl substituents exhibited similar efficiency on the process (entries 2, 4, 7, 8). Good results were also obtained for 2,4,5-trifluorophenyl-substituted (precursor of ABT-341) and 2-furyl-substituted α,β-unsaturated aldehyde (entries 10 and 11). Moreover, the reaction could be successfully extended to α,β-unsaturated aldehydes with alkyl substituents; however, the yields and diastereoselectivities were slightly lower, and a longer reaction time was needed (entries 12 and 13).

Absolute Structure Determination and Proposed Mechanism

To determine the absolute configuration of the products, a single crystal of compound **2b** was obtained for X-ray crystallographic analysis (Figure 2).[18] The newly formed chiral centers of **2b** were confirmed as (4*S*,5*R*). On the basis of this observation, a plausible catalytic cycle for the asymmetric domino nitro-Michael/HWE reaction is proposed in Scheme 2. The reaction starts with the iminium activation of the α,β-unsaturated aldehyde **3** by the secondary amine, followed by the nitro-Michael addition of the nitro compound **4** to the iminium ion to give the intermediate **A**. After enamine/iminium transformation, the intermediate **B** then hydrolyzes to release **C** and regenerates the secondary amine catalyst. The following cas-

Table 2. Substrate scope of the asymmetric domino nitro-Michael/HWE reaction.[a]

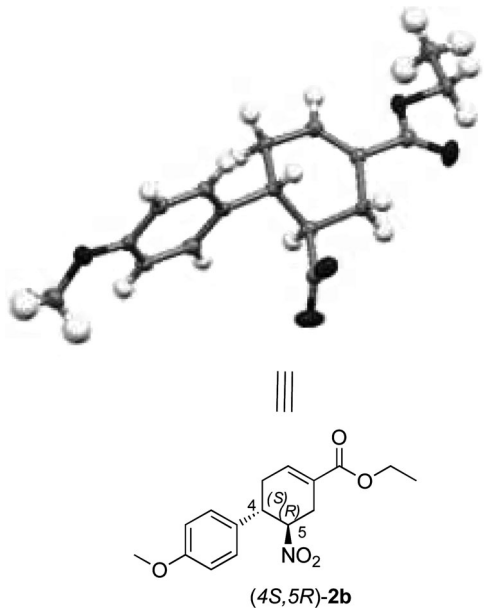


3a–m 4a 2a–m

Entry	R group	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	**2a**	60	75	>20:1	92
2	*p*-MeO-C_6H_4	**2b**	72	68	>20:1	92
3	*o*-MeO-C_6H_4	**2c**	72	62	10:1	89
4	*p*-Me-C_6H_4	**2d**	72	66	>20:1	89
5	*o*-Cl-C_6H_4	**2e**	60	66	6:1	89
6	*m*-Cl-C_6H_4	**2f**	60	65	10:1	87
7	*p*-Cl-C_6H_4	**2g**	60	61	>20:1	88
8	*p*-F-C_6H_4	**2h**	60	63	>20:1	90
9	*o*-NO_2-C_6H_4	**2i**	48	76	>20:1	86
10	2,4,5-F_3-C_6H_2	**2j**	48	65	10:1	83
11	2-furyl	**2k**	72	54	10:1	88
12	*n*-Pr	**2l**	96	44	2:1	83
13	$(CH_3O)_2CH$	**2m**	72	51	3:1	89

[a] Reactions were performed with α,β-unsaturated aldehyde **3** (0.3 mmol), nitro phosphonate **4a** (0.36 mmol), DABCO (0.3 mmol) and $LiClO_4$ (0.3 mmol), **III** (0.06 mmol) as catalyst in CH_2Cl_2 (1.5 mL) at room temperature.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy of the crude products.
[d] Determined by chiral HPLC analysis.

cade reaction involves intramolecular HWE cyclization of **C** to yield the disubstituted cyclohexenecarboxylate **5**. Then the *cis* isomer **5** is converted to the *trans* isomer for the latter is thermodynamically more stable under basic conditions.



(*4S,5R*)-**2b**

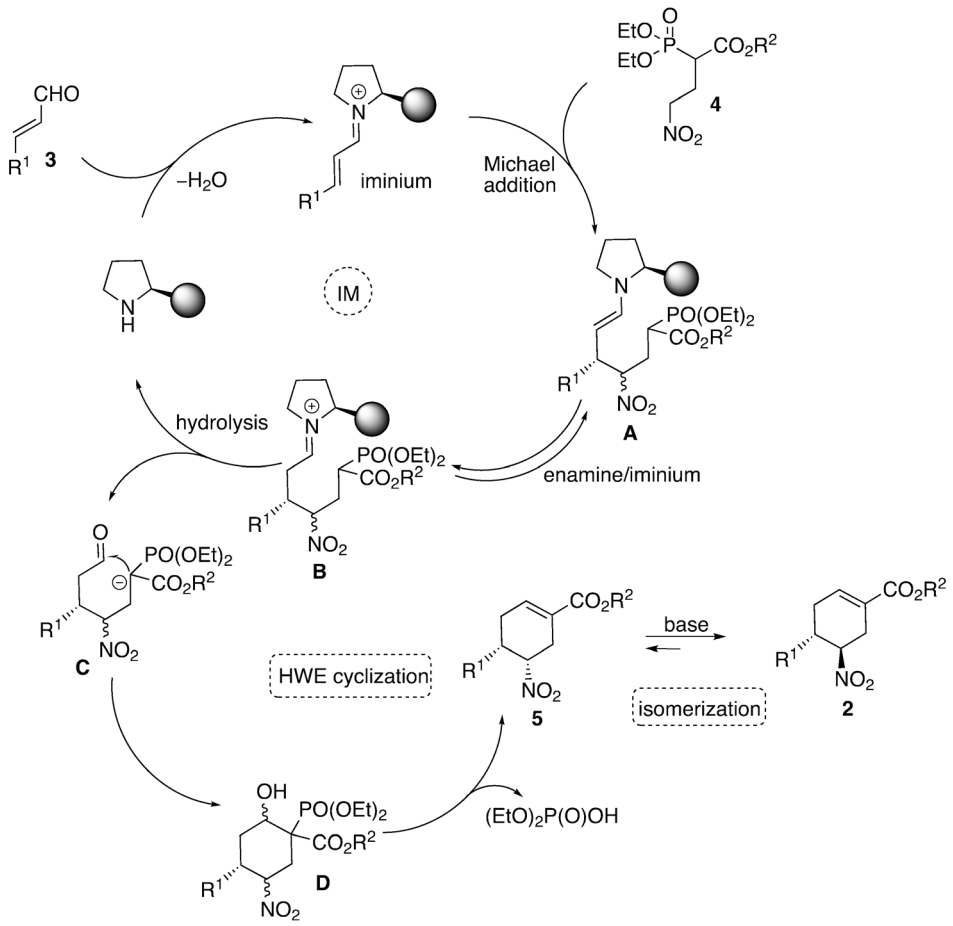
Figure 2. X-ray crystal structure of the compound **2b**.

Application in the Synthesis of DPP-4 Inhibitor ABT-341

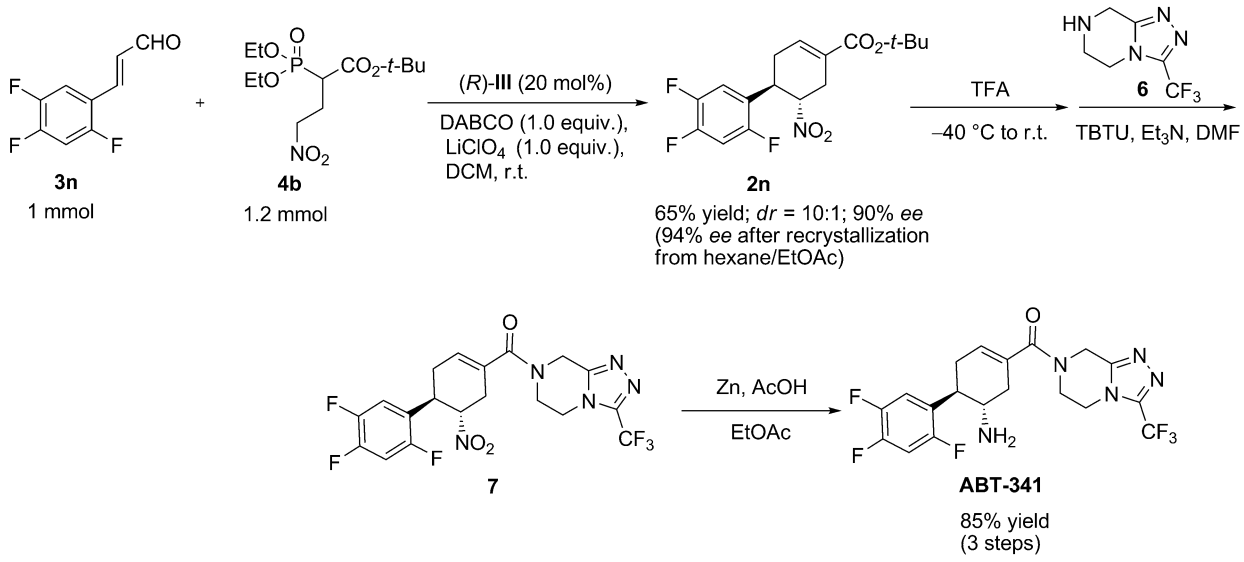
As shown in Figure 1 and Scheme 1, the disubstituted cyclohexenecarboxylate (**1**) can be the key precursor for oseltamivir, tamiphosphor and ABT-341. The usefulness of our methodology in organic synthesis was further illustrated by the short synthesis of ABT-341 as outlined in Scheme 3. The asymmetric domino nitro-Michael/HWE reaction of the α,β-unsaturated aldehyde **3n** with nitro phosphonate **4b** in the presence of 20 mol% catalyst (*R*)-**III** provided the cyclization product **2n** (65% isolated yield, 10:1 *dr,* 90% *ee*). Then we adopted Hayashi's strategy[12] to convert **2n** to ABT-341 in a one-pot operation: deprotection of the *tert*-butyl ester group with CF_3CO_2H, amidation with the amine **6** in the presence of the coupling reagent TBTU, and reduction of the nitro moiety of **7** with Zn and AcOH. ABT-341 was obtained in 55% overall yield from α,β-unsaturated aldehyde **3n**.

Application in the Synthesis of Influenza Neuraminidase Inhibitor

Furthermore, using this methodology as a key step, a short method for the synthesis of NA inhibitors has also been established. The selection of our NA inhibitor scaffold was based on the structures of oseltamivir

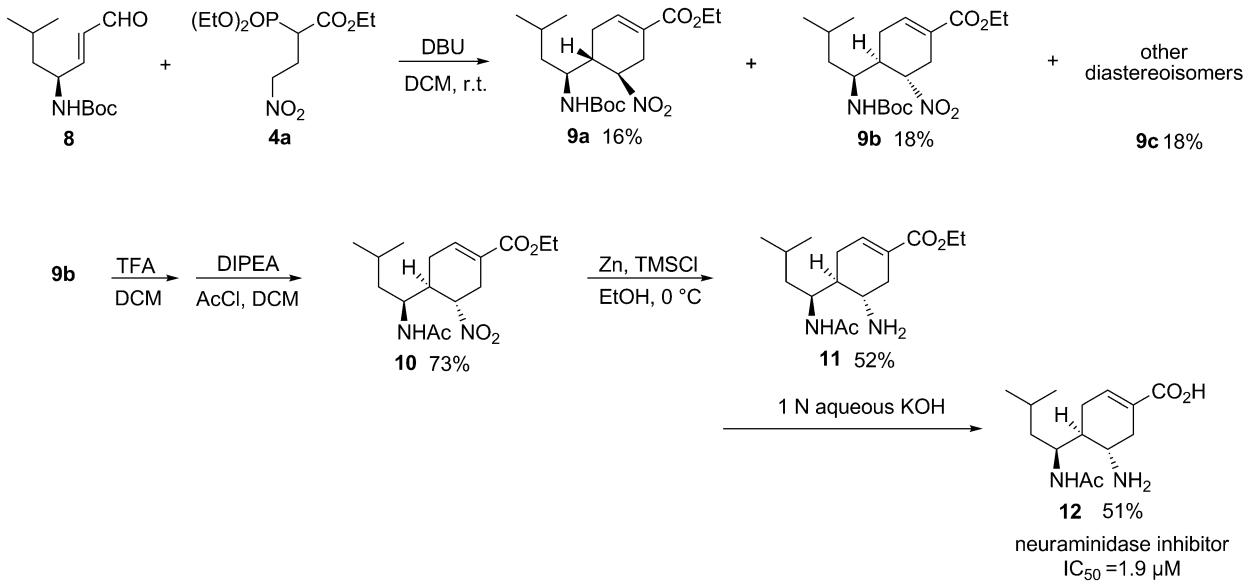


Scheme 2. Proposed mechanism for the domino nitro-Michael/HWE reaction.



Scheme 3. Synthesis of DPP-4 inhibitor ABT-341.

and peramivir.[19] As illustrated in Scheme 4, we have developed an efficient method for the diversity-oriented synthesis of a new type of NA inhibitor such as **12**. Our synthesis started with the construction of a disubstituted cyclohexenecarboxylate **9** from γ-amino-α,β-unsaturated aldehyde **8** and nitro phospho-



Scheme 4. Synthesis of the neuraminidase inhibitor **12**.

nate **4a**. Substrate **8** can be easily prepared from L-leucinol. Initially the catalytic reaction of **8** and **4a** was performed under the optimized reaction condition using (*R*)-**III**, but low yield and stereoselectivity (12% **9b** and 11% **9a)** were obtained even after 96 h. Then a stoichiometric organic base was adopted to accelerate the reaction. The treatment of **8** and **4a** with stoichiometric DBU in CH_2Cl_2 at ambient temperature yielded the cyclization products **9a–c** in 52% yield. The absolute configurations of the diastereoisomers **9a** and **9b** were determined by X-ray crystallographic analysis. Then after deprotection and acetylation of the diastereoisomer **9b**, **10** was obtained in 73% overall yield. The following reduction of **10** gave the amine **11** in 52% isolated yield. After hydrolysis of the ester **11**, the desired inhibitor **12** was obtained with $IC_{50} = 1.9$ μM for NA inhibition. Using this domino nitro-Michael/HWE reaction as a key step, diversity-oriented synthesis of new types of NA inhibitors is currently being developed in our laboratory, together with their biological testing as anti-influenza agents.[20]

Conclusions

In summary, motivated by the lack of an efficient method for the preparation of the DPP-4 inhibitor ABT-341 and its analogues, we have developed an efficient asymmetric domino nitro-Michael/HWE reaction involving α,β-unsaturated aldehydes and nitro phosphonates. This mild and simple experiment protocol yields disubstituted cyclohexenecarboxylates with high diastereo- and enantioselectivity. Using this methodology as a key step, the short synthesis of DPP-4 inhibitor ABT-341, influenza neuraminidase inhibitors and other therapeutically useful compounds can be achieved. Further investigations into the application of this methodology are currently ongoing, the results of which will be presented in due course.

Experimental Section

General Remarks

All the commercial reagents were used as such without further purification. All solvents were used as commercial anhydrous grade without further purification. The flash column chromatography was carried out over silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts in ^1H NMR spectra were reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS, $\delta = 0$ ppm). Chemical shifts in ^{13}C NMR spectra were reported relative to the central line of the chloroform signal ($\delta = 77.0$ ppm). Peaks were labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High-resolution mass spectra were obtained with an LC-MS-IT-TOF mass spectrometer. Enantiomeric excesses of compounds were determined by HPLC using a Daicel Chiralpak IC, AD-H or AS-H column.

General Procedure for the Asymmetric Domino Michael/HWE Reactions

To a solution of α,β-unsaturated aldehyde **3a** (40.0 mg, 0.3 mmol), $LiClO_4$ (31.5 mg, 0.3 mmol), DABCO (33.6 mg, 0.3 mmol) and catalyst **III** (22.9 mg, 0.06 mmol) in CH_2Cl_2 (1.5 mL) was added nitro phosphonate **4a** (0.36 mmol, 106.9 mg), and the resulting solution was stirred for 60 h at ambient temperature. The reaction mixture was directly purified by silica gel chromatography eluted with EtOAc/pe-

troleum ether, and fractions were collected and concentrated under vacuum to provide the pure desired product **2a**.

(4*S*,5*R*)-Ethyl 5-nitro-4-phenylcyclohex-1-enecarboxylate (2a): yield: 75%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5H), 7.06 (m, 1H), 4.94 (td, J = 5.4, 13.0 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.44 (td, J = 5.9, 10.4 Hz, 1H), 3.16–3.09 (m, 1H), 3.00–2.92 (m, 1H), 2.78–2.70 (m, 1H), 2.57–2.48 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 139.0, 137.4, 129.0, 127.9, 127.3, 127.1, 86.7, 61.0, 43.2, 32.9, 29.7, 14.2; HR-MS (ESI): m/z = 298.1036, calcd. for $C_{15}H_{17}NNaO_4^+$ $[M+Na]^+$: 298.1050; $[\alpha]_D^{25}$: −34.7 (c 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 29.9 min, t_{minor} = 28.3 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(4-methoxyphenyl)cyclohex-1-enecarboxylate (2b): yield: 68%; white solid; mp 149–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.11 (m, 2H), 7.05 (m, 1H), 6.86–6.83 (m, 2H), 4.90–4.84 (td, J = 5.2, 10.1 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.38 (td, J = 6.4, 10.8 Hz, 1H), 3.18–3.08 (m, 1H), 2.99–2.95 (m, 1H), 2.73–2.66 (m, 1H), 2.54–2.49 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 159.2, 137.6, 130.9, 128.3, 127.0, 114.4, 87.1, 60.9, 55.2, 42.6, 33.0, 29.8, 14.2; HR-MS (ESI): m/z = 328.1155, calcd. for $C_{16}H_{19}NNaO_5^+$ $[M+Na]^+$: 328.1155; $[\alpha]_D^{25}$: −60.0 (c 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC (Chiralpak AS-H column, hexane/*i*-PrOH = 95/5, 0.8 mL min^{-1}, 230 nm): t_{major} = 22.5 min, t_{minor} = 18.9 min;

(4*S*,5*R*)-Ethyl 5-nitro-4-(2-methoxyphenyl)cyclohex-1-enecarboxylate (2c): yield: 62%; white solid; mp 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.21 (m, 1H), 7.11–7.06 (m, 2H), 6.91–6.87 (m, 2H), 5.28 (td, J = 6.4, 9.2 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.75–3.68 (m, 1H), 3.07–2.89 (m, 2H), 2.69–2.67 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 157.3, 138.1, 129.0, 128.9, 126.8, 121.0, 111.3, 84.3, 60.8, 55.4, 39.6, 30.7, 29.5, 14.2; HR-MS (ESI): m/z = 328.1145, calcd. for $C_{16}H_{19}NNaO_5^+$ $[M+Na]^+$: 328.1155; $[\alpha]_D^{25}$: −28.6 (c 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 26.2 min, t_{minor} = 22.1 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(4-methylphenyl)cyclohex-1-enecarboxylate (2d): yield: 66%; white solid; mp 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.05 (m, 5H), 4.90 (td, J = 5.6, 10.4 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.39 (td, J = 6.0, 10.4 Hz, 1H), 3.14–3.08 (m, 1H), 2.99–2.90 (m, 1H), 2.75–2.68 (m, 1H), 2.56–2.45 (m, 1H), 2.31 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 137.6, 137.5, 136.0, 129.7, 127.1, 127.0, 86.9, 60.9, 42.9, 33.0, 29.8, 21.0, 14.2; HR-MS (ESI): m/z = 312.1204, calcd. for $C_{16}H_{19}NNaO_4^+$ $[M+Na]^+$: 312.1206; $[\alpha]_D^{25}$: −54.9 (c 0.72, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 28.1 min, t_{minor} = 26.2 min.

(4*S*,5*R*)-Ethyl-5-nitro-4-(2-chlorophenyl)cyclohex-1-enecarboxylate (2e): yield: 66%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 1H), 7.26–7.19 (m, 3H), 7.07 (m, 1H), 5.13 (td, J = 5.6, 9.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.09 (td, J = 6.0, 9.6 Hz, 1H), 3.12–2.96 (m, 2H), 2.86–2.78 (m, 1H), 2.47–2.40 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 137.2, 136.7, 133.9, 130.4, 128.9, 127.6, 127.2, 127.1, 84.2, 61.0, 39.3, 31.4, 29.4, 14.2; HR-MS (ESI): m/z = 332.0655, calcd. for $C_{15}H_{16}ClNNaO_4^+$ $[M+Na]^+$: 332.0660; $[\alpha]_D^{25}$: −19.1 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 254 nm): t_{major} = 27.8 min, t_{minor} = 25.9 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(3-chlorophenyl)cyclohex-1-enecarboxylate (2f): yield: 65%; white solid; mp 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 2H), 7.21 (m, 1H), 7.12–7.09 (m, 1H), 7.04 (m, 1H), 4.91 (td, J = 5.4, 10.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.42 (td, J = 5.6, 10.4 Hz, 1H), 3.18–3.12 (m, 1H), 2.99–2.91 (m, 1H), 2.77–2.69 (m, 1H), 2.54–2.46 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 141.1, 137.0, 134.8, 130.3, 128.2, 127.6, 127.2, 125.5, 86.4, 61.0, 43.0, 32.8, 29.8, 14.2; HR-MS (ESI): m/z = 332.0672, calcd. for $C_{15}H_{16}ClNNaO_4^+$ $[M+Na]^+$: 332.0660; $[\alpha]_D^{25}$: −41.8 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 90/10, 1.0 mL min^{-1}, 230 nm): t_{major} = 25.2 min, t_{minor} = 16.7 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(4-chlorophenyl)cyclohex-1-enecarboxylate (2g): yield: 61%; white solid; mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 2H), 7.16–7.14 (m, 2H), 7.05–7.03 (m, 1H), 4.89 (td, J = 5.6, 10.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.41 (td, J = 6.0, 10.4 Hz, 1H), 3.17–3.10 (m, 1H), 2.98–2.90 (m, 1H), 2.76–2.68 (m, 1H), 2.53–2.43 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 137.5, 137.1, 133.8, 129.2, 128.7, 127.2, 86.6, 61.0, 42.8, 32.9, 29.8, 14.2; HR-MS (ESI): m/z = 332.0658, calcd. for $C_{15}H_{16}ClNNaO_4^+$ $[M+Na]^+$: 332.0660; $[\alpha]_D^{25}$: −48.2 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 33.9 min, t_{minor} = 30.3 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(4-fluorophenyl)cyclohex-1-enecarboxylate (2h): yield: 63%; white solid; mp 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.17 (m, 2H), 7.05–6.99 (m, 3H), 4.92–4.86 (td, J = 5.6, 10.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.42 (td, J = 6.4, 10.4 Hz, 1H), 3.17–3.15 (m, 1H), 2.99–2.91 (m, 1H), 2.76–2.69 (m, 1H), 2.53–2.45 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 162.2, 137.2, 134.7, 128.9, 127.1, 116.0, 115.8, 86.9, 61.0, 42.6, 33.0, 29.8, 14.2; HR-MS (ESI): m/z = 316.0953, calcd. for $C_{15}H_{16}FNNaO_4^+$ $[M+Na]^+$: 316.0956; $[\alpha]_D^{25}$: −36.4 (c 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 31.1 min, t_{minor} = 28.4 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(2-nitrophenyl)cyclohex-1-enecarboxylate (2i): yield: 76%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 1H), 7.63–7.58 (m, 1H), 7.45–7.41 (m, 2H), 7.07 (m, 1H), 5.09 (td, J = 5.2, 10.4 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.09 (td, J = 4.8, 10.8 Hz, 1H), 3.24 (dd, J = 5.2, 17.6 Hz, 1H), 3.11–3.03 (m, 1H), 2.92–2.86 (m, 1H), 2.49–2.42 (m, 1H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 150.4, 137.1, 134.0, 133.4, 128.6, 127.3, 127.1, 125.1, 85.2, 61.1, 37.9, 32.9, 30.3, 14.2; HR-MS (ESI): m/z = 343.0910, calcd. for $C_{15}H_{16}N_2NaO_6^+$ $[M+Na]^+$: 343.0901; $[\alpha]_D^{25}$: +92.5 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 87/13, 0.8 mL min^{-1}, 254 nm): t_{major} = 14.4 min, t_{minor} = 16.4 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(2,4,5-trifluorophenyl)cyclohex-1-enecarboxylate (2j): yield: 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.91 (m, 3H), 5.02 (td, *J* = 6.0, 10.4 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.63 (td, *J* = 6.0, 10.4 Hz, 1H), 3.19–3.13 (m, 1H), 2.98–2.89 (m, 1H), 2.76–2.69 (m, 1H), 2.61–2.51 (m, 1H) 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 136.5, 127.2, 122.3, 122.1, 117.6, 117.0, 106.5, 106.2, 84.5, 61.1, 38.1, 31.2, 29.7, 14.2; HR-MS (ESI): *m/z* = 352.0783, calcd. for $C_{15}H_{14}F_3NNaO_4^+$ $[M+Na]^+$: 352.0767; $[\alpha]_D^{25}$: −93.0 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 254 nm): t_{major} = 18.9 min, t_{minor} = 15.3 min.

(4*S*,5*R*)-Ethyl 5-nitro-4-(furan-2-yl)cyclohex-1-enecarboxylate (2k): yield: 54%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 1.3 Hz, 1H), 7.03 (m, 1H), 6.28 (dd, *J* = 1.9, 3.0 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 4.93 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.65 (td, *J* = 9.2, 12.4 Hz, 1H), 3.00–2.97 (m, 2H), 2.73–2.68 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 151.9, 142.4, 136.5, 126.7, 110.4, 107.3, 84.6, 60.9, 36.4, 29.1, 28.6, 14.2; HR-MS (ESI): *m/z* = 288.0832, calcd. for $C_{13}H_{15}NNaO_5^+$ $[M+Na]^+$: 288.0842; $[\alpha]_D^{25}$: −40.7 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 230 nm): t_{major} = 25.3 min, t_{minor} = 23.8 min.

(4*R*,5*R*)-Ethyl 5-nitro-4-propylcyclohex-1-enecarboxylate (2l): yield: 44%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 4.50 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.91 (m, 2H), 2.59–2.51 (m, 1H), 2.32–2.27 (m, 1H), 2.07–1.99 (m, 1H), 1.47–1.24 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 137.2, 126.6, 86.6, 60.8, 35.7, 33.9, 29.3, 28.5, 19.2, 14.2, 13.9; HR-MS (ESI): *m/z* = 264.1202, calcd. for $C_{12}H_{19}NNaO_4^+$ $[M+Na]^+$: 264.1206; $[\alpha]_D^{25}$: −48.4 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 95/5, 1.0 mL min^{-1}, 210 nm): t_{major} = 20.2 min, t_{minor} = 15.2 min.

(4*R*,5*R*)-Ethyl 5-nitro-4-(dimethoxymethyl)cyclohex-1-enecarboxylate (2m): yield: 51%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1H), 4.94 (dt, *J* = 2.9, 5.6 Hz, 1H), 4.43–4.30 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 3.31 (s, 3H), 3.06 (d, *J* = 18.8 Hz, 1H), 2.72–2.55 (m, 1H), 2.49–2.20 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 136.6, 125.2, 103.4, 78.6, 59.8, 54.8, 52.5, 37.8, 27.0, 23.5, 13.2; HR-MS (ESI): *m/z* = 296.1102, calcd. for $C_{12}H_{19}NO_6Na^+$ $[M+Na]^+$: 296.1105; $[\alpha]_D^{25}$: −37.4 (*c* 0.5, CH_2Cl_2). The enantiomeric excess was determined by HPLC (Chiralcel OD-H column, hexane/-*i*PrOH = 90/10, 0.8 mL min^{-1}, 210 nm); t_{major} = 8.8 min, t_{minor} = 8.4 min.

(4*R*,5*S*)-*tert*-Butyl 5-nitro-4-(2,4,5-trifluorophenyl)cyclohex-1-enecarboxylate[11] (2n): yield: 65%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.90 (m, 3H), 5.02 (ddd, *J* = 5.6, 10.8, 10.8 Hz, 1H), 3.60 (ddd, *J* = 6.0, 10.8, 10.8 Hz, 1H), 3.13 (dd, *J* = 5.2, 17.2 Hz, 1H), 2.94–2.83 (m, 1H), 2.70 (ddd, *J* = 5.2, 5.2, 19.6 Hz, 1H), 2.59–2.47 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 157.2, 148.2, 146.2, 135.5, 128.5, 122.4, 117.2, 106.5, 84.5, 81.4, 38.2, 31.3, 30.0, 28.0; HR-MS (ESI): *m/z* = 380.1085, calcd. for $C_{17}H_{18}F_3NNaO_4^+$ $[M+Na]^+$: 380.1080; $[\alpha]_D^{25}$: +40.6 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC (Chiralpak IC column, hexane/*i*-PrOH = 99/1, 1.0 mL min^{-1}, 210 nm): t_{major} = 20.4 min, t_{minor} = 26.1 min.

tert-Butyl 2-(Diethoxyphosphoryl)-4-nitrobutanoate (4b)

Product **4b** was synthesized from *tert*-butyl 2-(diethoxyphosphoryl)acrylate[11] according to the literature;[12] yield: 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57–4.43 (m, 2H), 4.16–4.10 (m, 1H), 2.96 (td, *J* = 7.3, 19.3 Hz, 1H), 2.51 (td, *J* = 7.2, 16.6 Hz, 1H), 1.45 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7 (d, *J* = 5.6 Hz), 82.7, 73.1 (d, *J* = 12.8 Hz), 62.9 (t, *J* = 6.3 Hz), 43.5, 42.2, 27.7, 24.5, 16.2, 16.1; HR-MS (ESI): *m/z* = 348.1180, calcd. for $C_{12}H_{24}NNaO_7P^+$ $[M+Na]^+$: 348.1183.

(4*R*,5*S*)-Ethyl 4-{(*S*)-1-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl}-5-nitrocyclohex-1-enecarboxylate (9b)

To a solution of α,β-unsaturated aldehyde **8** (121 mg, 0.5 mmol) and nitro phosphonate **4a** (149 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added DBU (152 mg, 1 mmol) at 0 °C, and the resulting solution was stirred for 24 h at ambient temperature. The reaction mixture was directly purified by silica gel chromatography eluted with EtOAc/petroleum ether, and fractions were collected and concentrated under vacuum to provide pure products **9a, 9b** and other diastereoisomers **9c**. Data for **9b**: $[\alpha]_D^{25}$: +15.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 4.75–4.54 (m, 1H), 4.27 (d, *J* = 8.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.97–3.77 (m, 1H), 3.21–2.98 (m, 1H), 2.75 (d, *J* = 15.4 Hz, 1H), 2.58–2.24 (m, 2H), 2.16 (s, 1H), 1.70–1.47 (m, 2H), 1.43 (s, 10H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.98–0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 155.5, 137.0, 126.9, 83.1, 79.7, 60.8, 48.2, 41.5, 39.6, 29.8, 28.2, 25.0, 24.8, 23.0, 21.9, 14.2; HR-MS (ESI): *m/z* = 407.2156, calcd. for $C_{19}H_{32}N_2NaO_6^+$ $[M+Na]^+$: 407.2153.

(4*S*,5*R*)-Ethyl 4-{(*S*)-1-[(*tert*-butoxycarbonyl)amino]-3-methylbutyl}-5-nitrocyclohex-1-enecarboxylate (9a): $[\alpha]_D^{25}$: −24.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 4.76 (dd, *J* = 6.5, 13.7 Hz, 1H), 4.63 (d, *J* = 9.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.74–3.47 (m, 1H), 3.02–2.91 (m, 2H), 2.51–2.21 (m, 3H), 1.73–1.49 (m, 2H), 1.43 (s, 10H), 1.30 (t, *J* = 7.1 Hz, 4H), 0.89 (dd, *J* = 6.5, 16.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 155.7, 136.4, 126.6, 82.9, 79.5, 60.7, 49.8, 41.7, 40.8, 28.2, 27.8, 26.7, 24.9, 23.4, 21.3, 14.1; HR-MS (ESI): *m/z* = 407.2153, calcd. for $C_{19}H_{32}N_2NaO_6^+$ $[M+Na]^+$: 407.2153.

(4*R*,5*S*)-Ethyl 4-[(*S*)-1-Acetamido-3-methylbutyl]-5-nitrocyclohex-1-enecarboxylate (10)

To a solution of **9b** (140 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) was added CF_3COOH (0.3 mL, 0.4 mmol) at 0 °C and the resulting solution was stirred for 3 h at ambient temperature. The reaction was quenched by saturated $NaHCO_3$ solution (5 mL), then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, DIPEA (93 mg, 0.72 mmol) and AcCl (37 mg, 0.47 mmol) were successively added to the free amine in dry DCM (2 mL) and stirred for 3 h at room temperature. The resulting mixture was careful-

ly quenched by saturated NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3×10 mL). Then the combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography (SiO_2, 2:1 hexane: EtOAc as eluent) afforded compound **10** as a light yellow white solid; yield: 86 mg (73%); $[\alpha]_D^{25}$: +16.3 (*c* 0.38, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 5.28 (d, *J* = 8.6 Hz, 1H), 4.63 (td, *J* = 5.6, 9.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.15–4.10 (m, 1H), 3.06–3.01 (m, 1H), 2.81–2.75 (m, 1H), 2.66–2.39 (m, 2H), 2.22–2.05 (m, 1H), 1.95 (s, 3H), 1.70–1.37 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.39–1.12 (m, 3H), 0.93 (dd, *J* = 6.5, 18.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 165.4, 136.8, 126.8, 83.0, 60.9, 47.6, 40.3, 39.6, 29.7, 25.6, 25.1, 23.2, 23.1, 21.8, 14.2; HR-MS (ESI): *m/z* = 349.1724, calcd. for $C_{16}H_{26}N_2NaO_5^+$ $[M+Na]^+$: 349.1734.

(4*S*,5*S*)-Ethyl 4-[(*S*)-1-Acetamido-3-methylbutyl]-5-aminocyclohex-1-enecarboxylate (11)

To a solution of **10** (43 mg, 0.13 mmol) in EtOH (3 mL) was added activated Zn powder (425 mg, 6.5 mmol) and trimethylsilyl chloride (1.14 mL, 37.2 mmol) slowly at room temperature under an N_2 atmosphere. The resulting mixture was stirred for 2 h. After filtration, the mixtute was neutralized with ammonia (2 mL) and extracted with CH_2Cl_2 (3×5 mL). Then the combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography (SiO_2, 30:1 CH_2Cl_2: methanol as eluent) afforded compound **11** as a light yellow oil; yield: 20 mg (52%); $[\alpha]_D^{25}$: +15.0 (*c* 1.07, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1H), 5.77 (d, *J* = 9.4 Hz, 1H), 4.37–4.31 (m, 1H), 4.18 (dd, *J* = 7.1, 14.2 Hz, 2H), 2.82–2.67 (m, 1H), 2.53–2.27 (m, 2H), 2.00 (s, 3H), 1.98–1.94 (m, 2H), 1.71–1.32 (m, 3H), 1.30–1.26 (m, 3H), 0.97–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 166.9, 137.1, 129.4, 60.4, 46.1, 42.0, 38.7, 29.7, 28.6, 25.5, 25.2, 23.3, 23.0, 22.1, 14.2; HR-MS (ESI): *m/z* = 297.2164, calcd. for $C_{16}H_{28}N_2O_3^+$ $[M+H]^+$: 297.2173.

(4*S*,5*S*)-4-[(*S*)-1-Acetamido-3-methylbutyl]-5-aminocyclohex-1-enecarboxylic Acid (12)

To a solution of **11** (20 mg, 0.068 mmol) in THF (1 mL) was added aqueous NaOH solution (1 N, 1 mL) and the mixture was stirred at room temperature for 3 h. Then the solvent was removed under vacuum, and the pH value was adjusted to 3–4 by addition of Amberlite IR-120. After filtration and concentration, the crude product was purified by flash chromatography (C_{18} column, pure water as eluent) to give compound **12** as a light yellow oil; yield: 9.3 mg (51%); $[\alpha]_D^{25}$: +28.3 (*c* 0.5, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 6.84 (s, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 3.12 (td, *J* = 5.2, 10.5 Hz, 1H), 2.77–2.58 (m, 1H), 2.43 (d, *J* = 19.0 Hz, 1H), 2.31–2.17 (m, 1H), 2.10–1.83 (m, 5H), 1.62–1.47 (m, 2H), 1.21 (dd, *J* = 5.5, 9.8 Hz, 1H), 0.81 (dd, *J* = 6.3, 17.6 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ = 175.5, 171.4, 138.4, 127.3, 48.4, 46.3, 40.6, 39.9, 28.9, 24.6, 24.3, 22.2, 21.4, 20.9; HR-MS (ESI): *m/z* = 291.1681, calcd. for $C_{14}H_{24}N_2NaO_3^+$ $[M+Na]^+$: 291.1679.

Acknowledgements

This work was financially supported by The European Commission through the project FP7–201431(CATAFLU.OR) and the introduction of innovative R&D program of Guangdong Province (No. 2009010058). We also thank Dr. Jia-Mei Chen (Sun Yat-sen University) for X-ray crystal structure analysis.

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