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Synthesis of (–)-Oseltamivir by Using a Microreactor in the Curtius Rearrangement

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A microflow reaction of the Curtius rearrangement by using trimethylsilyl azide as an azide source, followed by trapping of the generated isocyanate with a nucleophile was established, which is safe, inexpensive, and suitable for large-scale synthesis. By this flow reaction in the Curtius rearrangement and recrystallization of the late-stage acetamide intermediate the third-generation synthesis of (–)-Oseltamivir has been established, which is efficient, practical, and safe.

Introduction

(–)-Oseltamivir phosphate (Tamiflu) is a neuraminidase inhibitor used in the treatment of both Type A and Type B human influenza.[1] In addition, it is also one of the most promising therapeutics for the treatment of infection from the H5N1 avian flu virus, and the development of an efficient asymmetric synthesis of (–)-Oseltamivir (**1**) is a high priority. Many syntheses of (–)-Oseltamivir have been reported so far.[2] Our group has reported the synthesis of (–)-Oseltamivir by three one-pot reactions,[3] and more recently, we have developed its synthesis by two one-pot reactions using 3-(pentyloxy)acetaldehyde and *tert*-butyl 3-nitropropenoate to afford an overall yield of 60% by employing an uninterrupted sequence of reactions (Scheme 1).[4] We have also reported a column-free synthesis using acid/base extraction of the key intermediates.[4] Further modification of the synthesis is being continuously investigated to synthesize this important drug more effectively.

The Curtius rearrangement[5] of acyl azide has been employed in the sequence of two one-pot reactions for the formation of acetamide **7** from carboxylic acid **3**. As acyl azide **5** is a potentially explosive compound, because of its nitro and azide moieties, its safety needs to be checked for large-scale synthesis. Thus, we have investigated the danger of **5** by differential scanning calorimetry (DSC).

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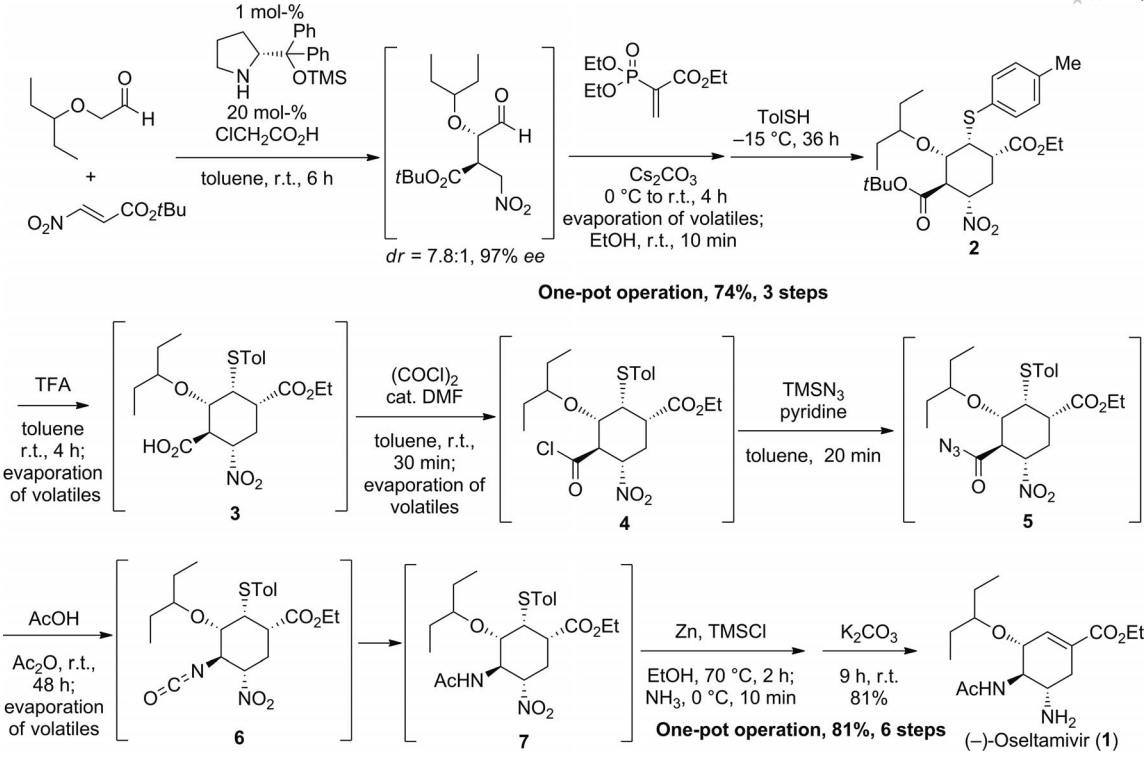
Continuous-flow synthesis offers the generation and consumption of dangerous intermediates in situ, preventing their accumulation, and so represents a potential solution for dealing with hazardous reaction intermediates and products.[6] In a microreactor, the mixing and chemical reactions take place on a scale with characteristic dimensions in the submillimeter range, and with reaction volumes in the nanoliter to milliliter range. As a result, both mixing and heat transfer in the microreactor occur very rapidly. The advantages of microreactor technology are particularly evident in highly exothermic reactions, and with toxic and corrosive gases as well as with reactions that involve the formation of explosive intermediates or products.

There have been a few reports on Curtius rearrangements in microflow systems. For example, Jensen reported multiple continuous-flow reactions involving the Curtius rearrangement of acyl chloride and sodium azide.[7] Ley and co-workers reported the Curtius rearrangement of carboxylic acid under continuous-flow conditions using diphenylphosphoryl azide (DPPA).[8] The same group also developed the Curtius rearrangement in a flow system using acyl chloride and azide monoliths.[9] In these methods, the sodium azide, DPPA, and azide monoliths were employed as azide sources. Trimethylsilyl azide ($TMSN_3$) is an alternative azide source that is safe and inexpensive, and the by-product, TMSCl, can be easily removed. Hence, first we investigated the Curtius rearrangement under flow conditions using $TMSN_3$ as an azide source and studied the generality of the method. Then, it was applied to the synthesis of (–)-Oseltamivir.

To prepare (–)-Oseltamivir with a high purity in each batch, it is preferable to purify the late-stage intermediate by recrystallization; hence, the physical properties of the intermediates were investigated, and purification by recrystallization was examined.



Scheme 1. Previous sequence of two one-pot reactions for the preparation of (–)-Oseltamivir.

All the modifications to the synthesis of (–)-Oseltamivir by two one-pot reactions based on these considerations are described in this paper.

Results and Discussion

Differential Scanning Calorimetry

One of the key issues in the synthesis of (–)-Oseltamivir is the safety of the acyl azide **5**, as azides are a known hazard. In our previous synthesis, **5** was prepared from carboxylic acid **3** after conversion to acyl chloride **4**, which was treated with NaN_3 in aqueous acetone in the first-generation synthesis of (–)-Oseltamivir,[3] and $TMSN_3$ with pyridine in toluene in the second-generation synthesis (Scheme 1).[4] When NaN_3 in aqueous acetone was used, **5** was extracted into the organic phase, and crude **5** was used directly without any further purification. In the reaction of $TMSN_3$ and pyridine, the solution was treated directly with AcOH and Ac_2O, without extraction or purification. The Curtius rearrangement proceeded at room temperature, without heating. Thus, the second-generation synthesis avoids extraction, concentration, and heating of **5**, which reduces the risk of explosion. However, to perform a large-scale synthesis, the safety concerns of the reactant have to be investigated, and the heat capacity of **5** was measured by using DSC.

DSC measurements on **5** were performed by increasing the temperature at a rate of 10 °C/min, and the results are shown in Figure 1. Two major peaks were observed: the first peak began at 61.3 °C and had a decomposition energy of 310.5 J/g. The second peak began at 175.6 °C and had a large decomposition energy of 1246 J/g. The following experiments were performed to investigate the reactions characterized by these two peaks. Pure **5** was heated to 60 °C for 30 and 45 min, and its ^1H NMR spectrum was measured [Equation (1)]. After 30 min, isocyanate **6** was obtained in a ca. 80% yield after the Curtius rearrangement, and the starting material and other unidentified products were present in ca. 10 and 5% yields, respectively. From this, we con-

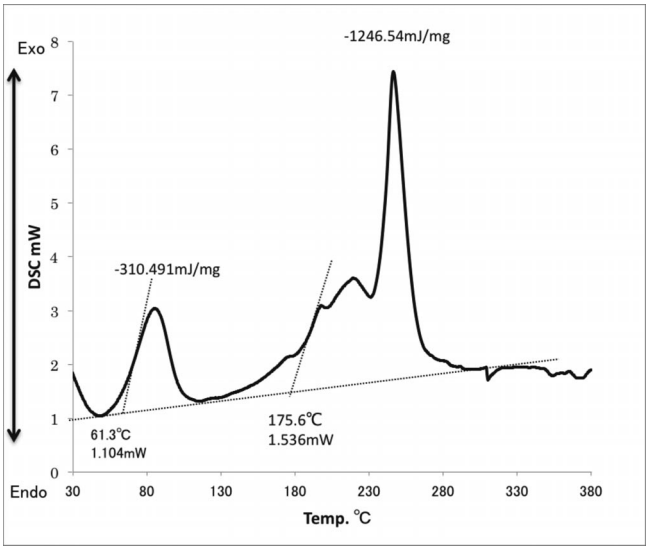
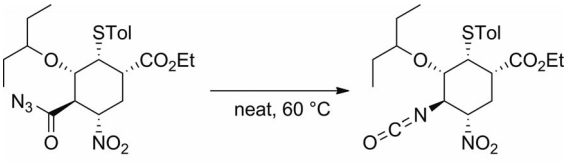


Figure 1. DSC data for **5**.

cluded that the Curtius rearrangement was not complete within a period of 30 min at 60 °C as 10% of the starting material remained. After heating for a period of 45 min, all the starting material had been used, with the formation of ca. 90% of **6** with ca. 10% unidentified products remaining. This result indicates that the Curtius rearrangement proceeded at 60 °C over 45 min, and so part of **5** in the DSC experiment was converted into **6**.



5 **6**

30 min: ca. 80%, **5** was recovered in 10%
45 min: ca. 90% (1)

Next, the ^{1}H NMR spectrum of the sample was measured after heating of **5** to 60 °C for 45 min and then to 175 °C for 30 min. Broad NMR signals were observed, with no assignable peaks except for those attributed to toluenethiol, which indicated that the decomposition of **6** occurred without the formation of any specific products. Our NMR studies indicated that a partial Curtius rearrangement proceeded in the first DSC peak and that several reactions occurred in the second DSC peak, such as the Curtius rearrangement of the remaining **5**, the decomposition of the nitro groups, and the decomposition of **6** generated by the above Curtius rearrangement. This explains the observation that the second DSC peak was a combination of several peaks, indicating that several reactions occurred over this temperature range. In general, the decomposition temperature of nitro compounds is high (260–360 °C) with a large decomposition energy (310–360 kJ/mol), whereas the decomposition temperature of azide compounds is low (approx. 140 °C) with a lower decomposition energy (200–240 kJ/mol).[10] These general trends coincide with our experimental results. The reaction of the azides occurred at a lower temperature with a small DSC peak area, and the decomposition of the nitro groups occurred mainly in the second DSC peak at a higher temperature with a large decomposition energy.

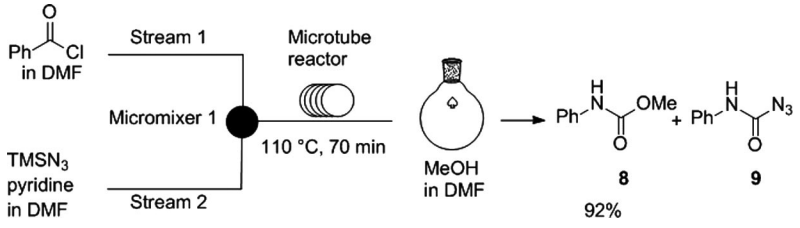
The Curtius rearrangement of **5** proceeded at room temperature over 19 h. In the sequence of two one-pot reactions, we treated crude **5** as a toluene solution, and the concentration and isolation stages of **5** were omitted. This reduces the risk of decomposition and explosion, and is important in performing the reaction safely and for synthesizing the desired product in good yield and high purity. However, it is still desirable to develop a safer method.

Curtius Rearrangement in a Microreactor

Flow reactions[6] are a safer alternative to traditional batch reactions, as they reduce the risk of explosion from shock-sensitive compounds. Although there have been several reports on the Curtius rearrangement using flow systems,[7–9] none use $TMSN_3$ as an azide source. First, we optimized the Curtius rearrangement of $TMSN_3$ as an azide source employing the reaction of benzoyl chloride with $TMSN_3$ as a model reaction.

A DMF solution of benzoyl chloride was mixed with a DMF solution of $TMSN_3$ and pyridine using a Comet-X-01 micromixing device[11,12] at room temperature at a flow rate of 0.4 mL/min. After mixing the components, the mixture was allowed to flow in the apparatus for 20 min to allow the formation of acyl azide. The mixture was passed through the heated area at 110 °C for a fixed period to allow the Curtius rearrangement to take place, and then the reaction mixture was poured into MeOH. After stirring the mixture for 1 h to allow the reaction of isocyanate with MeOH, methyl phenylcarbamate was isolated. Optimization of the concentration of each reagent under the reaction parameters used (i.e. the flow rate and the length of the reaction tube) showed that both benzoyl chloride and $TMSN_3$ required a concentration of 0.5 M in DMF and pyridine required a concentration of 1 M in DMF. The flow rate of Streams 1 and 2 was 0.4 mL/h, and the reaction time at 110 °C was 70 min. It was also found that the amount of reagent used was important. An excess of $TMSN_3$ reacted further with the generated phenyl isocyanate to form phenylcarbamoyl azide (**9**), and a given amount of $TMSN_3$ was required to suppress this side reaction. By using the optimized conditions, the desired product was obtained in good yield (92%, Scheme 2).

We also investigated the Curtius rearrangement in the presence of a nucleophile. In this case, the Curtius rearrangement afforded the isocyanate, which was immediately trapped by the nucleophile, suppressing the generation of **9**. After the optimization of the conditions, the reaction was conducted by using two micromixing devices (T1 and T2) as follows. A DMF solution of benzoyl chloride (0.5 M) was mixed with a DMF solution of $TMSN_3$ (0.5 M) and



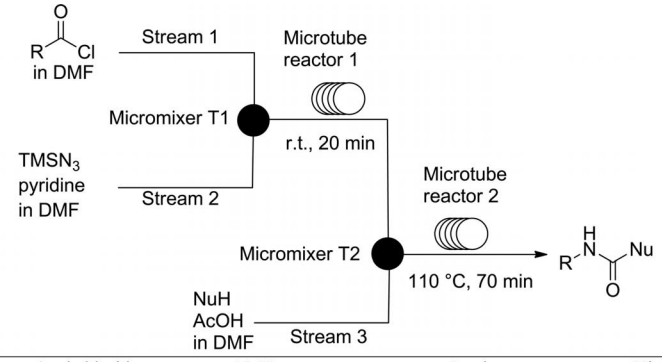
8 **9**
92%

Scheme 2. Reaction of benzoyl chloride and $TMSN_3$ by the Curtius rearrangement.

pyridine (1 M) in T1 at 0.4 mL/h. After the reaction mixture had been allowed to flow for 20 min at room temperature, it was mixed with a DMF solution of acetic acid (5 M)[13] and benzyl alcohol (2.5 M) in T2. The reaction mixture was allowed to run through the reaction tube at 110 °C for 70 min. After isolation, the desired carbamate was obtained in an excellent yield (91%). As a good result was obtained in the above case, the generality of the reaction was then investigated, and the results are summarized in Table 1.

Regarding the acyl chloride unit, not only benzoic acid, but also electron-rich and electron-deficient benzoic acid derivatives were successfully employed in this role. 2-Furoyl chloride, 2-thenoyl chloride, and nicotinoyl chloride afforded the corresponding carbamates in good to excellent yields. The reaction proceeded efficiently with acyl chlorides derived from aromatic acids, heteroaromatic acids, and aliphatic acids to afford the corresponding carbamates in good yields. As for the nucleophile, homoallyl alcohol, benzyl alcohol, allyl alcohol, and the sterically hindered *tert*-butyl alcohol were successfully employed to afford carbamates in good yields. Amines and thiols are also suitable nucleophiles for this purpose.

Table 1. Generality of a domino Curtius rearrangement under microfluidic conditions.[a]



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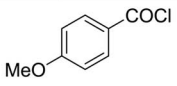
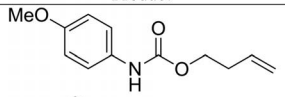
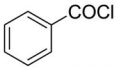
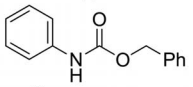
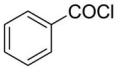
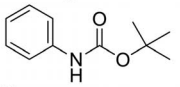
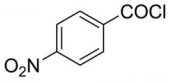
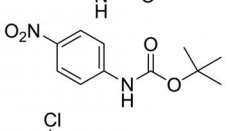
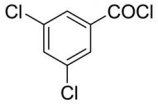
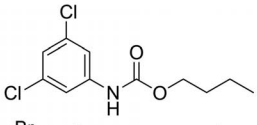
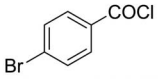
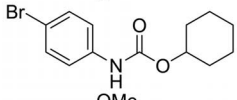
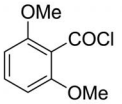
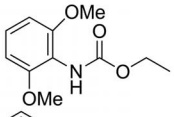
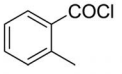
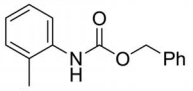
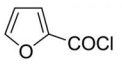
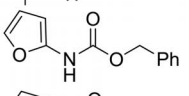
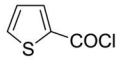
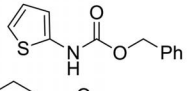
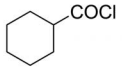
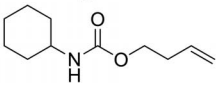
1		homoallyl alcohol		quant.
2		BnOH		91
3		*t*BuOH		88
4		*t*BuOH		84
5		*n*BuOH		quant.
6		cyclohexanol		87
7		EtOH		81
8		BnOH		quant.
9		BnOH		83
10		BnOH		quant.
11		homoallyl alcohol		71

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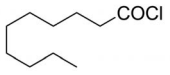
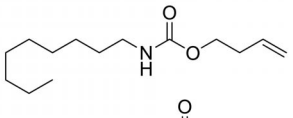
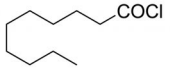
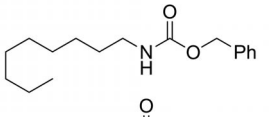
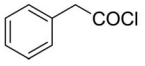
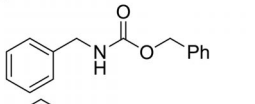
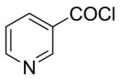
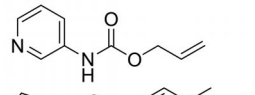
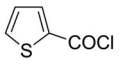
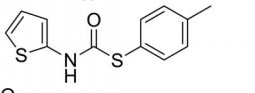
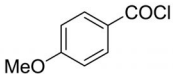
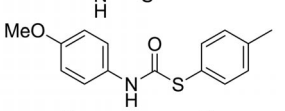
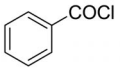
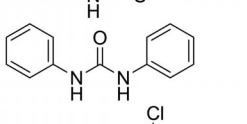
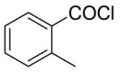
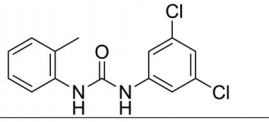
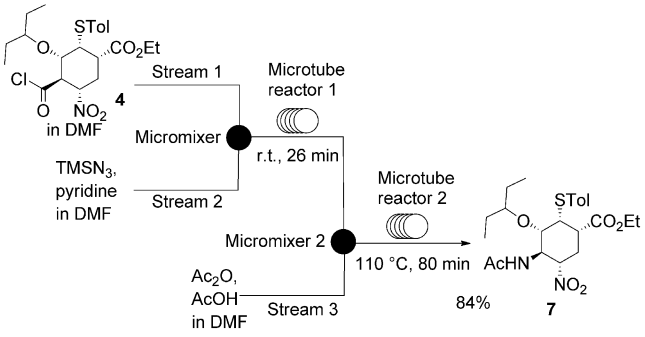
12		homoallyl alcohol		76
13		BnOH		82
14		BnOH		73
15		allyl alcohol		91
16		*p*-toluenethiol		96
17		*p*-toluenethiol		92
18		aniline		95
19		3,5-dichloroaniline		quant.

[a] Reaction conditions: acyl chloride (0.5 M in DMF), $TMSN_3$ (0.5 M in DMF), pyridine (1 M in DMF), nucleophile (2.5 M in DMF), AcOH (5 M in DMF); Reactor 1: room temperature, 20 min; Reactor 2: 110 °C, 70 min. [b] Isolated yield.

Application of the Microflow System to the Synthesis of (–)-Oseltamivir

As the generality of the Curtius rearrangement by using $TMSN_3$ as an azide source was established, this method was applied to the synthesis of (–)-Oseltamivir. The transformation from **4** to **7** consists of three reactions (Scheme 1): (1) the first reaction is between **4** and $TMSN_3$ in the presence of pyridine to generate **5**; (2) the second reaction is the Curtius rearrangement of **5** to give **6**, and (3) the final reaction is the transformation of **6** to *N*-acetylamide **7**. In previous batch reactions, **5** was treated with AcOH and Ac_2O in toluene, and the domino Curtius rearrangement/acetamide formation afforded **7** in a good yield at room temperature in toluene after 48 h. These conditions are not suitable for a flow system because of the long reaction time. When the reaction was carried out at 100 °C in DMF, the reaction was found to proceed smoothly to afford the desired product in 81% yield with a batch system. After further optimization of the reaction conditions for a microflow system, the reaction was performed as follows (Scheme 3): **4** (0.5 M solution in DMF) and a mixture of $TMSN_3$ (0.55 M solution in DMF) and pyridine (1.0 M solution in DMF) were loaded into Channels 1 and 2, respectively, and a mixture of AcOH (5.0 M in DMF) and Ac_2O (2.5 M in DMF) was loaded into Channel 3. The streams from Channels 1 and 2 were united by using a Comet-X-01 micromixing device,[11,12] and the streams from this mixture and Channel 3 were united by using a Comet-X-01 T-section mixing piece. The total flow rate was 1.2 mL/h, and the length of the tube between the two mixing pieces was 40 cm, therefore, the mixing time of the acyl chloride and $TMSN_3$ was 26 min. This is a long enough period, because this reaction was complete within 5 min in the batch system. The tube length after the second mixing piece was 1.8 m, which was immersed in an oil bath at 110 °C. Thus, the total residence time at 110 °C was 80 min, which is the same as that of the batch system. By using this method, **7** was isolated in an 84% yield after purification. This reaction was performed on a 10 g scale by



Scheme 3. Synthesis of **7** by using a flow system.

using a continuous-flow system, and the same yield was obtained. By parallel experiments, the reaction was easily scaled up.

Recrystallization of 3 and 7

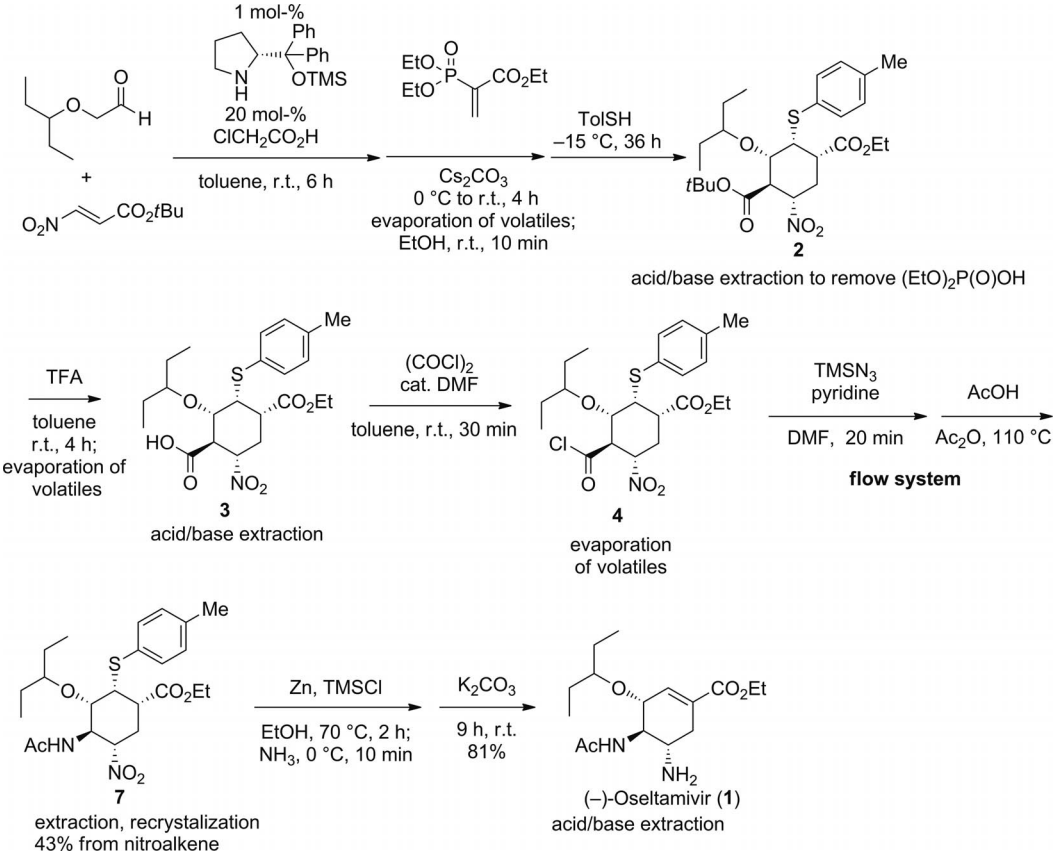
After removing any impurities by passing the compound through a short SiO_2 pad, recrystallization of **3** (2.28 g) was performed by using AcOEt and hexane to obtain racemic crystals (54 mg). A second recrystallization from the filtrate was carried out, which yielded a further 1.88 g of crystals with a 99% *ee*.

These results indicate that racemic crystals of **3** preferentially form under the crystallization conditions used to generate chiral crystals. Even though nearly optically pure **3** was obtained after recrystallization, the recrystallization had to be performed carefully, and the enantioselectivity had to be checked, as racemic crystals formed preferentially under our experimental conditions.

We have already reported that **7** can be purified by recrystallization.[3] As crystals of **7** form more easily than those of **3** and optically pure crystals of **7** are obtained, it is acceptable to crystallize and purify **7** at this stage of the process. There is also a synthetic merit that the recrystallization be carried out at this stage; namely, as (–)-Oseltamivir is synthesized by using only two additional reactions from **7**, a high degree of purity of the final product would be guaranteed, regardless of the batch used, because the same quality of **7** would be employed.

Synthesis of (–)-Oseltamivir

Based on the above investigation, we summarize the practical synthetic route of our third-generation synthesis of (–)-Oseltamivir according to Scheme 4. By starting from 3-(pentyloxy)acetaldehyde and *tert*-butyl 3-nitropropenoate, the highly substituted cyclohexanecarboxylate **2** was obtained in excellent diastereo- and enantioselectivity after an acid/base extraction to remove acidic $(EtO)_2P(O)OH$.[4] Without further purification, crude **2** was treated with CF_3CO_2H to afford **3** after an acid/base extraction and a short-pad SiO_2 filtration. Without further purification, crude **3** was transformed into acyl chloride **4** by treatment with $(COCl)_2$ and a catalytic amount of DMF in toluene. Crude **4** was used directly in the next stage. A flow system employing a microreactor worked effectively on up to a 10 g scale to afford **7** after extraction. Acetamide **7** was purified by recrystallization, and diastereo- and enantiomerically pure **7** was obtained in a 43% overall yield from the nitroalkene. The treatment of **7** with Zn and TMSCl in EtOH reduced the nitro group to an amine group, and (–)-Oseltamivir was obtained after bubbling with NH_3, followed by



Scheme 4. Third-generation synthesis of (–)-Oseltamivir.

the addition of K_2CO_3. As the final compound is an amine, it was isolated in excellent purity after acid/base extraction without purification by column chromatography.

Conclusions

The third-generation synthesis of (–)-Oseltamivir has been established by using several modifications of our previous synthesis, with the development of the Curtius rearrangement by a microflow system using $TMSN_3$ as an azide source. This new synthesis is more efficient, more practical, and safer than our previous syntheses. The new synthesis has several noteworthy features: (1) By adapting the Curtius rearrangement from a batch reaction to a flow reaction, the potentially hazardous acyl azide was transformed into the acetamide in small quantities, so reducing the risk of explosion. (2) Recrystallization of acetamide **7** gave an optically pure compound as a late-stage intermediate; from this recrystallization, the purity of (–)-Oseltamivir is guaranteed. (3) This is a column-free synthesis with three acid/base extractions and a single recrystallization. Thus, we believe that our procedure can be easily scaled up to a large-scale synthesis.

Experimental Section

General Remarks: All reactions were carried out under argon and monitored by TLC using Merck 60 F_{254} precoated silica gel plates (0.25 mm thickness). Preparative TLC was performed by using Wakogel B-5F purchased from Wako Pure Chemical Industries, Tokyo, Japan. Flash chromatography was performed by using silica gel 60N from Kanto Chemical Co. Int., Tokyo Japan. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM400 (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) instrument. Data for ^1H NMR spectra are reported as chemical shift (δ [ppm]), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J [Hz]), and number of protons. Data for ^{13}C NMR spectra are reported as chemical shift (δ [ppm]). HRMS measurements were carried out by using a Bruker ESI-TOF instrument. FTIR spectra were recorded with a JASCO FT/IR-410 spectrometer. All solvents were purchased and used as received or dried and purified according to usual procedures. A Comet X-01 micromixing device was obtained from Techno Applications Co., Ltd., 34-16-204 Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan.

General Procedure for Curtius Rearrangement in a Microflow System: To a dried 5 mL graduated flask was added the acyl chloride (2.5 mmol) followed by DMF up to the 5 mL mark. The solution was loaded into the first syringe and attached to a syringe pump (Stream 1). To a second 5 mL flask were added $TMSN_3$ (2.5 mmol, 1.0 equiv.) and pyridine (5 mmol, 2 equiv.) followed by DMF up to the 5 mL mark. This solution was loaded into the second syringe and attached to a syringe pump (Stream 2). To a third 5 mL flask were added the nucleophile (10 mmol, 4 equiv.), AcOH (25 mmol, 10 equiv.), and DMF up to the 5 mL mark. This solution was loaded into a third syringe and attached to a syringe pump (Stream 3). Then syringe pumps were switched on at the flow rate of 0.4 mL/h. *Syringe 3 containing the nucleophile was switched on with a delay so that reagents from Micromixer T1 and Stream 3 reached Micromixer T2 at the same time.* Streams 1 and 2 were united at Micromixer T1 (Comet-X-01), and the reaction mixture was allowed to flow for 20 min through Microtube reactor 1 at room temperature (tube diameter 0.5 mm, tube length 340 mm) at a pumping rate of 0.4 mL/h for each stream, totaling 0.8 mL/h after Micromixer T1. Streams 1 and 2 were united with Stream 3 in Micromixer T2 (Comet-X-01), and the reaction mixture was allowed to flow for 70 min through Microtube reactor 2 (tube diameter 0.52 mm, tube length 1600 mm) immersed in an oil bath heated to 110 °C. The reaction was run until all the reagents were eluted. The solution eluted from the microfluidic reactor system was washed with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, and washed with water several times to remove DMF. The ethyl acetate layer was dried with $MgSO_4$, concentrated in vacuo, and purified through a short silica pad or silica column to remove hydrophilic byproducts, to afford the pure desired material. The results are shown in Table 1.

But-3-enyl (4-Methoxyphenyl)carbamate: Table 1, Entry 1. The general procedure was applied with *p*-methoxybenzoyl chloride (2.5 mmol, 426 mg, 338 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), homoallyl alcohol (10 mmol, 720 mg, 856 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give 553 mg, 99% of the title compound as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.43 (q, J = 6.7 Hz, 2 H), 3.78 (s, 3 H), 4.22 (t, J = 6.7 Hz, 2 H), 5.09–5.17 (m, 2 H), 5.83 (ddt, J = 17.1, 10.3, 6.7 Hz, 1 H), 6.84 (d, J = 9 Hz, 2 H), 6.88 (br. s, 1 H), 7.28–7.31 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.4, 55.4, 64.1, 114.2, 117.2, 120.6, 130.9, 134.1, 153.9, 155.9 ppm. IR (neat): $\tilde{\nu}$ = 3309, 2958, 1698, 1600, 1514, 1416, 1227, 1030, 918, 827 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{15}NO_3Na$ [M + Na^+] 244.0954; found 244.0944.

Benzyl Phenylcarbamate: Table 1, Entry 2. The general procedure was applied with benzoyl chloride (2.5 mmol, 337 mg, 279 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give 517 mg, 91% of the title compound as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.21 (s, 2 H), 6.8 (br. s, 1 H), 7.1 (t, J = 7.3 Hz, 1 H), 7.30–7.43 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 66.8, 118.7, 123.4, 128.17, 128.22, 128.5, 128.9, 135.9, 137.7, 153.4 ppm. Analytical data is in accordance with literature data.[14]

***tert*-Butyl Phenylcarbamate:** Table 1, Entry 3. The general procedure was applied with benzoyl chloride (2.5 mmol, 337 mg, 279 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), *tert*-butyl alcohol (10 mmol, 940 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to give 425 mg, 88% of the title compound as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.54 (s, 9 H), 6.48 (br. s, 1 H), 7.03–7.07 (m, 1 H), 7.28–7.39 (m, 4 H) ppm. Analytical data is in accordance with literature data.[15]

***tert*-Butyl (4-Nitrophenyl)carbamate:** Table 1, Entry 4. The general procedure was applied with *p*-nitrobenzoyl chloride (2.5 mmol, 464 mg), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), *tert*-butyl alcohol (10 mmol, 940 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to give 500 mg, 84% of the title compound as a yellowish solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.5 (s, 9 H), 7.16 (br. s, 1 H), 7.53 (d, J = 9.2 Hz, 2 H), 8.14 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz):

δ = 28.1, 81.8, 117.5, 125.1, 142.4, 144.6, 152.0 ppm. Analytical data is in accordance with literature data.[15]

Butyl (3,5-Dichlorophenyl)carbamate: Table 1, Entry 5. The general procedure was applied with 3,5-dichlorobenzoyl chloride (2.5 mmol, 524 mg, 354 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), butanol (10 mmol, 914 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 7:1) to give 655 mg, 99% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (t, J = 7.4 Hz, 3 H), 1.32 (sext, J = 7.5 Hz, 2 H), 1.56 (quint, J = 7.3 Hz, 2 H), 4.09 (t, J = 6.7 Hz, 2 H), 6.88 (br. s, 1 H), 6.94 (s, 1 H), 7.26 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.6, 18.9, 30.8, 65.6, 116.8, 123.1, 135.2, 139.9, 153.4 ppm. IR (neat): $\tilde{\nu}$ = 3320, 3050, 2961, 2830, 1714, 1583, 1538, 1415, 1216, 1078, 926, 842, 806 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{13}NO_2Cl_2Na$ [M + Na$^+$] 284.0216; found 284.0211.

Cyclohexyl (4-Bromophenyl)carbamate: Table 1, Entry 6. The general procedure was applied with *p*-bromobenzoyl chloride (2.5 mmol, 549 mg), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), cyclohexanol (10 mmol, 1.05 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6:1) to give 648 mg, 87% of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.27–1.60 (m, 6 H), 1.76 (dt, J = 6.1, 3.1 Hz, 2 H), 1.93–1.96 (m, 2 H), 4.76 (td, J = 8.6, 4.1 Hz, 1 H), 6.65 (br. s, 1 H), 7.3 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.6, 25.2, 31.8, 73.8, 115.5, 120.1, 131.8, 137.3, 153.0 ppm. IR (NaCl): $\tilde{\nu}$ = 3358, 3087, 2932, 2860, 1903, 1696, 1594, 1519, 1399, 1371, 1307, 1228, 1115, 893 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}NO_2BrNa$ [M + Na$^+$] 320.0257; found 320.0246.

Ethyl (2,6-Dimethoxyphenyl)carbamate: Table 1, Entry 7. The general procedure was applied with 2,6-dimethoxybenzoyl chloride (2.5 mmol, 500 mg), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), ethanol (10 mmol, 590 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 6:1) to give 456 mg, 81% of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, J = 7.1 Hz, 3 H), 3.8 (s, 6 H), 4.17 (q, J = 7.1 Hz, 2 H), 6.0 (br. s, 1 H), 6.55 (d, J = 8.4 Hz, 2 H), 7.13 (t, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.4, 55.8, 61.0, 104.2, 114.5, 127.1, 158.8, 155.4 ppm. IR (NaCl): $\tilde{\nu}$ = 3243, 3050, 2964, 1703, 1595, 1480, 1258, 1114, 1020, 781 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}NO_4Na$ [M + Na$^+$] 248.0851; found 248.0840.

Benzyl *o*-Tolylcarbamate: Table 1, Entry 8. The general procedure was applied with 2-methylbenzoyl chloride (2.5 mmol, 325 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 9:1) to give 603 mg, 99% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.28 (s, 3 H), 5.28 (s, 2 H), 6.64 (br. s, 1 H), 7.1 (td, J = 7.4, 1.2 Hz, 1 H), 7.22 (d, J = 7.5 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.39–7.50 (m, 5 H), 7.88 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.5, 67.0, 121.3, 124.2, 126.7, 128.20, 128.22, 128.5, 130.3, 135.7, 136.1, 153.7 ppm. Analytical data is in accordance with literature data.[16]

Benzyl Furan-2-ylcarbamate: Table 1, Entry 9. The general procedure was applied with 2-furoyl chloride (2.5 mmol, 246 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to give 451 mg, 83% of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.23 (s, 2 H), 6.13 (br. s, 1 H), 6.37 (dd, J = 3.1, 2.0 Hz, 1 H), 6.92 (br. s, 1 H), 7.1 (d, J = 2.0 Hz, 1 H), 7.33–7.43 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.8, 111.5, 117.1, 123.8, 124.4, 129.7, 135.2, 139.2, 139.8, 162.2 ppm. This is a known compound.[17]

Benzyl Thiophen-2-ylcarbamate: Table 1, Entry 10. The general procedure was applied with thiophene-2-carbonyl chloride (2.5 mmol, 366 mg, 277 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to give 583 mg, 99% of the title compound as a brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.24 (s, 2 H), 6.65 (d, J = 2.2 Hz, 1 H), 6.85 (dd, J = 5.5, 3.6 Hz, 1 H), 6.89 (d, J = 5.1 Hz, 1 H), 7.35–7.43 (m, 5 H), 7.69 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 67.5, 112.6, 117.4, 124.5, 128.1, 128.2, 128.4, 135.6, 139.6, 153.5 ppm. IR (neat): $\tilde{\nu}$ = 3296, 3065, 2950, 1715, 1574, 1520, 1215, 1054, 847 cm^{-1}.

But-3-enyl Cyclohexylcarbamate: Table 1, Entry 11. The general procedure was applied with cyclohexanecarbonyl chloride (2.5 mmol, 336 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), homoallyl alcohol (10 mmol, 720 mg, 856 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 12:1) to give 350 mg, 71% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07–1.21 (m, 3 H), 1.29–1.39 (m, 2 H), 1.56–1.62 (m, 1 H), 1.69 (td, J = 8.6, 4.6 Hz, 2 H), 1.92 (dd, J = 8.4, 3.1 Hz, 2 H), 2.36 (q, J = 6.1 Hz, 2 H), 3.46 (br. s, 1 H), 4.10 (t, J = 6.1 Hz, 2 H), 4.53 (br. s, 1 H), 5.05–5.13 (m, 2 H), 5.80 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.7, 25.4, 33.3, 33.5, 49.7, 63.6, 116.9, 134.3, 155.7 ppm. IR (neat): $\tilde{\nu}$ = 3329, 3029, 2937, 2855, 1683, 1538, 1476, 1448, 1316, 12777, 1253, 1233, 1146, 1046, 968, 891 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{19}NO_2Na$ [M + Na$^+$] 220.1308; found 220.1315.

But-3-enyl Nonylcarbamate: Table 1, Entry 12. The general procedure was applied with decanoyl chloride (2.5 mmol, 477 mg, 515 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403μL), homoallyl alcohol (10 mmol, 720 mg, 856 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to give 485 mg, 76% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.17–1.32 (m, 11 H), 1.48 (t, J = 6.7 Hz, 2 H), 1.60 (br. s, 1 H), 2.36 (t, J = 6.2 Hz, 2 H), 3.13–3.20 (m, 2 H), 4.09–4.15 (m, 2 H), 4.61 (br. s, 1 H), 5.05–5.14 (m, 2 H), 5.79 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.6, 26.7, 29.2, 29.3, 29.5, 30.0, 31.8, 33.51, 41.0, 63.8, 117.0, 134.3, 156.6 ppm. IR (neat): $\tilde{\nu}$ = 3325, 2926, 2867, 1697, 1539, 1232 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{27}NO_2Na$ [M + Na$^+$] 264.1934; found 264.1930.

Benzyl Nonylcarbamate: Table 1, Entry 13. The general procedure was applied with decanoyl chloride (2.5 mmol, 477 mg, 515 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to give 597 mg, 82% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, J = 6.9 Hz, 3 H), 1.20–1.35 (m, 12 H), 1.45–1.52 (m, 2 H), 3.20 (q, J = 6.3 Hz, 2 H), 4.83 (br. s, 1 H),

5.12 (s, 2 H), 7.31–7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 22.6, 26.7, 29.21, 29.25, 29.5, 29.9, 31.8, 41.1, 66.5, 128.0, 128.05, 128.5, 136.7, 156.4 ppm. This is a known compound.[18]

Benzyl Benzylcarbamate: Table 1, Entry 14. The general procedure was applied with phenylacetyl chloride (2.5 mmol, 386 mg, 330 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), benzyl alcohol (10 mmol, 1.03 mL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 9:1) to give 440 mg, 73% of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.40 (s, 2 H), 4.42 (s, 2 H), 5.72 (br. s, 1 H), 7.28–7.41 (m, 10 H) ppm. Analytical data is in accordance with literature data.[14]

Allyl Pyridin-3-ylcarbamate: Table 1, Entry 15. The general procedure was applied with nicotinoyl chloride hydrochloride (2.5 mmol, 445 mg), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), allyl alcohol (10 mmol, 682 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to give 391 mg, 91% of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.65 (dt, J = 5.7, 1.2 Hz, 2 H), 5.20 (dq, J = 10.4, 1.2 Hz, 1 H), 5.30 (dq, J = 17.2, 1.5 Hz, 1 H), 5.90 (ddt, J = 17.2, 10.5, 5.7 Hz, 1 H), 7.2 (dd, J = 8.4, 4.8 Hz, 1 H), 8.1 (d, J = 6.2 Hz, 1 H), 8.31 (dd, J = 4.8, 1.4 Hz, 1 H), 8.59 (d, J = 2.6 Hz, 1 H), 8.92 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 65.9, 118.2, 123.8, 126.0, 132.2, 135.7, 139.9, 143.7, 153.7 ppm. IR (NaCl): $\tilde{\nu}$ = 3380, 2937, 1725, 1605, 1553, 1478, 1424, 1253, 1060, 926, 810 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{10}N_2O_2Na$ [M + Na$^+$] 201.0494; found 201.0490.

***S*-(*p*-Tolyl) Thiophen-2-ylthiocarbamate:** Table 1, Entry 16. The general procedure was applied with thiophene-2-carbonyl chloride (2.5 mmol, 366 mg, 277 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), *p*-toluenethiol (10 mmol, 1.24 g), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to give 598 mg, 96% of the title compound as a brownish solid. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 2.37 (s, 3 H), 6.73 (d, J = 2.65 Hz, 1 H), 6.87 (dd, J = 5.4, 3.8 Hz, 1 H), 6.99 (d, J = 5.1 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 11.62 (br. s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 20.8, 111.5, 117.1, 123.8, 124.4, 129.7, 135.2, 139.2, 139.8, 162.1 ppm. IR (NaCl): $\tilde{\nu}$ = 3244, 3090, 3005, 1645, 1562, 1491, 1439, 1342, 1263, 1160, 890, 808, 692 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{11}NOS_2Na$ [M + Na$^+$] 272.0174; found 272.0169.

***S*-(*p*-Tolyl) (4-Methoxyphenyl)thiocarbamate:** Table 1, Entry 17. The general procedure was applied with *p*-methoxybenzoyl chloride (2.5 mmol, 426 mg, 338 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), *p*-toluenethiol (10 mmol, 1.24 g), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to give 628 mg, 92% of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H), 3.80 (s, 3 H), 6.84 (d, J = 8.9 Hz, 2 H), 7.21 (s, 1 H), 7.26 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 9.0 Hz, 2 H), 7.51 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.3, 55.4, 114.1, 121.6, 124.7, 130.3, 130.6, 135.5, 140.2, 156.7, 165.1 ppm. IR (NaCl): $\tilde{\nu}$ = 3288, 3020, 2960, 1656, 1524, 1408, 1241, 1153, 1032, 896, 821 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{15}NO_2SNa$ [M + Na$^+$] 296.0664; found 296.0657.

1,3-Diphenylurea: Table 1, Entry 18. The general procedure was applied with benzoyl chloride (2.5 mmol, 337 mg, 279 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), aniline (10 mmol, 931 mg, 912 μL), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to give 504 mg, 95% of the title compound as a white solid. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 6.97 (t, J = 7.4 Hz, 2 H), 7.29 (t, J = 8.0 Hz, 4 H), 7.47 (d, J = 7.6 Hz, 4 H), 8.66 (s, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 118.2, 121.8, 128.8, 139.7, 152.5 ppm. Analytical data is in accordance with literature data.[19]

3,5-Dichlorophenyl *o*-Tolylcarbamate: Table 1, Entry 19. The general procedure was applied with 2-methylbenzoyl chloride (2.5 mmol, 325 μL), $TMSN_3$ (2.5 mmol, 288 mg, 330 μL), pyridine (5 mmol, 395 mg, 403 μL), 3,5-dichloroaniline (10 mmol, 405 mg), and AcOH (25 mmol, 1.3 mL). The crude residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to give 738 mg, 99% of the title compound as a white solid. ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 2.24 (s, 3 H), 7.0 (d, J = 7.2 Hz, 1 H), 7.15–7.21 (m, 3 H), 7.53 (d, J = 1.9 Hz, 2 H), 7.72 (d, J = 8.0 Hz, 1 H), 8.01 (s, 1 H), 8.33 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]-DMSO, 75 MHz): δ = 17.8, 116.06, 120.7, 122.0, 123.5, 126.2, 128.6, 130.2, 134.1, 136.7, 142.4, 152.3 ppm. IR (neat): $\tilde{\nu}$ = 3283, 1644, 1583, 1553, 1412, 1252, 669 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{12}Cl_2NO_2Na$ [M + Na$^+$] 318.0059; found 318.0055.

Preparation of the Azide for the DSC Experiment. Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(Azidocarbonyl)-5-nitro-3-(pent-3-yloxy)-2-(*p*-tolylthio)cyclohexanecarboxylate (5): A saturated aqueous NaN_3 solution (0.5 mL) was added to a solution of crude **4** (82.8 mg, 0.176 mmol) in acetone (0.5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min before being quenched by addition of H_2O. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with H_2O, dried with $MgSO_4$, and concentrated under reduced pressure to give **5** (85.6 mg, quantitative yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J = 8.0 Hz, 2 H), 7.07 (d, J = 8.0 Hz, 2 H), 4.66 (dt, J = 4.8, 12.0 Hz, 1 H), 4.07–4.18 (m, 1 H), 4.00 (t, J = 3.2 Hz, 1 H), 3.85–3.97 (m, 1 H), 3.78 (dd, J = 10.8, 3.6 Hz, 1 H), 3.47 (t, J = 11.2 Hz, 1 H), 3.13 (quint, J = 4.8 Hz, 1 H), 2.76 (dt, J = 13.2, 3.6 Hz, 1 H), 2.68 (dt, J = 13.2, 3.6 Hz, 1 H), 2.31 (s, 3 H), 2.28 (q, J = 13.2 Hz, 1 H), 1.28–1.48 (m, 2 H), 1.21 (t, J = 7.2 Hz, 3 H), 1.03–1.18 (m, 2 H), 0.76 (t, J = 7.2 Hz, 3 H), 0.63 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4, 169.7, 137.7, 132.9 (2 C), 130.8, 129.6 (2 C), 82.8, 80.4, 61.6, 52.5, 49.8, 43.4, 27.0, 24.8, 23.2, 21.0, 14.0, 8.9, 8.0 (signal of 1 C overlapped with signal of $CDCl_3$) ppm. IR (film): $\tilde{\nu}$ = 2967, 2937, 2878, 2142, 1733, 1556, 1493, 1461, 1369, 1174, 1124, 1028, 810 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{30}N_4O_6SNa$ [M + Na]$^+$ 501.1778; found 501.1776. $[a]_D^{23}$ = –55 (c = 1.01, $CHCl_3$).

Decomposition of 5 into 6 at 60 °C. Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-Isocyanato-5-nitro-3-(pent-3-yloxy)-2-(*p*-tolylthio)cyclohexanecarboxylate (6): Acyl azide **5** (21 mg, 0.044 mmol) was placed into a dry 5 mL round-bottomed flask and heated at 60 °C. After the designated time, an NMR measurement was performed. After 30 min, 80% of **5** was converted into **6** with 10% **5** remaining. After 45 min, 90% conversion to **6** was observed (pale yellow oil). ^{1}H NMR (400 MHz, C_6D_6): δ = 7.47 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.1 Hz, 2 H), 4.57 (t, J = 10.4 Hz, 1 H), 3.89–4.00 (m, 2 H), 3.80 (dt, J = 4.4, 11.8 Hz, 1 H), 3.67–3.75 (m, 1 H), 3.01 (dd, J = 10.0, 3.6 Hz, 1 H), 2.97–3.05 (m, 2 H), 2.37 (q, J = 13.2 Hz, 1 H), 2.08–2.17 (m, 1 H), 1.98 (s, 3 H), 1.92 (dt, J = 13.2, 3.6 Hz, 1 H), 1.40–1.50 (m, 1 H), 1.28–1.38 (m, 1 H), 1.00–1.20 (m, 1 H), 0.90 (t, J = 7.2 Hz, 3 H), 0.74 (t, J = 7.2 Hz, 3 H), 0.61 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.4, 137.7, 133.1 (2 C), 131.8, 129.8 (2 C), 86.6, 80.0, 77.5, 61.3, 57.1, 52.4, 43.2, 27.6, 25.2, 23.7, 20.8,

14.0, 8.8, 8.7 (O=*C*=N– undetected) ppm. IR (film): $\tilde{\nu}$ = 2968, 2938, 2878, 2245, 1736, 1559, 1493, 1456, 1369, 1251, 1201, 1100, 1029, 952, 862, 810 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{30}N_2O_6SNa$ $[M + Na]^+$ 473.1717; found 473.1719. $[\alpha]_D^{23}$ = –6.9 (*c* = 1.41, $CHCl_3$).

Conversion of Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(Chlorocarbonyl)-5-nitro-3-(pent-3-yloxy)-2-(*p*-tolylthio)cyclohexanecarboxylate (4) into Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-Acetamido-5-nitro-3-(pent-3-yloxy)-2-(*p*-tolylthio)cyclohexanecarboxylate (7) in a Microreactor: To a dried 50 mL graduated flask were added **4** (10 g, 21 mmol) and DMF up to the 42 mL mark. The solution was loaded into the first syringe and attached to a syringe pump (Stream 1). To a second 50 mL flask were added $TMSN_3$ (3 mL, 0.23 mmol), pyridine (5.5 mL, 42 mmol), and DMF up to the 42 mL mark. This solution was loaded into the second syringe and attached to a syringe pump (Stream 2). To a third 50 mL flask were added AcOH (12.2 mL, 0.21 mol), Ac_2O (8.8 mL, 105 mmol), and DMF up to the 42 mL mark, and this solution was loaded into a third syringe and attached to a syringe pump (Stream 3). Then the syringe pumps were switched on at the flow rate of 0.4 mL/h. *Syringe 3 containing the nucleophile was switched on with a delay set up so that reagents from Micromixer 1 and Stream 3 reached Micromixer 2 at the same time.* Streams 1 and 2 were united by using Micromixing device 1 (Comet-X-01), and the reaction mixture was allowed to flow for 26 min through Microtube reactor 1 at room temperature (tube diameter 0.5 mm, tube length 400 mm), and a pumping rate of 0.4 mL/h for each stream was used totaling 0.8 mL/h after Micromixer 1. Streams 1 and 2 were united with Stream 3 by using Micromixer 2 (Comet-X-01), and the reaction mixture was allowed to flow for 80 min through Microtube reactor 2 (tube diameter 0.52 mm, tube length 1800 mm) immersed in an oil bath at 110 °C. The reaction was run until all the reagents were eluted. The eluted solution was washed with aqueous saturated $NaHCO_3$, extracted with ethyl acetate, and washed with water several times to remove DMF. The ethyl acetate layer was dried with $MgSO_4$, concentrated in vacuo, and filtered through a short silica pad to remove hydrophilic byproducts affording the desired material (8.4 g, 84%) as a brownish solid. Recrystalization from toluene afforded **7** in 61% yield (43% from nitroalkene) as white crystals possessing >99% enantiomeric purity. Chiral-phase HPLC analysis indicated that the enantiomeric excess of the product was >99% (Diacel CHIRALPAK IC column; hexane/*i*PrOH = 10:1; flow rate = 1 mL/min; detection wavelength = 220 nm; minor enantiomer t_R = 20.25 min; major enantiomer t_R = 35.05 min). M.p. 192–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 5.88 (d, *J* = 6.4 Hz, 1 H), 5.50 (dt, *J* = 4.8, 12.0 Hz, 1 H), 4.42 (dd, *J* = 4.0, 10.4 Hz, 1 H), 4.08–4.14 (m, 1 H), 4.05–4.06 (m, 1 H), 3.84–3.94 (m, 2 H), 3.15–3.21 (m, 1 H), 2.87 (td, *J* = 2.8, 13.2 Hz, 1 H), 2.52–2.55 (m, 1 H), 2.35 (q, *J* = 12.8 Hz, 1 H), 2.30 (s, 3 H), 1.93 (s, 3 H), 1.31–1.50 (m, 2 H), 1.17 (t, *J* = 7.0 Hz, 3 H), 1.05–1.14 (m, 2 H), 0.81 (t, *J* = 7.4 Hz, 3 H), 0.61 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 170.0, 137.4, 132.7 (2 C), 131.4, 129.5 (2 C), 82.8, 80.8, 73.4, 61.3, 55.6, 54.1, 43.0, 27.9, 25.2, 24.1, 23.7, 20.9, 13.9, 9.0, 8.8 ppm. IR (film): $\tilde{\nu}$ = 3274, 2965, 2878, 1738, 1660, 1556, 1494, 1455, 1370, 1199, 1098, 1031, 947, 863, 810, 737, 606 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{34}N_2O_6SNa$ $[M + Na]^+$ 489.2030; found 489.2020. $[\alpha]_D^{23}$ = –41 (*c* = 0.32, $CHCl_3$).

Column-Free Procedure from *tert*-Butyl (*E*)-3-Nitroacrylate to (1*R*,2*S*,3*R*,4*S*,6*S*)-4-(Ethoxycarbonyl)-6-nitro-2-(pent-3-yloxy)-3-(*p*-tolylthio)cyclohexanecarboxylic Acid (3): Chloroacetic acid (112.1 mg, 1.16 mmol) was added to a solution of aldehyde (1.13 g, 8.67 mmol), nitroalkene (1 g, 5.78 mmol), and (*R*)-diphenylprolinol trimethylsilyl ether (18.8 mg, 0.058 mmol) in toluene (10 mL) at 23 °C under argon. The reaction mixture was stirred at 23 °C for 6 h followed by addition of **6** (2.05 g, 8.67 mmol) and Cs_2CO_3 (5.65 g, 17.3 mmol) at 0 °C. After the resulting suspension had been stirred at 23 °C for 2 h, the solvent was removed under reduced pressure. EtOH (20 mL) was added, and the resulting mixture was stirred at 23 °C for 10 min before the addition of toluenethiol (3.59 g, 28.9 mmol) at –15 °C. The resulting mixture was stirred at the same temperature for 36 h before being quenched with cold saturated aqueous NH_4Cl solution. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed twice with 28% NH_4OH in H_2O, dried with $MgSO_4$, and concentrated under reduced pressure. Trifluoroacetic acid (1.5 mL, 19.5 mmol) was added to a solution of crude **2** in toluene (5 mL) at 23 °C under argon. The reaction mixture was stirred at 23 °C for 4 h before removing the solvent and trifluoroacetic acid under reduced pressure; 28% NH_4OH in H_2O (10 mL) was added at 23 °C, and the mixture was stirred for 30 min. The aqueous layer was washed with EtOAc followed by an adjustment to pH = 2 with 2 N HCl. The aqueous layer was extracted three times with EtOAc. The combined organic layers werer washed with saturated aqueous NaCl, dried with $MgSO_4$, and concentrated under reduced pressure to afford crude **3**. The crude **3** was filtered through 20 g of SiO_2, eluted with 60% EtOAc/*n*-hexane, and concentrated under reduced pressure to afford **3** (1.87 g, 71%) as white crystals. M.p. 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.0 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 4.66 (dt, *J* = 4.8, 12.0 Hz, 1 H), 4.09–4.20 (m, 1 H), 4.03 (t, *J* = 3.2 Hz, 1 H), 3.89–3.99 (m, 1 H), 3.82 (dd, *J* = 10.8, 3.6 Hz, 1 H), 3.54 (t, *J* = 10.8 Hz, 1 H), 3.17 (quint, *J* = 4.8 Hz, 1 H), 2.77 (dt, *J* = 13.2, 3.2 Hz, 1 H), 2.67 (dt, *J* = 13.2, 4.0 Hz, 1 H), 2.31 (s, 3 H), 2.29 (q, *J* = 13.2 Hz, 1 H), 1.30–1.50 (m, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H), 1.05–1.20 (m, 2 H), 0.75 (t, *J* = 7.2 Hz, 3 H), 0.62 (t, *J* = 7.2 Hz, 3 H) (CO_2H signal undetected) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 169.8, 137.7, 132.8 (2 C), 130.9, 129.6 (2 C), 82.6, 80.3, 76.3, 61.6, 52.3, 48.3, 43.4, 27.1, 24.9, 23.2, 21.0, 14.0, 8.9, 8.2 ppm. IR (film): $\tilde{\nu}$ = 2967, 2937, 2878, 1722, 1556, 1492, 1457, 1370, 1282, 1253, 1200, 1098, 1029, 950, 811 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{31}NO_7SNa$ $[M + Na]^+$ 476.1713; found 476.1722. $[\alpha]_D^{23}$ = –27 (*c* = 1.64, $CHCl_3$).

Ethyl (1*S*,2*R*,3*S*,4*R*,5*S*)-4-(Chlorocarbonyl)-5-nitro-3-(pent-3-yloxy)-2-(*p*-tolylthio)cyclohexanecarboxylate (4): To a solution of **3** (109 mg, 0.24 mmol) in toluene (2 mL) were added catalytic DMF (2 mL) and oxalyl chloride (201 mL, 2.4 mmol) at 0 °C. The resulting mixture was stirred at 23 °C for 30 min. Removal of the solvent and excess oxalyl chloride under reduced pressure provided **4** (113 mg, quantitative yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 4.70–4.80 (m, 1 H), 4.10–4.20 (m, 1 H), 4.03 (br. s, 1 H), 3.89–4.00 (m, 3 H), 3.18 (quint, *J* = 4.4 Hz, 1 H), 2.75 (dt, *J* = 13.2, 3.2 Hz, 1 H), 2.75 (dt, *J* = 13.2, 4.0 Hz, 1 H), 2.31 (s, 3 H), 2.28 (q, *J* = 13.2 Hz, 1 H), 1.32–1.52 (m, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.00–1.20 (m, 2 H), 0.76 (t, *J* = 7.2 Hz, 3 H), 0.62 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 169.5, 137.9, 132.8 (2 C), 130.5, 129.5 (2 C), 82.6, 80.0, 76.5, 61.6, 58.7, 52.1, 43.2, 26.7, 24.6, 23.0, 21.0, 14.0, 8.6, 8.2 ppm. IR (film): $\tilde{\nu}$ = 2967, 1792, 1732, 1684, 1653, 1557, 1521, 1507, 1491, 1474, 1457, 1370, 1282, 1200, 1102, 1028, 950, 810 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{30}ClNO_6SNa$ $[M + Na]^+$ 494.1375; found 494.1381. $[\alpha]_D^{23}$ = –18 (*c* = 0.61, $CHCl_3$).

One-Pot Procedure from 7 to (–)-Oseltamivir (1): Activated Zn powder (28 g, 0.42 mol, washed with 1 N HCl, H_2O, EtOH, and Et_2O before use) was added to a solution of **7** (4 g, 8.5 mmol) in EtOH (200 mL) and trimetylsilyl chloride (32 mL, 256 mmol) at 23 °C un-

der argon. The resulting mixture was stirred at 70 °C for 2 h before bubbling NH_3 gas at 0 °C for 10 min. To the resulting suspension was added K_2CO_3 (11.78 g, 0.85 mol) at 23 °C with stirring for 9 h before filtration. After excess EtOH had been removed under reduced pressure, 2 N HCl was added to the residue at 0 °C. The aqueous layer was washed with EtOAc followed by an adjustment to pH = 11 with 28% NH_4OH in H_2O. The aqueous layer was extracted three times with 10% MeOH/$CHCl_3$. The combined organic layers were washed with saturated aqueous NaCl, dried with $MgSO_4$, and concentrated under reduced pressure to afford **1** (2.15 g, 81% from **7**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (t, J = 2.0 Hz, 1 H), 5.62 (d, J = 7.6 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.15–4.20 (m, 1 H), 3.52 (q, J = 8.0 Hz, 1 H), 3.34 (quint, J = 5.6 Hz, 1 H), 3.24 (dt, J = 5.2, 10.0 Hz, 1 H), 2.75 (dd, J = 17.6, 5.2 Hz, 1 H), 2.15 (ddt, J = 17.6, 10.0, 2.8 Hz, 1 H), 2.04 (s, 3 H), 1.40–1.60 (m, 4 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H) (NH_2 signal undetected) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 166.3, 137.5, 129.6, 81.7, 74.8, 60.8, 59.0, 49.2, 33.6, 26.3, 25.8, 23.7, 14.2, 9.5, 9.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 3276, 3077, 2965, 2936, 2877, 1715, 1655, 1558, 1464, 1374, 1303, 1244, 1195, 1127, 1064, 1031, 944, 861, 778, 736 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{28}N_2O_4Na$ [M + Na]$^+$ 335.1941; found 335.1934. $[\alpha]_D^{23}$ = –54.9 (c = 0.68, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, and IR spectra of all compounds.

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