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High-Yielding Synthesis of the Anti-Influenza Neuraminidase Inhibitor (−)-Oseltamivir by Two "One-Pot" Sequences

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Abstract: The efficient asymmetric total synthesis of (−)-oseltamivir, an antiviral reagent, has been accomplished by using two "one-pot" reaction sequences, with excellent overall yield (60%) and only one required purification by column chromatography. The first one-pot reaction sequence consists of a diphenylprolinol silyl ether mediated asymmetric Michael reaction, a domino Michael reaction/Horner–Wadsworth–Emmons reaction combined with retro-aldol/Horner–Wadsworth–Emmons reaction and retro Michael reactions, a thiol Michael reaction, and a base-catalyzed isomerization. Six reactions can be successfully conducted in the second one-pot reaction sequence; these are deprotection of a *tert*-butyl ester and its conversion into an acyl chloride then an acyl azide, Curtius rearrangement, amide formation, reduction of a nitro group into an amine, and a retro Michael reaction of a thiol moiety. A column-free synthesis of (−)-oseltamivir has also been established.

Keywords: asymmetric synthesis · domino reactions · organocatalysis · Tamiflu

Introduction

Influenza remains a major health problem, and the recent global pandemic of AH1N1 influenza resulted in many deaths. Moreover, a great deal of attention has been paid to the high potential risk of a worldwide spread of the avian H5N1 influenza virus, the death rate for which is over 50%.[1] Indeed, if this virus should acquire the ability to spread easily and directly from human to human, it could very possibly cause a disastrous pandemic. (−)-Oseltamivir phosphate (Tamiflu)[2] and zanamivir (Relenza)[3] are antiviral flu drugs in clinical use and are both neuraminidase inhibitors. Tamiflu has been extensively used worldwide for the treatment of influenza caused by the AH1N1 virus. As a result of the intense interest in, and need for, this life-saving medicine, many synthetic organic chemists have investigated its effective preparation, and a large number of syntheses have been reported.[4] Even though Tamiflu is effective at present, the recent emergence of Tamiflu-resistant virus strains has prompted efforts by the chemical community to develop medicines that are active against the mutated virus.[5] This has led to the need for simple syntheses capable of rapidly producing a wide and diverse range of derivatives.

We set the following objectives at the start of our projected synthesis of Tamiflu because they would allow a large quantity to be prepared in a short time: 1) The number of reactions required should be not more than 10, and the number of separate operations should be as few as possible. 2) The overall yield should be over 50%. 3) Only inexpensive reagents should be employed. 4) Purification by column chromatography should be avoided as much as possible. 5) The use of metal-containing reagents should be avoided as much as possible. The preparation of a molecule of this complexity, possessing three contiguous chiral centers, in no more than 10 reactions and in over 50% overall yield is a very challenging target. Even if each individual reaction of a sequence proceeds with 90% yield, which represents an ex-

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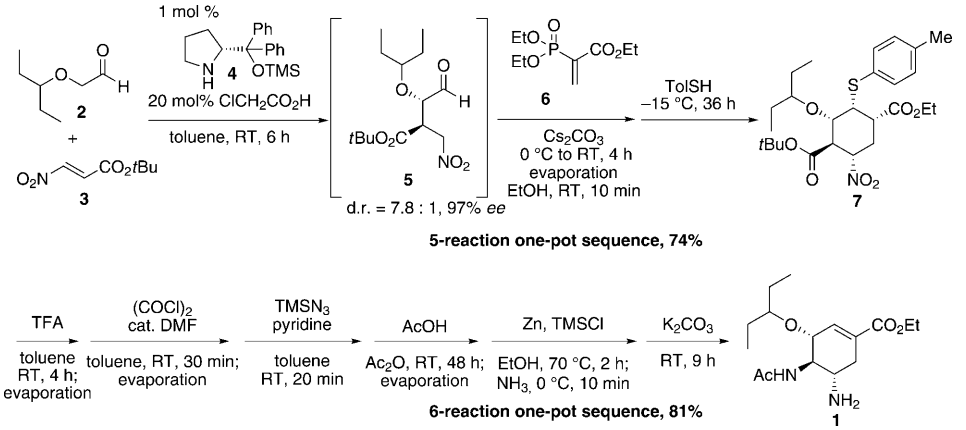
cellent yield in organic synthesis, the total yield falls to 35% after 10 reactions ($0.9^{10}=0.35$). The best yield yet achieved for the total synthesis of Tamiflu is approximately 35%.[4b,d] Moreover, to supply Tamiflu to developing countries where influenza might spread, production costs should be kept low. This requires that only inexpensive reagents be used. To prevent metal contamination of the final drug, it is desirable to avoid metal use as much as possible. Although many syntheses of Tamiflu have been reported,[4] previous methods do not meet all of these requirements, and the development of a method that does so remains a great challenge for the chemical community.

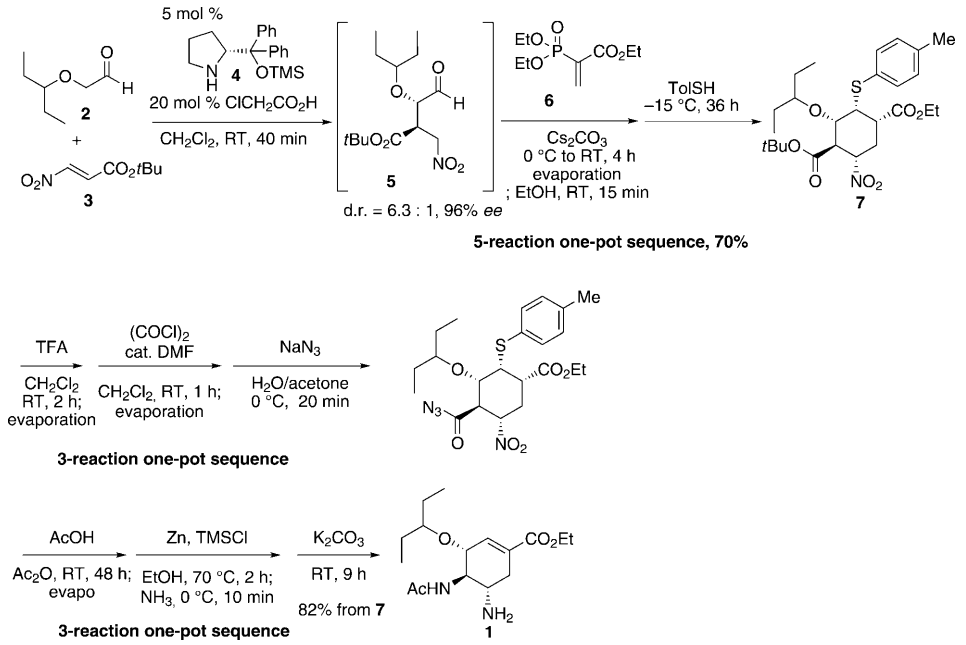
A "one-pot" reaction sequence[6] is an effective method for carrying out several transformations and forming several bonds in a single vessel, while at the same time cutting out several purifications, minimizing chemical-waste generation, and saving time. To simplify the actual process of synthesis, we investigated the preparation of Tamiflu in a small number of one-pot operations. We have already reported a synthesis of (−)-oseltamivir (**1**) through three one-pot sequences.[7] Intensive modification of the reactions has allowed us to prepare **1** in a more efficient manner, and a synthesis in two one-pot sequences has been accomplished.

Our synthesis of **1** through two one-pot sequences is summarized in Scheme 1. The first one-pot sequence starts from α-alkoxyaldehyde **2** and nitroalkene **3** in the presence of the diphenylprolinol silyl ether **4**,[8–11] independently developed by our group and Jørgensen's group. The first one-pot sequence is composed of five reactions: 1) an asymmetric Michael reaction, 2) the domino reaction of a Michael reaction of the nitroalkane and an intramolecular Horner–Wadsworth–Emmons reaction, 3) retro Michael and retro-aldol reactions, followed by an intramolecular Horner–Wadsworth–Emmons reaction, 4) a Michael reaction with toluenethiol, and 5) isomerization to the 5*S* isomer (see below). This sequence affords the highly substituted cyclohexane **7** in 74% yield. The second one-pot sequence, from cyclohexene derivative **7** to **1**, proceeds in 81% yield and is comprised of six reactions (see below).

Several modifications were made to the previous three one-pot sequences (Scheme 2) to allow the whole sequence to be carried out in just two pots and to increase the total overall yield from 57 to 60%. The major modifications are as follows: 1) In the previous synthesis, NaN_3 in aqueous acetone was employed to prepare the acyl azide. As aqueous conditions cannot be employed in the following reaction, they were replaced with nonaqueous conditions by using $TMSN_3$ in toluene. 2) Through the use of $TMSN_3$, the extraction and concentration of the acyl azide, a potential hazard, can be omitted, which makes the synthesis safer. 3) After optimization of the solvent, loading of the organocatalyst could be reduced from 5 to 1 mol%, a reduction that is synthetically useful and makes this reaction practical.



Scheme 1. Synthesis of (−)-oseltamivir (**1**) through two one-pot sequences. TFA: trifluoroacetic acid; TMS: trimethylsilyl; Tol: tolyl.



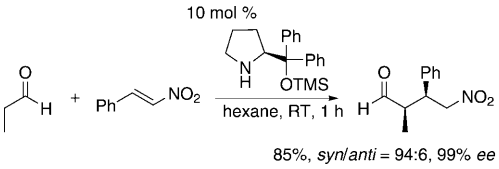
Scheme 2. Previous synthesis of **1** through three one-pot sequences.

4) No halogenated solvents are used. In particular, CH_2Cl_2 was replaced with toluene, which is environmentally friendly. This synthesis requires nine reactions, a total of two separate one-pot sequences, and one purification by column chromatography. The total yield of **1** from nitroalkene **3** is 60%. Full details of the two one-pot sequences and of the previous three one-pot sequences will be described herein.

Results and Discussion

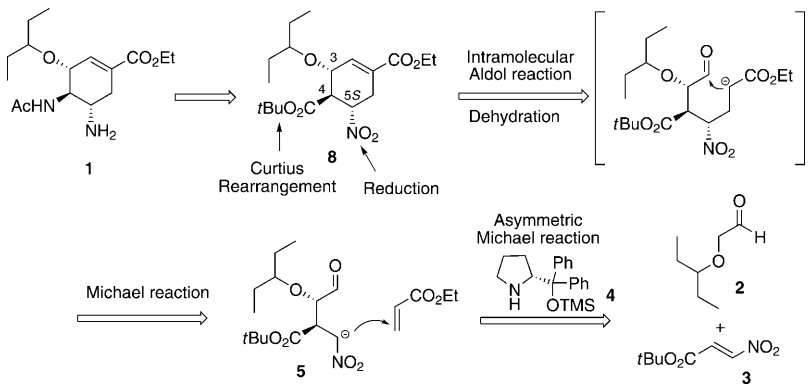
The retrosynthetic analysis: Our retrosynthetic analysis is shown in Scheme 3. In 2005, we found that the enantioselective Michael reaction of an alkyl aldehyde and a nitroalkene[12,13] catalyzed by a diphenylprolinol silyl ether,[8a,10] a catalyst developed independently in our group[8] and by Jørgensen's group,[9] affords the product in good yield with excellent diastereo- and enantioselectivities. Enders and coworkers have elegantly employed this process in a domino reaction[14] with α,β-unsaturated aldehydes to prepare tetrasubstituted cyclohexenecarbaldehydes,[15] so we expected that, by using ethyl acrylate, a substituted cyclohexenecarboxylate would be formed as follows: If α-alkoxyaldehyde **2** and β-alkoxycarbonyl nitroalkene **3** should undergo the Michael reaction, adduct **5** will be formed. If addition product **5** can be trapped with ethyl acrylate, then consecutive Michael addition, intramolecular aldol reaction, and dehydration reaction might occur to generate cyclohexene carboxylate **8**. The configurations of the C3 and C4 atoms of cyclohexene carboxylate **8** would be determined by the first Michael reaction to form **5**, the diastereoselectivity of which is predicted to be high from our previous results.[8a] We expected that the configuration of the C5 atom could be easily isomerized owing to its position α to the nitro group and that the substituents at the C3, C4, and C5 positions would be equatorial because this is the most stable conformer; in other words, we expected that the configuration of the C5 atom would be thermodynamically controlled. Once cyclohexene carboxylate **8** has been prepared, the remaining transformations necessary are the conversion of the *tert*-butoxycarbonyl group into an acetamide and reduction of the nitro group to an amine group. If this plan could be achieved, it should result in a highly efficient method for the synthesis of **1**. The realization of each individual reaction will be described in detail.

The first one-pot sequence for the synthesis of substituted cyclohexane 7: In our reported procedure for the Michael reaction of propanal and nitrostyrene, the reaction was complete within 1 h when catalyzed by the diphenylprolinol silyl ether (10 mol%) in hexane at room temperature, and it afforded the product in good yield (85%) with high diastereoselectivity (*syn*/*anti* = 94:6) and excellent enantioselectivity (99% *ee*) [Eq. (1)].[8a] The same reaction conditions were applied to the reaction of 3-pentyloxyacetaldehyde (**2**) and *tert*-butyl 3-nitropropenoate (**3**), with catalyst **4** derived from D-proline. To our surprise, the reaction was very slow; only 26% yield was obtained even after 60 h, and this had a low diastereomer ratio (Table 1, entry 1). The yield was increased when CH_2Cl_2 was employed as the solvent, but the diastereomer ratio decreased even further (1.7:1; Table 1, entry 2).



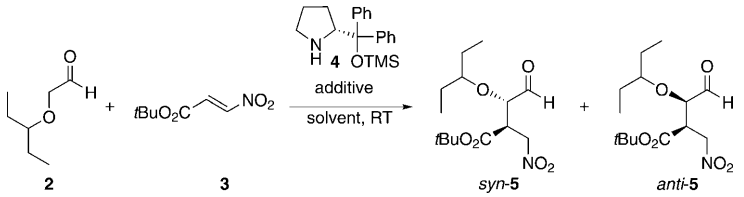
(1)

As the presence of acid increases the reactivity in some Michael reactions of aldehydes and nitroalkenes catalyzed by organocatalyst,[13c,k,h] the addition of various acids was investigated (Table 1). The pK_a value of the acid is found to be very important, not only for the activity but also for the diastereomer ratio of the product. With the exception of Cl_3CCO_2H, a strong acid, the reaction time shortens and the diastereomer ratio (*syn*/*anti*) increases as the acidity of the additive increases. For instance, it takes 24, 14, and 2 h for completion of the reaction when *p*-nitrophenol, benzoic acid, and formic acid are used, with the product diastereomer ratios being 1.7:1, 2.0:1, and 4.8:1, respectively (Table 1, entries 4–6). The best additive is $ClCH_2CO_2H$: in the presence of 20 mol% of $ClCH_2CO_2H$ and 5 mol% of the diphenylprolinol silyl ether, the reaction proceeded smoothly within 1 h to afford the product quantitatively in a high diastereomer ratio (*syn*/*anti* = 6.3:1) and with excellent enantioselectivity (96% *ee*, *syn* isomer; Table 1, entry 7). Further optimization of the reaction conditions revealed that the loading of the



Scheme 3. The retrosynthesis of **1**.

Table 1. Effect of acid in the Michael reaction of **2** and **3** catalyzed by **4**.[a]



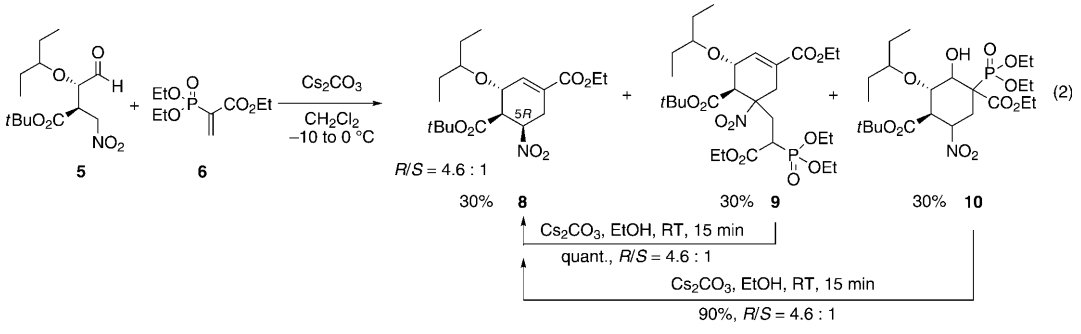
Entry	Catalyst [mol%]	Acid ([mol%])	pK_a[b]	Solvent	t [h]	Yield [%][c]	*syn*/*anti*	*ee* [%][d]
1	20	–	–	hexane	60	26	2.5:1	n.d.
2	20	–	–	CH_2Cl_2	60	quant.	1.7:1	n.d.
3	20	CF_3CH_2OH (40)	12.5	CH_2Cl_2	24	50	2.3:1	n.d.
4	20	*p*-NO_2PhOH (40)	7.1	CH_2Cl_2	24	quant.	1.7:1	n.d.
5	20	$PhCO_2H$ (40)	4.2	CH_2Cl_2	14	quant.	2.0:1	n.d.
6	5	HCO_2H (20)	3.8	CH_2Cl_2	2	quant.	4.8:1	n.d.
7	5	$ClCH_2CO_2H$ (20)	2.9	CH_2Cl_2	1	quant.	6.3:1	96
8	5	Cl_3CCO_2H (20)	0.7	CH_2Cl_2	28	0	–	–
9	5	$ClCH_2CO_2H$ (20)	2.9	toluene	2	quant.	7.6:1	n.d.
10	1	$ClCH_2CO_2H$ (20)	2.9	toluene	6	quant.	7.8:1	97

[a] Unless otherwise shown, reactions were performed by employing aldehyde **2** (0.29 mmol), nitroalkene **3** (0.19 mmol), acid, catalyst **4**, and solvent (0.5 mL) at room temperature for the indicated time. [b] Value in H_2O. [c] Yield of isolated product. [d] Optical purity of the major isomer, which was determined by chiral HPLC analysis of the corresponding ester prepared by reaction with ethyl(triphenylphosphoranylidene)acetate. n.d.: not determined.

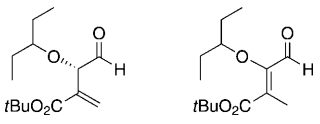
organocatalyst could be reduced to 1 mol% and CH_2Cl_2 could be replaced with a nonhalogenated solvent such as toluene (*syn*/*anti* = 7.8:1, 97% *ee*; Table 1, entry 10). These conditions are advantageous to process chemistry. The mechanism of this effect of the acid is currently under investigation.

Having optimized the first Michael reaction of aldehyde **2** and nitroalkene **3**, we then considered the reaction of Michael adduct **5** and ethyl acrylate. As described in the retrosynthesis section, the functionalized cyclohexene derivative **8** would be generated by a domino reaction sequence of the Michael reaction of an anion at the α position of the nitro group of **5** with ethyl acrylate, an intramolecular aldol reaction, and then dehydration. However, when isolated Michael adduct **5** was treated with ethyl acrylate under a variety of basic conditions, neither the desired product nor even the initial Michael product could be obtained. In some cases, the starting materials were recovered. In other cases, those with tetrabutylammonium fluoride (TBAF) or Cs_2CO_3 as a base, the ethyl acrylate was inert, as evidenced by ^1H NMR spectroscopy experiments, whereas a dimer of the nitroaldehyde, the molecular weight of which was 629 [*M*+Na], was obtained. Although its structure was not fully elucidated, we suppose that the anion at the α position of the nitro group does not react with ethyl acrylate, but rather with the formyl moiety of a second molecule in a Henry reaction. Ethyl acrylate is expected to be a reactive Michael acceptor, but α-alkoxyaldehyde is an even more reactive electrophile. To improve the electrophilicity of the Michael acceptor, vinylphosphonate derivative **6**[16] was selected, in which the double bond is doubly activated by two electron-withdrawing groups, the ethoxycarbonyl and diethylphosphonyl moieties. In this case, cyclohexene derivative **8** should be formed by successive Michael and intramolecular Horner–Wadsworth–Emmons reactions.

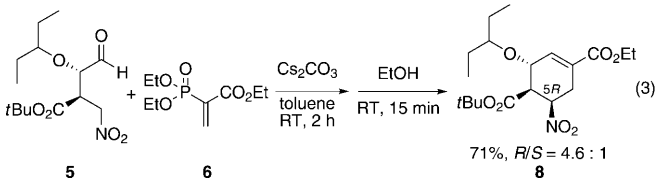
When Michael adduct **5** was treated with **6** in the presence of Cs_2CO_3 in CH_2Cl_2, several products were obtained [Eq. (2)]. One was cyclohexene derivative **8** in 30% yield as an inseparable 5*R*/*S* diastereomer mixture, with the undesired 5*R* isomer predominating. Another was adduct **9**, which was formed in 30% yield by an over-reaction of the initially generated, desired product **8** with the reactive Michael acceptor **6**. The third was **10**, which was formed in 30% yield. The stereochemistry of **10** has not been verified, but it is expected that the configuration of hydroxy and diethylphosphonyl groups is *anti*, so *syn* elimination cannot occur. Preliminary attempts to optimize the reaction conditions to achieve selective synthesis of **8** without the formation of **9** and **10** all failed. In some cases, other byproducts such as **11** or **12** were generated by elimination of nitrous acid and isomerization. At this stage, we reasoned as follows: If a retro Michael reaction occurs from **9**, then **9** would be transformed back into the desired product **8**. If retro-aldol and then Horner–Wadsworth–Emmons reactions



occur, compound **10** would also be converted into **8**. The solvent was found to be crucial for the success of these transformations. When isolated **9** and **10** were treated separately with Cs_2CO_3 in EtOH, cyclohexene derivative **8** was obtained in quantitative and 90% yields, respectively. Retro-reactions are accelerated in a polar solvent such as EtOH and EtOH is a particularly suitable solvent for the reaction of **9** to give **8** because the vinylphosphonate generated, **6**, is immediately trapped with EtOH to prevent its further reaction with **8**.



The reaction proceeded well both in CH_2Cl_2 and toluene. Toluene is more suitable in terms of the industrial process. Whereas Cs_2CO_3 in toluene was employed in the first reaction of the Michael adduct **5** and vinylphosphonate derivative **6**, the reaction conditions in the retro Michael reaction of **9** and the retro-aldol and Horner–Wadsworth–Emmons reactions of **10** involved Cs_2CO_3 in EtOH. When the first reaction was examined in EtOH, the desired product **8** was obtained in only 20% yield and the Michael addition product of the vinylphosphonate with EtOH was the major product. These reactions are therefore performed in one pot as follows: First, the reaction of **5** with **6** is performed with Cs_2CO_3 in toluene at room temperature for 2 h, affording several spots on the TLC plate, then EtOH is added to the same reaction vessel and the reaction mixture is stirred for 15 min, during which time the several spots on the TLC plate converge into a single spot as the cyclohexene derivative **8** is formed in 71% yield [Eq. (3)].



With the cyclohexene derivative **8** in hand, the next problem was isomerization of the *R* isomer into the desired *S* isomer, which was found to be difficult (Table 2). When the inseparable mixture was treated with a base such as K_2CO_3 or Cs_2CO_3, both of which are only partially soluble in EtOH, at −5 °C for 10 min, the same diastereomer ratio of products was formed with the *R* isomer predominating (Table 2, entries 1 and 2). When the reaction was performed for a longer reaction time or at a higher temperature, aromatization proceeded to generate a *tert*-butyl ethyl terephthalate as a side product. Equal amounts of the *R* and *S* isomers were generated with Et_3N as the base (Table 2, entry 3), and this ratio did not change even with longer reaction times, which indicated that equilibrium had been reached. This result indicates that the *R* and *S* isomers have similar thermodynamic stability. When the mixture was loaded onto silica, equal amounts of the *R* and *S* isomers were generated (Table 2, entry 4).

Table 2. The effect of base on the equilibration between the *R* and *S* isomers.[a]

Entry	Base	Solvent	*T* [°C]	*t* [min]	(*R*)-**8**/(*S*)-**8**[b]
1	K_2CO_3	EtOH	−5	10	4.3:1
2	Cs_2CO_3	EtOH	−5	10	4.6:1
3	Et_3N	EtOH	23	240	1:1
4[c]	SiO_2		23	–	1:1.2

[a] Unless otherwise shown, reactions were performed by employing an *R*/*S* mixture (*R*:*S* = 1.2:1 and 4.5:1, 0.03 mmol) in solvent (0.5 mL) with base (0.15 mmol) at the indicated temperature. [b] The diastereomer ratio was determined by ^{1}H NMR spectroscopy. [c] See the reaction conditions in the Supporting Information.

To understand these results relating to thermodynamic stability, stable conformations of the *R* and *S* isomers were investigated[17] by calculation (B3LYP/6-31G(d)[18]), and the respective results for the *R* and *S* isomers, conformations A and B, are shown in Figure 1. These conformations are nearly the same as those in solution as determined by ^{1}H NMR spectroscopy (Scheme 4). It was found that the difference in energy between these two conformers is small (0.11 kcal mol^{-1}; Table 3). This result is in good agreement with the experimental result that the *R* and *S* isomers are obtained in nearly 1:1 ratio. It can be seen that the 3-pentyloxy moiety and *tert*-butoxycarbonyl group occupy axial positions in conformer A and that their relative configuration is antiperiplanar (Figure 1). As this is a cyclohexene ring, the 1,3 steric repulsion is not as large as it would be in a cyclohexane ring system, so the diaxial arrangement of these two substituents in A is slightly more stable than the diequatorial positioning in B, in which a 1,2-*gauche* repulsion would occur.

If the cyclohexene were to be converted into a cyclohexane framework, the epimerizable substituents would be oriented to be equatorial where possible under equilibration. To achieve this, the thiol Michael reaction was examined, because thiol groups are good Michael donors and could be removed by the retro Michael reaction under mild conditions at the last stage of the synthesis. When derivative **8** was treated with toluenethiol in the presence of base, the Michael reaction proceeded and isomerization occurred as expected to afford the cyclohexane derivative **7** with the desired 5*S* stereochemistry. The stereochemistry was determined by the coupling constants and NOESY spectra. The base and temperature are crucial for this transformation (Table 4). When K_2CO_3 was employed at −5 °C, the desired

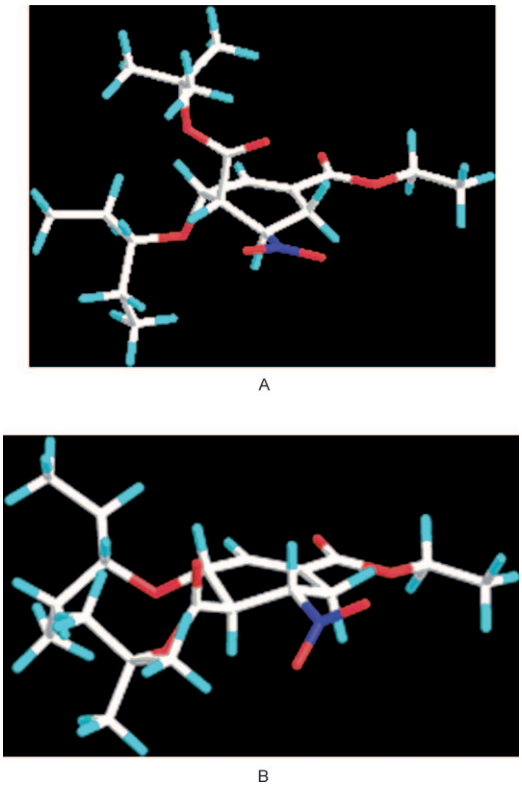
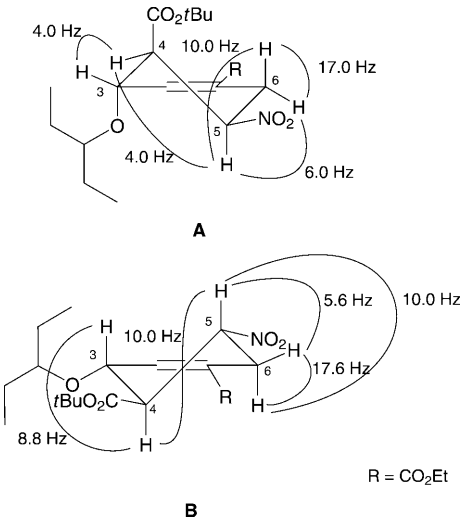


Figure 1. The stable conformations of the *R* (A) and *S* isomers (B).



Scheme 4. The stable conformations of **8** showing the coupling constants (*J*) between protons: A: *R* isomer; B: *S* isomer.

Table 3. Energies of the *R* and *S* conformers of **8**.

Entry	Substrate	*E* [au][a]	ΔE [kcal mol^{-1}][b]
1	*R* isomer (A)	−1323.944735	0.00
2	*S* isomer (B)	−1323.944568	0.11

[a] Total energy. [b] Relative energy. 1 kcal = 4.184 kJ.

compound **7** was obtained in good yield (85%; Table 4, entry 3). As Cs_2CO_3 was used in the previous reactions, it would be preferable to conduct this Michael/isomerization reaction with the same base to enable a one-pot operation. When **8** was treated with Cs_2CO_3 at −5°C, the desired product **7** was obtained in only 35% yield and the major product was the aromatized compound, the *tert*-butyl ethyl terephthalate (Table 4, entry 4). Cs_2CO_3 is a stronger base than K_2CO_3, which led to this over-reaction. To suppress generation of this side product, the reaction conditions were screened in detail, and temperature was found to be important. A good result (90% yield) was obtained when the reaction was carried out at −15°C (Table 4, entry 5).

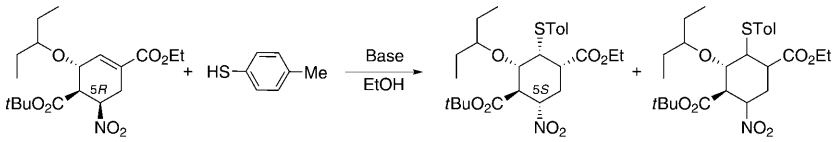
To summarize, cyclohexane derivative **7** was prepared in one pot from 3-pentyloxyacetaldehyde (**2**) and *tert*-butyl 3-nitropropenoate (**3**) as follows (Scheme 5): After a mixture of α-alkoxyaldehyde **2** and nitroalkene **3** had been treated with diphenylprolinol silyl ether **4** (1 mol%) and $ClCH_2CO_2H$ (20 mol%) in toluene for 6 h, vinylphosphonate derivative **6** and Cs_2CO_3 were added, and the reaction mixture was stirred for 4 h at 0°C to room temperature. After evaporation of the toluene, EtOH was added, then after 10 min, the reaction mixture was cooled to −15°C and toluenethiol was added. After isolation and purification by silica-gel column chromatography, highly substituted cyclohexane derivative **7** of the required configuration was obtained in 74% yield as a single isomer.

It should be noted that the same reagent was employed in several reactions in one pot with control of the reactivity by solvent and temperature. Cs_2CO_3 acts as a base in five different ways: 1) It acts as a base for the Michael reaction of nitroalkane **5** and vinylphosphonate **6** in toluene. 2) It also acts as a base for the intramolecular Horner–Wadsworth–Emmons reaction. 3) In EtOH, it acts as a base for the retro Michael reaction from **9** into **8** and the retro-aldol/Horner–Wadsworth–Emmons reaction from **10** into **8**. 4) It acts as a base for the Michael reaction of the thiol compound and **8**. 5) It acts as a base for the isomerization at the C5 atom, with the reaction performed at lower temperature (−15°C) to suppress over-reaction.

The successful realization of the synthesis of highly substituted cyclohexane **7** through the one-pot sequence can be summarized as follows: 1) The organocatalyst does not interfere with the remaining reactions. 2) As equimolar amounts of **2** and **3** are employed in the first reaction, no starting materials remain and, hence, they have no effect on subsequent reactions. 3) As each reaction proceeds in excellent yield, there are no significant side products. 4) As described above, the same base (Cs_2CO_3) acts in five different ways.

The second one-pot sequence from 7 to 1: With an efficient route to highly substituted cyclohexane derivative **7** established, the remaining transformations necessary are conversion of the *tert*-butyl ester into an acetylamino group, conversion of the nitro group into an amino group, and the retro Michael reaction of the thiol moiety. We next investigated the first of these. As shown in Scheme 6, carboxylic

Table 4. The effect of base and temperature on the reaction of **8** and toluenethiol.[a]

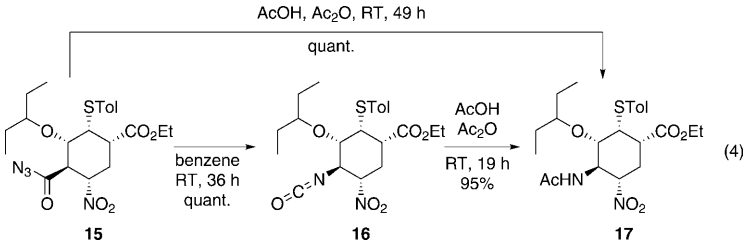


Entry	Base	T [°C]	t [h]	Yield [%]	
				7[b]	Other isomers[c]
1	Et_3N	23	12	71	29
2	$NaHCO_3$	23	24	78	8
3	K_2CO_3	−5	24	85	15
4	Cs_2CO_3	−5	13	35[d]	<5
5	Cs_2CO_3	−15	36	90	<5

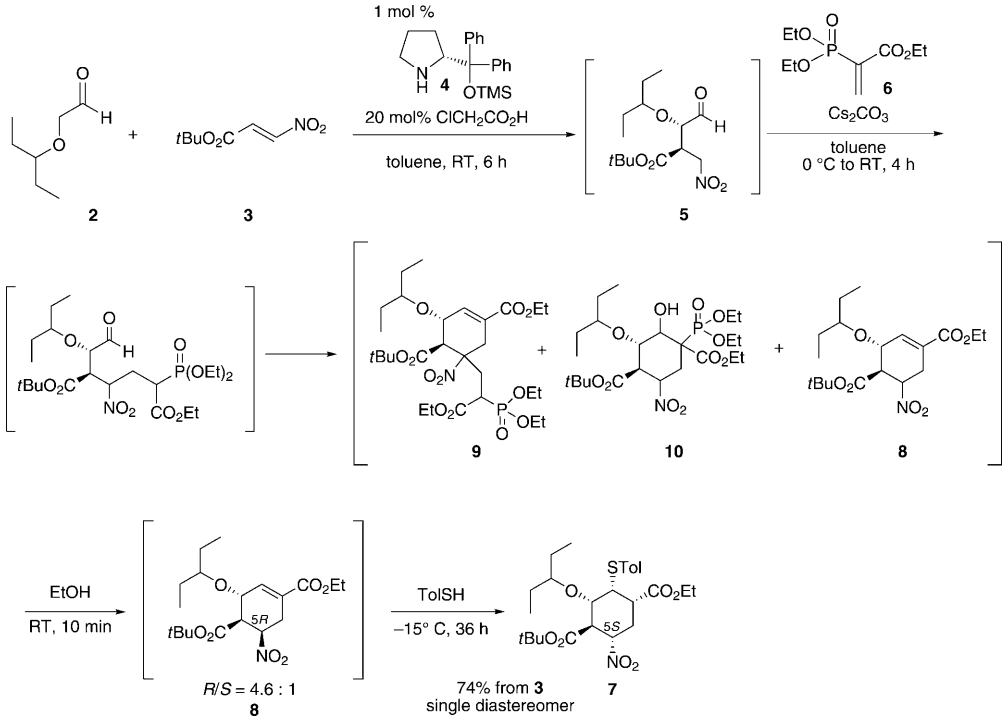
[a] Unless otherwise shown, reactions were performed by employing ethyl ester **8** (0.04 mmol), toluenethiol (0.2 mmol), base (0.12 mmol), and EtOH (0.5 mL) at the indicated temperature. [b] Yield of isolated product. [c] Yield of a mixture of other isomers. [d] *tert*-Butyl ethyl terephthalate was generated in 65% yield.

acid **13** was obtained quantitatively by treatment of *tert*-butyl ester **7** with CF_3CO_2H and subsequent evaporation of the volatile CF_3CO_2H. Acid chloride **14** was obtained by the reaction of the carboxylic acid with oxalyl chloride in the presence of a catalytic amount of DMF. After removal of the excess oxalyl chloride, addition of NaN_3 to an aqueous acetone solution of **14** gave acyl azide derivative **15**. As the NMR spectrum of crude acyl azide **15** indicated that it was rather pure, and it may be an explosively unstable compound, we used it directly without purification. It should be noted that crude acyl azide **15** was obtained in a single-pot reaction from *tert*-butyl ester derivative **7**.

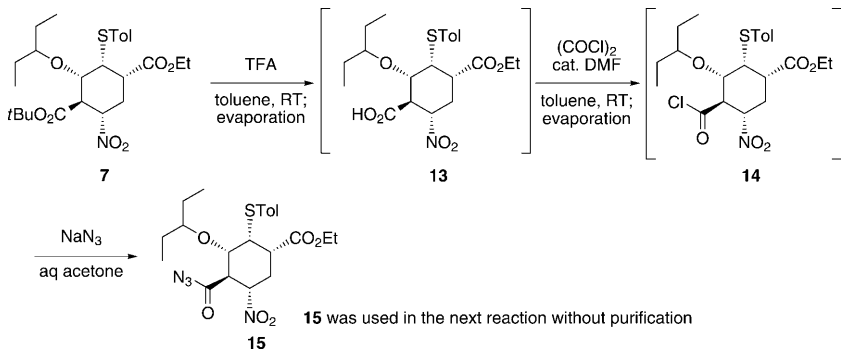
Curtius rearrangement of acyl azide **15** proceeded slowly at room temperature in benzene to afford isocyanate **16** quantitatively [Eq. (4)]. Usually a higher temperature is necessary for the Curtius rearrangement, but it proceeds at room temperature for this particular substrate, which is a synthetic advantage because it suppresses the risk of explosion. When isocyanate **16** was treated with AcOH and Ac_2O at room temperature under the conditions described by Barnum and Hamilton,[19b] the acetylamino group was formed in 95% yield. These two reactions, the Curtius rearrangement and acetylamino formation, can be performed in a single pot. On treatment of acyl azide **15** with AcOH and Ac_2O, they proceed



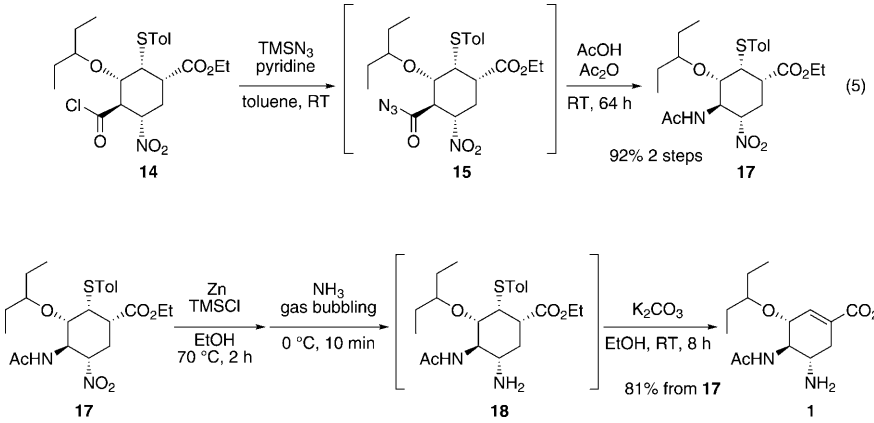
(4)



Scheme 5. The one-pot synthesis of cyclohexane **7** from aldehyde **2** and nitroalkene **3**.



Scheme 6. The conversion of *tert*-butyl ester **7** into acyl azide **15**.



together to generate acetylamino derivative **17** quantitatively.

In this sequence, in the conversion of the *tert*-butoxycarbonyl moiety into an acetylamino group, aqueous NaN_3 was employed. The product, acyl azide **15**, has to be extracted because aqueous conditions were used in this step. It would be synthetically desirable not to have to isolate and concentrate this potentially hazardous compound. Moreover, if aqueous conditions could be avoided, it might be possible to perform the synthesis of **1** from **7** in a one-pot sequence without any isolation of the intermediates. Instead of aqueous NaN_3, $TMSN_3$ and pyridine in toluene were found to convert acyl chloride **14** into acyl azide **15** quantitatively. The use of pyridine is advantageous because other bases, such as Et_3N, gave substantial amounts of the addition product of the azide with isocyanate **16**. Without concentration of the reaction mixture, direct addition of Ac_2O and AcOH provided acetylamino derivative **17** in 92% yield over 2 steps [Eq. (5)].

The next transformation required is reduction of the nitro group to form an amine, which at first was performed by treatment with Zn and aqueous 2 N HCl solution to afford amine **18** in 86% yield. Compound **1** was obtained in 91% yield by retro Michael reaction of the thiol when **18** was treated with K_2CO_3 in EtOH. We then investigated how to achieve these two steps in a single pot. As the aqueous conditions of the first reduction do not permit this, the use of Zn and TMSCl in EtOH was employed to generate HCl in situ [Eq. (6)]. After reduction of the nitro group, K_2CO_3 was added into the reaction mixture to promote the retro Michael reaction. In contrast to the success of the stepwise process, no reaction occurred even at a higher temperature (80 °C), probably because the Zn^{II} species present may chelate the amine moieties and prevent the retro Michael reaction. To capture the Zn^{II} species, NH_3 was bubbled through the reaction mixture, after which treatment with K_2CO_3 promoted a clean retro Michael reaction to provide **1** in 81% yield from nitro derivative **17** over 2 steps.

As each individual process had been optimized, they were now combined to investigate the synthesis of **1** from the highly substituted cyclohexane derivative **7** in a one-pot sequence (Scheme 1). All of the reactions can be conducted in the same reaction vessel, with no isolation of the intermediates. As the final compound is an amine, it could be isolated in excellent purity by a simple acid–base extraction with no need for purification by column chromatography. The ^1H NMR spectra of our synthetic material and of an authentic sample are shown in Figure S1 of the Supporting Information. In this way, compound **1** was synthesized in 81% yield from **7**.

Synthesis without column chromatography: In the two one-pot sequences, we purified *tert*-butyl ester **7** by column chromatography, the only column necessary in the whole synthesis. This process should be avoided in a large-scale synthesis. The next reaction after formation of **7** is the transformation of the *tert*-butyl ester into carboxylic acid **13** upon treatment with CF_3CO_2H (Scheme 6). As **13** is an acid, it might be possible to purify it by acid–base extraction without any purification at the stage of **7**. When we looked at this, we found that carboxylic acid **13** and phosphoric acid diethyl ester, $(EtO)_2P(O)OH$, which is generated by the Horner–Wadsworth–Emmons reaction in the first one-pot reaction, cannot be separated at this stage. However $(EtO)_2P(O)OH$ can be removed in the previous step by an acid–base extraction; that is, *tert*-butyl ester **7** was separated from $(EtO)_2P(O)OH$ by washing the organic phase twice with NH_4OH solution. Crude **7**, which is then free from $(EtO)_2P(O)OH$, was treated with CF_3CO_2H to afford crude carboxylic acid **13**, and acid–base extraction of **13** followed

by filtration through a short silica pad gave a good purity of **13**. By using this acid–base extraction technique, we can establish a column-free synthesis of **1**.

Conclusion

An efficient, enantioselective, total synthesis of **1** through two one-pot sequences has been accomplished. The present synthesis has several noteworthy features: 1) Only two pots are needed for the synthesis of the rather complex **1**. 2) A highly functionalized chiral cyclohexane framework of the correct relative and absolute configuration can be synthesized in the first one-pot sequence, which consists of a sequence of reactions made up of a diphenylprolinol silyl ether mediated asymmetric Michael reaction as developed in our group, a domino Michael reaction/Horner–Wadsworth–Emmons reaction combined with retro-aldol/Horner–Wadsworth–Emmons and retro Michael reactions, a thiol Michael reaction, and a base-catalyzed isomerization. 3) Six transformations can be successfully conducted in the second one-pot sequence, including deprotection of a *tert*-butyl ester and its conversion into an acid chloride then an acid azide, Curtius rearrangement, amide formation, reduction of a nitro group into an amine, and the retro Michael reaction of a thiol. 4) The Curtius rearrangement proceeds at room temperature without heating, which decreases potential hazards. 5) The domino reaction of a Curtius rearrangement and amide formation is a direct method for the synthesis of **12**. 6) Only 1 mol% loading of the diphenylprolinol silyl ether, which was developed in our group as an efficient organocatalyst, is needed to promote the asymmetric direct Michael reaction, which is suitable for large-scale synthesis. 7) No halogenated solvents are used. 8) Isolation and concentration of the potentially hazardous acyl azide **15** can be avoided, which makes the synthesis safer. 9) The intermediate can be purified by an acid–base extraction process. Efficient purification of **1** was achieved by a simple acid–base extraction at the final stage. Thus, the synthesis is free from column chromatography.

This synthesis requires nine transformations in a total of two separate reaction pots. The total yield of **1** from nitroalkene **3** is 60%. All of the reagents are inexpensive. The metals employed in the present total synthesis are alkali metals (Na, K, and Cs) and relatively nontoxic zinc. No special care needs be taken to exclude water or air. We have performed the first one-pot sequence with 1.13 g of aldehyde **2** and 1.0 g of nitroalkene **3** to afford 2.18 g of cyclohexane **7**. In the second one-pot sequence, 3.0 g of cyclohexane **7** can be successfully converted into 1.49 g of **1**. Thus, we believe that the present procedure can be scaled up. The synthetic route itself is completely different from those previously described and should enable the synthesis of a wide variety of novel derivatives. This will be valuable in the search for agents effective against Tamiflu-resistant viruses.

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