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An alternative synthesis of Tamiflu®: a synthetic challenge and the identification of a ruthenium-catalyzed dihydroxylation route

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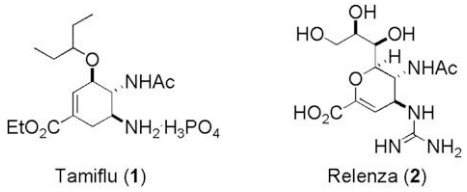
ABSTRACT

Synthetic studies of Tamiflu® and the identification of a ruthenium-catalyzed dihydroxylation route are disclosed. This newly developed synthetic process circumvents the need for a Mitsunobu inversion step and the use of explosive reagents. This route, therefore, compares favorably to the previously developed synthetic process.

1. Introduction

Influenza viruses pose a serious threat to public health worldwide. In particular, the currently spreading avian H5N1 virus strain is a serious menace due to its high lethality rate and the rapid spread of this virus to many countries in Asia, Europe, and Africa. There are now increasing concerns that this virus might acquire the ability to spread between humans, leading to a worldwide pandemic. Two of the drugs currently used to treat influenza patients are Tamiflu® (**1**, Fig. 1) ((−)-oseltamivir phosphate)[1] and Relenza® (**2**) (zanamivir),[2] both of which inhibit viral neuraminidase. Tamiflu® is an orally active prodrug, whereas Relenza® has low bioavailability and is administered by inhalation. Because neuraminidase is a fundamental enzyme for the life cycle of general influenza viruses, neuraminidase inhibitors are considered to be effective against H5N1 virus types. Neuraminidase inhibitors are currently the only effective molecular weapons available to protect humans against an influenza pandemic.



Tamiflu (**1**) Relenza (**2**)

Figure 1. Structures of Tamiflu® and Relenza®.

Currently, Tamiflu® is produced and supplied by Roche using (−)-shikimic acid as the starting material.[3] Production of (−)-shikimic acid with a consistent purity, however, is both time-consuming and costly. In addition, dependence on a single synthetic route for the supply of such an important drug is unwise. There is, therefore, an urgent demand to develop alternative practical syntheses of Tamiflu® starting from easily available materials. Several chemists, including our group, are currently involved in developing alternative synthetic methods for Tamiflu®.[4,5] Improving synthetic efficiency remains a challenge and is a major research focus. We report herein the details of our efforts to improve the synthetic process of Tamiflu®, and the identification of a ruthenium-catalyzed dihydroxylation route is disclosed.

2. Results and discussion

We previously reported[4n] the development of a Ba–F_2–FujiCAPO complex-catalyzed asymmetric Diels–Alder-type reaction, and Tamiflu® was successfully synthesized from the cycloadduct via a Curtius rearrangement, palladium-catalyzed allylic substitution reaction, and Mitsunobu reaction as key transformations (Scheme 1). This synthetic process is easily conducted, and gram-scale synthesis of Tamiflu® can be performed. There is, however, still room for improvement of the synthetic efficiency. One area that can be improved is the use of two Mitsunobu reactions. One Mitsunobu reaction is for the inversion of allylic alcohol (**9** to **10**), and the other is for the synthesis of aziridine (**10** to **11**). The Mitsunobu reaction is a well-established reliable process,[6] but it generates a large amount of waste, namely, phosphine oxide and hydrazine byproducts. It usually requires tedious column chromatography purification of the targeted product.[7] Thus, it is desirable to avoid Mitsunobu reactions for industry-scale processes. In terms of our synthetic process of Tamiflu®, the most straightforward and promising approach to circumvent these steps seems to be the direct introduction of a 3-pentyl ether moiety via an epoxide opening reaction with **8**. Thus, we began our investigation to establish a more efficient synthetic process from this intermediate.

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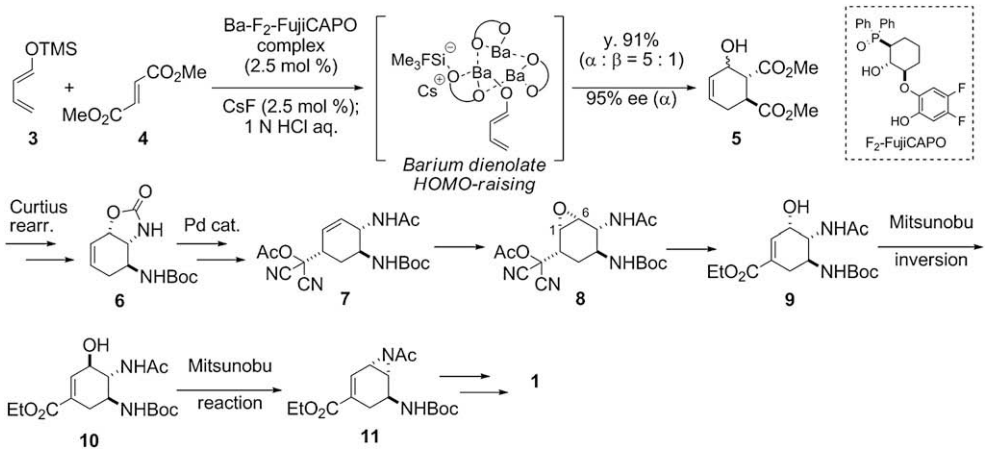


Scheme 1. Previously established synthetic process of Tamiflu®.

2.1. Epoxide opening reaction of derivatives of 8

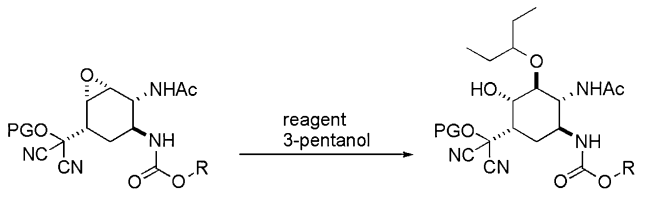
One concern about the epoxide opening reaction of derivatives of **8** with 3-pentanol is its regioselectivity. Based on reported precedents and analogy to the reported reactions of 2,3-epoxy alcohol,[8] nucleophiles might attack the C1 position via an intramolecular metal chelate. We expected, however, that the neighboring acetoxydicyanomethyl moiety would exhibit steric bias to achieve C6 position-selective attack of the nucleophiles. Thus, we began by examining the reaction conditions.

Representative results are shown in Table 1. As the first trial, we performed a Lewis acid-catalyzed epoxide opening reaction with **8** as the substrate. Only decomposition of the substrate, however, was observed (entries 1–3). Electrospray ionization-mass spectrometric (ESI-MS) analysis of the reaction mixture suggested that the acid lability of **8** was due to the acetoxydicyanomethyl moiety and *tert*-butoxycarbonyl group. Therefore, we produced compound **12**, in which we replaced the acetyl group and *tert*-butoxycarbonyl group with the TBS group and methoxycarbonyl group, respectively, and performed a Lewis acid-catalyzed epoxide opening reaction with this substrate. No reaction occurred, however, and the starting material was recovered unchanged (entries 4 and 5). Compound **12** was rather inert, and even acid–base combination conditions [$Sc(OTf)_3$, Pybox, and amine base or alkoxide base] rendered the starting material unchanged (data not shown).

We next examined the effect of basic conditions, namely, the formation of metal alkoxide from 3-pentanol and its use as a nucleophile. Metal, solvent, and temperature were screened, and eventually treatment of **13** with the sodium alkoxide of 3-pentanol generated by the reaction of 3-pentanol with NaHMDS in dimethylformamide (DMF)/tetrahydrofuran (THF) mixed solvent afforded a relatively clean reaction. The obtained product, however, was imidate **17** (60%), produced by the addition of the alkoxide to a cyano group (entry 6).

Because derivatives of **8** are inert under acidic conditions and labile under basic conditions, we next examined the reaction under neutral conditions. When we treated **8** with a substoichiometric amount of $Ni(cod)_2$ (0.5 equiv) and PBu_3 (1 equiv) in THF/3-pentanol mixed solvent, expecting an oxidative addition of Ni° to the epoxide group,[9] the obtained product was reduced product **18** (40%) (entry 7). This result might have been due to the ability of the cyano group to direct a soft metal, Ni° in this case, leading to an oxidative addition to the C–OAc bond and subsequent protonation. The epoxide groups in the derivatives of **8** were inert under acidic, basic, as well as neutral conditions, and other functionalities within the molecule reacted faster than the epoxide group. We, therefore, abandoned the epoxide opening strategy.

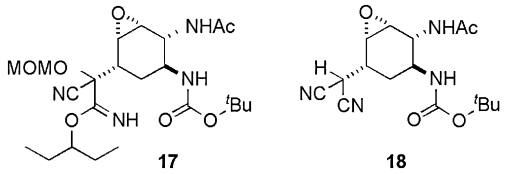
Table 1
Epoxide opening reaction with 3-pentanol



PG = Ac, R = ^{t}Bu : **8**
PG = TBS, R = Me : **12**
PG = MOM, R = ^{t}Bu : **13**

PG = Ac, R = ^{t}Bu : **14**
PG = TBS, R = Me : **15**
PG = MOM, R = ^{t}Bu : **16**

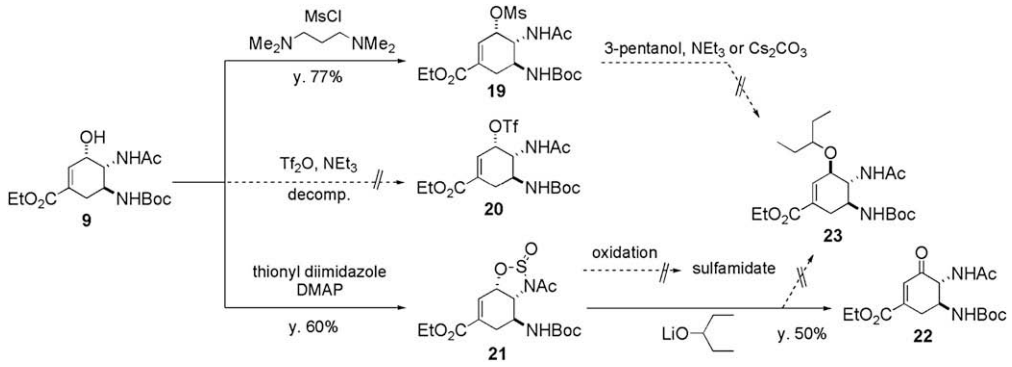
Entry	Substrate	Conditions	Results
1	**8**	$Al(OTf)_3$, CH_2Cl_2, rt	Decomp.
2	**8**	$Yb(OTf)_3$, CH_2Cl_2, rt	Decomp.
3	**8**	$BF_3{\cdot}OEt_2$, Toluene, 60 °C	Decomp.
4	**12**	$Al(OTf)_3$, DCE, 70 °C	NR
5	**12**	$Sc(OTf)_3$, DCE, 70 °C	NR
6	**13**	NaHMDS, DMF, THF, −43 °C	**17** (60%)
7	**8**	$Ni(cod)_2$, PBu_3, THF, rt	**18** (40%)



2.2. Inversive ether formation from derivatives of 9

Another strategy to avoid the Mitsunobu reaction is inversive ether formation from the derivatives of **9**. Several derivatives of **9** with a variety of leaving groups were produced, and we examined S_N2 displacement of the thus-formed leaving groups by nucleophiles derived from 3-pentanol.

First, we examined the reactivity of methanesulfonyl ester **19** (Scheme 2). For the synthesis of **19**, alcohol **9** was treated under standard mesylation conditions (MsCl, NEt_3), but only a messy reaction was observed, and ESI-MS analysis of the reaction mixture indicated that it was caused by the substitution of a methanesulfonyl ester by chloride anions. Therefore, we tried the Tanabe



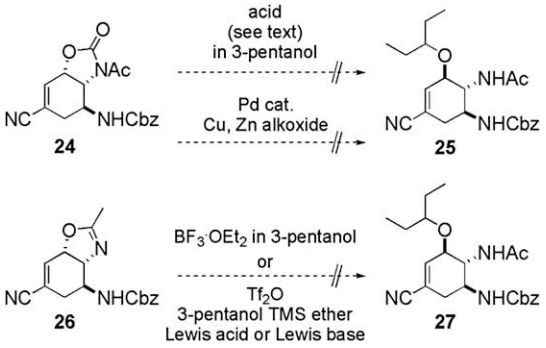
Scheme 2. Inversive ether formation under basic conditions.

condition (MsCl, *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine),[10] and obtained the desired methanesulfonyl ester **19** in 77% yield. The thus-produced mesylate **19** was then treated with 3-pentanol and base (NEt_3 or Cs_2CO_3), but no reaction occurred at room temperature and only decomposition of the substrate was observed at an elevated temperature. To increase the reactivity of the substrate, we tried to produce the corresponding trifluoromethanesulfonyl ester **20**, but only the decomposition of **20**, due to instability of **20**, was observed.

Next, we examined cyclic sulfamidate as an electrophile. Cyclic sulfamidate is a very strained functional group, and is therefore well-known as a very good leaving group. Cyclic sulfamidite **21** was successfully synthesized from alcohol **9** with thionyl diimidazole in 60% yield.[11] The oxidation of sulfamidite **21** to sulfamidate under several conditions [$NaIO_4$ with ruthenium catalyst in the presence and absence of ligands, CrO_3, phenyliodine bis(trifluoroacetate) (PIFA), OXONE®, and H_2O_2 with a molybdenum catalyst] did not afford the desired product. When using $NaIO_4$ with a ruthenium catalyst as the oxidant, sulfamidite was oxidized to sulfamidate, but overoxidation at the C–C double bond also occurred. Because the desired cyclic sulfamidate was not produced, we examined the reaction of the lithium alkoxide of 3-pentanol with cyclic sulfamidite **21** as an electrophile. Ketone **22** was obtained in 50% yield, however, which was probably generated through ester enolate formation via deprotonation at the γ position of the α,β-unsaturated ester group by lithium alkoxide and the subsequent release of sulfur monoxide.

The failure of the above-mentioned strategies under basic conditions led us to examine a cyclic carbamate or an oxazoline derived from **9** as electrophiles, expecting acid-activation of these functional groups or the formation of an η^3-allyl palladium species (Scheme 3). In these studies, compounds **24** and **26** were used as model substrates.[12] When cyclic carbamate **24** was treated with a variety of Lewis and Brønsted acids [$Sc(OTf)_3$, AgOTf, $Mg(OTf)_2$, TMSOTf, and Tf_2NH] in 3-pentanol, no reaction occurred at room temperature, and an acetyl group was cleaved at a higher temperature. In the case of oxazoline **26**, no reaction proceeded when using $BF_3 \cdot OEt_2$ as the Lewis acid. A Reissert-type reaction was also tried using Tf_2O as an activator of the oxazoline group. The use of 3-pentanol TMS ether in the presence of a Lewis acid [Et_2AlCl, $BF_3 \cdot OEt_2$, $Gd(OTf)_3$, or TMSOTf] or a Lewis base (CuF, CuI, AgF, or tetrabutylammonium difluorotriphenylsilicate) afforded only a messy reaction.

We then examined palladium catalysis to generate an η^3-allyl palladium species, which was expected to be trapped by 3-pentanol or its alkoxide. Alcohols are generally unfavorable nucleophiles toward an η^3-allyl palladium species, but Evans and Leahy[13a] and Lee and Kim[13b] recently reported that copper alkoxide and zinc alkoxide are good nucleophiles toward η^3-allyl rhodium and palladium



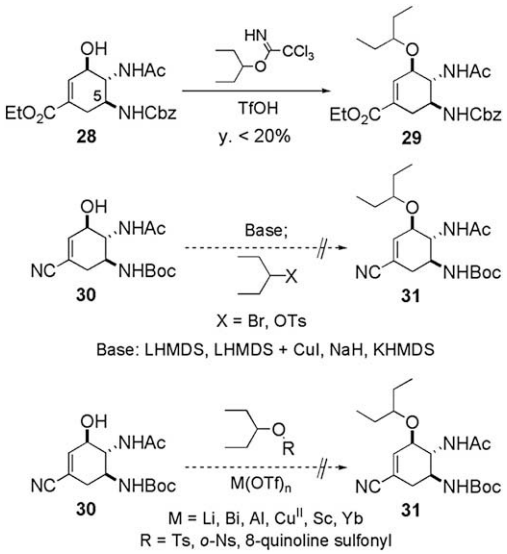
Scheme 3. Inversive ether formation under acidic conditions and palladium catalysis.

species. Thus, we examined the addition of copper and zinc alkoxide to an η^3-allyl palladium species that would be generated by the reaction of cyclic carbamate **24** and a palladium catalyst. When **24** was treated with palladium acetate (5 mol %), 2-(di-*tert*-butylphosphino)biphenyl (7.5 mol %), Et_2Zn (0.5 equiv), NH_4OAc (10 mol %), and 3-pentanol (1 equiv) in THF, however, no reaction occurred. On the other hand, when **24** was treated with $Pd(PPh_3)_4$ (10 mol %), 2-(di-*tert*-butylphosphino)biphenyl (40 mol %), $(CH_3CH_2)_2CHOLi$ (2 equiv), and CuOTf (1 equiv) in THF, cleavage of an acetyl group (ca. 60%) and the formation of dienamide (probably through β-hydride elimination of the η^3-allyl palladium species) (ca. 40%) were observed. In the latter case, the η^3-allyl palladium species should be successfully formed, but weak nucleophilicity of the copper alkoxide derived from 3-pentanol, perhaps due to its steric bulkiness, prevented C–O bond formation.

2.3. Non-inversive ether formation from derivatives of 10

In the above-mentioned strategies, 3-pentanol and its alkoxide were used as nucleophiles. The desired C–O bond formation did not occur under any of the conditions examined, because of the low nucleophilicity of 3-pentanol and its alkoxide, which might be due to the steric bulkiness of 3-pentanol. Therefore, based on these results, we changed the strategy to utilize the 3-pentanol unit as an electrophile and a cyclohexenol core as a nucleophile. Although this strategy required a Mitsunobu inversion step, the second Mitsunobu aziridine synthesis was avoided, so we thought this strategy was still advantageous.

At first, the trichloroacetimidate of 3-pentanol was examined as an electrophile because Fang and co-workers used the same strategy in their report on the synthesis of Tamiflu® (Scheme 4).[4h] Their substrate was different from ours only in the functional group at the C5 position. They used an azide group as the nitrogen functionality, whereas we used a benzylcarbamate group.



Scheme 4. Non-inversive ether formation from derivatives of **10**.

Following their procedure, we treated compound **28** with trichloroacetimidate derived from 3-pentanol in the presence of triflic acid (1.5 equiv in total, portionwise addition) in CH_2Cl_2. The desired ether product, however, was obtained in less than 20% yield. Solvent, temperature, amount of reagents, and the use of triflimide instead of triflic acid were examined, but there was no improvement. The reasons for the poor results are not known, but subtle structural differences in the substrates seemed to greatly change their reactivity.

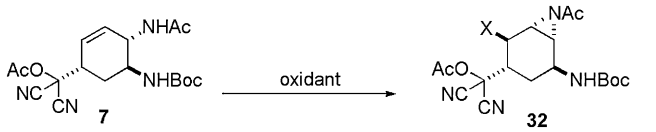
Other electrophiles (bromide and sulfonate esters) were also examined with model substrate **30**. Compound **30** was reacted with bromide or tosylate derived from 3-pentanol under 3 equiv of a variety of bases (LHMDS in the presence and absence of CuI, NaH, and KHMDS) in THF at 0 °C. Only decomposition of the starting material was observed. On the other hand, no reaction occurred when several sulfonate esters derived from 3-pentanol (tosylate, *o*-nosylate, and 8-quinoline sulfonate) were used under acidic conditions (metal triflate, see Scheme 4) in CH_2Cl_2 at room temperature, and cleavage of a Boc group occurred at an elevated temperature, during which the desired C–O bond formation was never observed. Thus, we abandoned the notion of non-inversive ether formation from derivatives of **10**.

2.4. Aziridine synthesis without using a Mitsunobu reaction

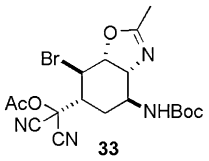
We tested the use of 3-pentanol derivatives as both nucleophiles and electrophiles to construct a sterically bulky 3-pentyl ether moiety, but it was unsuccessful. Thus, the only available method to construct a 3-pentyl ether moiety was via aziridine **11**. We therefore examined the synthesis of aziridine *without* the use of a Mitsunobu reaction.

Compound **7** was selected as a substrate because oxidation of the C–C double bond (e.g., formation of a halonium ion) would be followed by cyclization of the neighboring acetamide group to form aziridine (Table 2). When compound **7** was treated with 3 equiv of *N*-bromoacetamide (NBA) at room temperature, cyclization occurred. The obtained product, however, was not aziridine **32**, but oxazoline **33** (entry 1). Because solvent screening revealed no specific solvents with beneficial effects, we examined the effect of several additives on product selectivity. The addition of 1 equiv of KO^tBu did not change the product selectivity (entry 2), and 1 equiv of ^{n}BuLi resulted in decomposition of the starting material (entry 3). Recently, Ishihara and co-workers reported enantioselective halocyclization of polyprenoids induced by *N*-halosuccinimide and

Table 2
Synthesis of aziridine from **7**

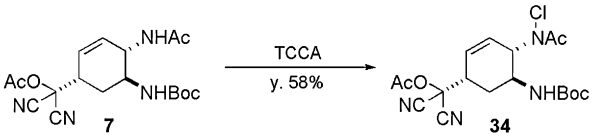


Entry	Oxidant	Results
1	NBA, THF, rt	**33** (>90%)
2	NBA, KO^tBu, THF, rt	**33** (ca. 60%)
3	NBA, ^{n}BuLi, THF, rt	Decomp.
4	NBA, PBu_3, THF, rt	**33** (ca. 20%)
5	Chloramine-T, I_2, CH_3CN, 50 °C	NR
6	^{t}BuOCl, NaI, CH_3CN, 50 °C	NR
7	CF_3COOAg, Br_2, CCl_4, rt	NR
8	PIFA, MgO, DCE, 60 °C	NR



nucleophilic phosphines or phosphoramidites.[14] Thus, we examined the addition of 1 equiv of tributylphosphine, expecting that the reactivity of a newly formed brominating reagent would differ from that of NBA, thereby leading to a change in product selectivity (entry 4). Although the reaction was messy, oxazoline **33** was obtained in approximately 20% yield. We investigated other oxidants such as chloramine-T (1 equiv) and I_2 (1 equiv) (entry 5),[15] ^{t}BuOCl (1 equiv) and NaI (1 equiv) (entry 6),[16] CF_3COOAg (1 equiv) and Br_2 (1 equiv) (entry 7), and PIFA (3 equiv) in the presence of MgO (entry 8), none of which promoted the reaction.

Compound **7** was successfully converted to an *N*-chlorinated compound. That is, when compound **7** was treated with 1.2 equiv of trichloroisocyanuric acid (TCCA) in 1,2-dichloroethane at room temperature, *N*-chlorinated compound **34** was obtained in 58% yield (Eq. 1).



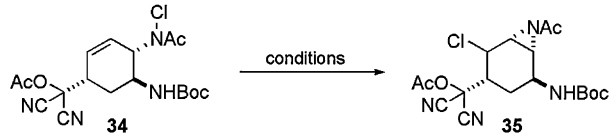
(1)

This substrate seemed appealing for the synthesis of aziridine through either homolytic or heterolytic cleavage of the *N*–Cl bond. Therefore, we examined the reaction conditions.

At first, homolytic cleavage of the *N*–Cl bond followed by trapping of the thus-formed amidyl radical by the C–C double bond was examined (Table 3). Although a toluene solution of **34** was heated at 100 °C in the presence of AIBN, no reaction took place (entry 1). When we heated a mesitylene solution of **34** at 160 °C, **34** was completely consumed, but the product was **7**, which was reduced (entry 2). Copper chloride was then used as a single electron reductant to facilitate generation of an amidyl radical.[17] Only decomposition of the starting material, however, was observed (entry 3). In the case of entry 2, an amidyl radical might have been generated, however, which did not react with the neighboring C–C double bond, resulting in H-abstraction, probably from the solvent.

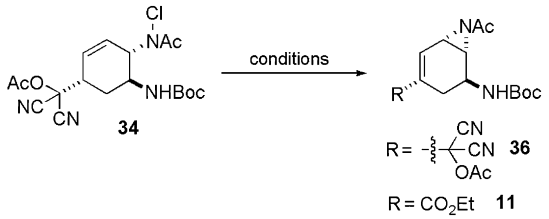
Representative results of our examination of heterolytic cleavage of the *N*–Cl bond are summarized in Table 4. Treatment of compound **34** with K_2CO_3 in EtOH was expected to generate potassium dienolate by unmasking the ester-equivalent moiety, followed by deprotonation at the α position of the thus-formed ethoxycarbonyl group, and intramolecular reaction with the *N*–Cl acetamide group,

Table 3
Synthesis of aziridine through homolytic cleavage of the *N*–Cl bond

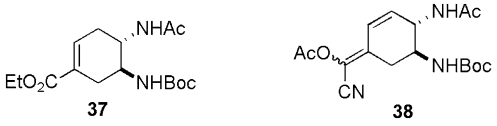


Entry	Conditions	Results
1	AIBN, toluene, 100 °C	NR
2	Mesitylene, 160 °C	**7**
3	CuCl, MeOH, 60 °C	Decomp.

Table 4
Synthesis of aziridine through heterolytic cleavage of the *N*–Cl bond



Entry	Conditions	Results
1	K_2CO_3, EtOH, rt	**37** (>80%)
2	$AgNO_3$, CH_3CN, 80 °C	NR
3	$Pd_2(dba)_3{\cdot}CHCl_3$, K_2CO_3, DMF, 65 °C	**38** (58%)

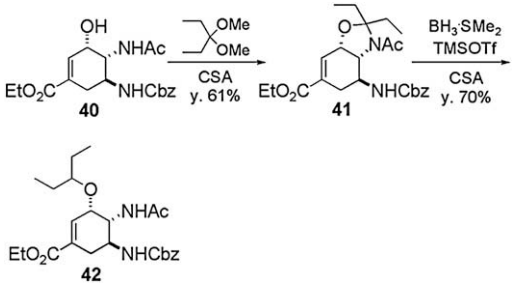


thus leading to the formation of aziridine. The afforded product was not aziridine **11**, however, but **37**, which was produced by protonation of the potassium dienolate at the γ position (entry 1).[18] When **34** was reacted with $AgNO_3$ in CH_3CN at 80 °C to activate the *N*–Cl bond, there was no reaction (entry 2). We anticipated that oxidative addition of Pd° to the *N*–Cl bond and intramolecular aza-Wacker reaction with a neighboring C–C double bond would lead to the formation of aziridine, and we therefore treated **34** with 10 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of K_2CO_3 in DMF at 65 °C. The obtained product was compound **38**, which was generated by a reduction of the *N*–Cl bond and the elimination of HCN (entry 3). *N*–Cl Acetamide **34** was rather labile and easily reduced to the corresponding *N*–H acetamide under homolytic and heterolytic cleavage of the *N*–Cl bond. Thus, we abandoned the notion of *N*–Cl acetamide **34** as a precursor of aziridine.

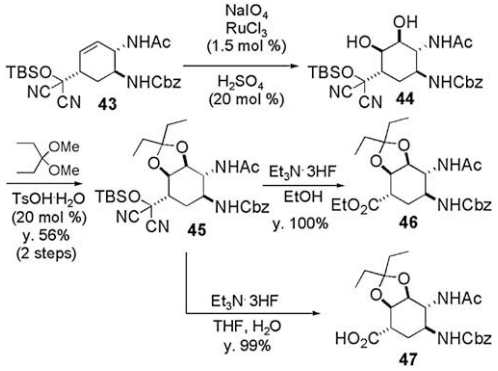
2.5. Pentylidene acetal (hemiaminal) opening strategy

We tested the use of 3-pentanol derivatives as both nucleophiles and electrophiles, and the synthesis of aziridine without a Mitsunobu reaction to construct a sterically bulky ether moiety, none of which was successful. To overcome this difficulty, we tried an indirect introduction of a sterically bulky alkyl group in a masked form, followed by structural modification to construct a 3-pentyl ether unit, and among the possible tactics, reductive opening of pentylidene acetal was appealing. Two options were considered, hemiaminal **41** (Scheme 5) and acetal **45** (Scheme 6) as substrates, and we started the examination with **41** because it could be produced from alcohol **40** in a straightforward manner.

We expected that reductive opening product **42**, which would be produced from hemiaminal **41**, would be isomerized to



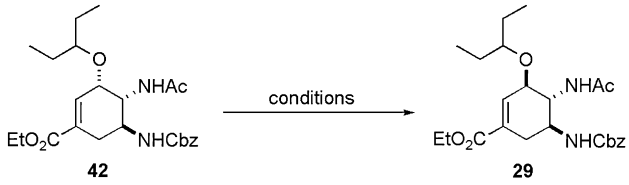
Scheme 5. Synthesis of α-ether **42**.



Scheme 6. Synthesis of pentylidene acetal.

a thermodynamically more stable β-ether under basic conditions (via deprotonation at the γ position of α,β-unsaturated ester) or a transition metal-catalyzed process. Alcohol **40** was converted to pentylidene hemiaminal **41** using 20 equiv of 3-pentanone dimethyl acetal in the presence of 0.3 equiv of CSA in toluene at 60 °C (Scheme 5). A reductive opening reaction of the resulting pentylidene hemiaminal proceeded well using 3 equiv of $BH_3{\cdot}SMe_2$ as the reductant, and 1.1 equiv of TMSOTf and 1.1 equiv of CSA as acids in CH_2Cl_2 at 0 °C.[19] With the α-ether in hand, we next examined the isomerization of **42** to β-ether **29** under a variety of reaction conditions (Table 5).

Table 5
Isomerization of α-ether **42** to β-ether **29**



Entry	Conditions	Results
1	EtONa, EtOH, rt	NR
2	NaH, THF, 40 °C	Decomp.
3	$La(OTf)_3$, Et_3N, DCE, rt	NR
4	TfOH, EtOH, 70 °C	NR
5	$[RhCl(PPh_3)_3]$, DABCO, wet-EtOH, 70 °C	NR
6	$[RhH(PPh_3)_4]$, TFA, EtOH, 70 °C	NR
7	$Fe(CO)_5$, xylene, 130 °C	NR

In the first trial, compound **42** was treated with 5 equiv of EtONa in EtOH, but the starting material remained unchanged (entry 1). When 5 equiv of sodium hydride was used as a base, decomposition of the substrate was observed (entry 2). Thus, we examined an acid–base combination to activate α,β-unsaturated ester, thereby increasing the acidity of the protons at the γ position. No reaction

occurred, however, using 0.42 equiv of $La(OTf)_3$ and 0.84 equiv of Et_3N in 1,2-dichloroethane at room temperature (entry 3). We then examined acidic conditions, but 1 equiv of TfOH afforded no isomerized products (entry 4). Because both the basic and acidic conditions failed, we next tried a transition metal-catalyzed isomerization of allyl ether. Both rhodium and iron catalysts were examined, but no reaction occurred and the desired β-ether was not obtained. At this point, we abandoned the isomerization strategy, and proceeded to the other option, the use of acetal **45**.

Acetal **45** was synthesized from compound **43** by a ruthenium-catalyzed dihydroxylation reaction (Scheme 6). Olefin **43** was treated with 1.5 equiv of $NaIO_4$ in the presence of 1.5 mol % of $RuCl_3$ catalyst and 20 mol % of H_2SO_4 cocatalyst at 0 °C to afford β-*cis* diol **44**.[20] In the case of epoxidation (10 equiv of trifluoroacetic anhydride, 20 equiv of urea·H_2O_2, and 15 equiv of Na_2HPO_4 in CH_2Cl_2), in situ generated trifluoroperacetic acid attacked C–C double bond from the α face of the molecule through hydrogen bonding between peracid and acetamide group to afford α epoxide (e.g., **8**, **12**, and **13**). On the other hand, catalytically generated RuO_4 attacked the C–C double bond from sterically less congested β face to afford β-*cis* diol. Diol **44** was converted to pentylidene acetal **45** in 56% yield (for two steps) with 5 equiv of 3-pentanone dimethyl acetal and 0.2 equiv of TsOH·H_2O. With the desired acetal in hand, we began to examine the reaction conditions for the reductive opening of this acetal (Table 6).

Several combinations of reductant and acid were examined using **45** as a substrate (entries 1–5). We found that when using 6 equiv of $BH_3·SMe_2$ in the presence of 1.1 equiv of TMSOTf, a reductive opening reaction of the pentylidene acetal proceeded (entry 5). The desired **48** was not obtained but its regioisomer **51** was exclusively obtained in 50% yield, likely because the neighboring acetamide group directed the Lewis acid, which led to activation of the undesired counterpart of an oxygen atom in the acetal moiety.[21]

Although the desired regiochemistry was not achieved, we successfully attained a promising reductive opening reaction that proceeded well. Therefore, we tried to reverse the regioselectivity by modifying the structure of the substrate. Expecting coordination ability and reduced steric bulkiness, we considered ester **46** to be a promising candidate, which was produced from compound **45** in quantitative yield ($Et_3N·3HF$ in EtOH) (Scheme 6). Furthermore, carboxylic acid **47** was also an appealing substrate, because we expected covalent bond formation between the carboxylic acid and Lewis acid to activate the desired counterpart of the oxygen atom. Carboxylic acid **47** was synthesized from compound **45** in 99% yield ($Et_3N·3HF$ in THF/H_2O).

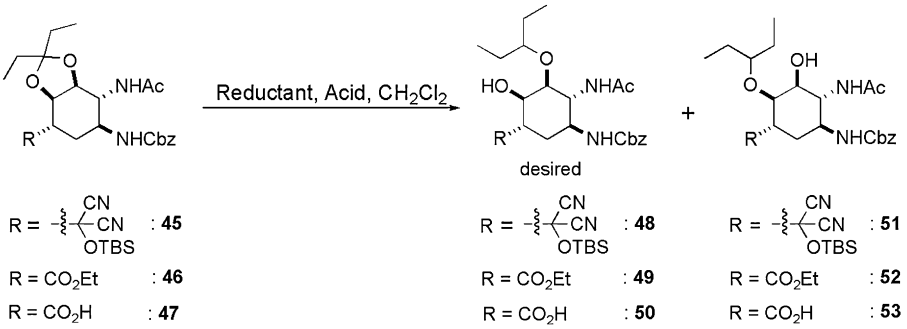
When ester **46** was used as a substrate, the reductive opening reaction proceeded under almost identical conditions (3 equiv of $BH_3·SMe_2$ in the presence of 1.1 equiv of TMSOTf) to afford a reduced product in 60% yield. Again, however, the product obtained was **52**, and the regiochemistry produced was undesirable (Table 6, entry 6). On the other hand, when using carboxylic acid **47** as a substrate, the use of TMSOTf as a Lewis acid afforded a complex reaction mixture (entry 7). Re-examination of a couple of Lewis acids indicated that the reaction proceeded with the use of 1.1 equiv of $TiCl_4$ to afford a reduced product in 40% yield. The obtained product was **53**, which was also an undesired regioisomer (entry 8). The use of $Ti(O^iPr)_2Cl_2$, expecting the formation of a covalent bond between titanium and carboxylic acid, resulted in decomposition of the starting material (entry 9). Therefore, altering the regioselectivity seemed difficult, and we abandoned the reductive opening strategy.

2.6. Identification of a ruthenium-catalyzed dihydroxylation route

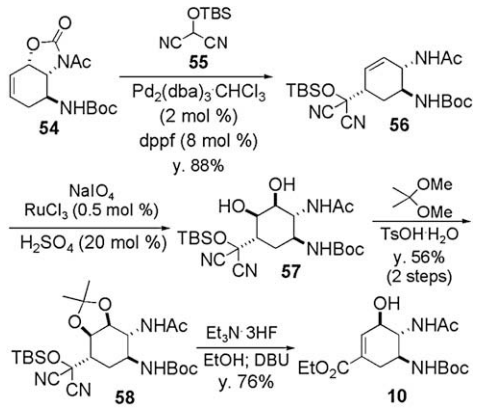
Although the strategy for a reductive opening of pentylidene acetal (hemiaminal) was not fruitful, β-*cis* diol **44** was an appealing intermediate. In our previous work,[4n] epoxidation of olefin **7** proceeded from the α face, which eventually led to the α-alcohol **9** after unveiling the ester-equivalent moiety (Scheme 1). Therefore, inversion of the thus-formed α-alcohol to β-one with a Mitsunobu reaction (from **9** to **10**) was required. In that sense, β-*cis* diol was quite appealing because we could circumvent the Mitsunobu inversion step with this substrate. Thus, we examined the synthesis of β-alcohol **10** from β-*cis* diol.

Cyclic carbamate **54** was reacted with masked acyl anion equivalent **55**[22] using 2 equiv of **55**, 2 mol % of $Pd_2(dba)_3·CHCl_3$, and 8 mol % of dppf to afford olefin **56** in 88% yield (Scheme 7). Compound **56** was converted to β-*cis* diol **57** via a ruthenium-catalyzed dihydroxylation reaction.[20] Intensive examination of the reaction conditions indicated that the dihydroxylation reaction best proceeded with the use of 0.5 mol % of $RuCl_3$, 1.5 equiv of $NaIO_4$, and 0.2 equiv of H_2SO_4 in an EtOAc/CH_3CN/H_2O mixed solvent system at

Table 6
Reductive opening of the pentylidene acetal



Entry	Substrate	Reductant	Acid	Temp (°C)	Results
1	**45**	Dibal-H	—	−78 to rt	No TM
2	**45**	Et_3SiH	TMSOTf	−20 to 60	NR
3	**45**	$BH_3·SMe_2$	$BF_3·OEt_2$	−78 to rt	No TM
4	**45**	$BH_3·SMe_2$	$TiCl_4$	−78 to rt	No TM
5	**45**	$BH_3·SMe_2$	TMSOTf	−20 to rt	**51** (50%)
6	**46**	$BH_3·SMe_2$	TMSOTf	−40 to 0	**52** (60%)
7	**47**	$BH_3·SMe_2$	TMSOTf	−20	No TM
8	**47**	$BH_3·SMe_2$	$TiCl_4$	−20 to rt	**53** (40%)
9	**47**	$BH_3·SMe_2$	$Ti(O^iPr)_2Cl_2$	−20 to rt	Decomp.



Scheme 7. Ruthenium-catalyzed dihydroxylation route to β-alcohol **10**.

4 °C. In the case of substrates with other protective groups (Ac, Piv, Bz, or MOM) instead of a TBS group at the ester-equivalent moiety, the dihydroxylation reaction resulted in a substantially lower yield. Then, β-cis diol **57** was transformed to acetonide **58** under standard conditions (5 equiv of 2,2-dimethoxypropane in the presence of 0.4 equiv of $TsOH \cdot H_2O$ in toluene at 55 °C) in 56% yield in two steps. In the next step, the thus-formed acetonide group functions as a leaving group. We, therefore, tried to produce a couple of compounds with leaving groups other than acetonide group, such as a carbonate group (through a reaction with 1,1′-carbonyldiimidazole: decomp.) and a thiocarbonate group (through a reaction with 1,1′-thiocarbonyldiimidazole: y. 46%), but the formation of acetonide afforded the best results. Acetonide **58** was treated with 1.4 equiv of $Et_3N \cdot 3HF$ in EtOH at room temperature to unmask the ester-equivalent moiety, and successive addition of 7.2 equiv of DBU successfully afforded β-alcohol **10** through β-elimination of acetone in 76% yield. As a result, β-alcohol **10**, which was the intermediate in our previous synthesis of Tamiflu®,[4n] was obtained from cyclic carbamate **54** without the need of a Mitsunobu inversion step.

3. Conclusion

We examined a number of strategies to construct the sterically bulky 3-pentyl ether moiety in Tamiflu® in a more efficient manner, i.e., avoiding Mitsunobu reactions, such as an epoxide opening reaction with 3-pentanol, inversive ether formation from α-alcohol, non-inversive ether formation from β-alcohol, synthesis of aziridine without a Mitsunobu reaction, and reductive opening of pentylidene acetal (hemiaminal). These synthetic studies eventually led to the identification of a ruthenium-catalyzed dihydroxylation route (Scheme 7). Although this established process still requires a single Mitsunobu reaction for the synthesis of aziridine, the second Mitsunobu inversion step was circumvented. Additionally, the ruthenium-catalyzed dihydroxylation reaction requires only 0.5 mol % of ruthenium catalyst, compared to the rather high amounts of reagents (10 equiv of TFAA and 20 equiv of $urea \cdot H_2O_2$) required for the epoxidation in the previously developed synthetic route.[4n] The use of explosive trifluoroperacetic acid, which is generated in situ, was also avoided. Thus, the newly established synthetic process is considered advantageous.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 or ECX500 spectrometer, operating at 500 MHz for ^1H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts were reported in parts per million on the δ scale relative to residual $CHCl_3$ (δ=7.24 for ^1H NMR and δ=77.0 for ^{13}C NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI-MS spectra were measured on a Waters-ZQ4000. FAB mass spectra were measured on a JEOL JMS-BU20 GCmate or a JEOL JMS-700V. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Reactions were performed in dry solvents under an argon atmosphere, unless otherwise stated. Dry solvents of THF and dichloromethane (CH_2Cl_2) were purchased from KANTO CHEMICAL Co., Inc. 3-Pentanol was distilled from CaH_2 before use. Other reagents were used as received from commercial sources, unless otherwise stated.

4.2. *tert*-Butyl (1*S*,2*S*,5*S*)-2-acetamido-5-((*tert*-butyldimethylsilyloxy)dicyanomethyl)cyclohex-3-enylcarbamate (56)

At room temperature, **55** (24.0 μl, 0.135 mmol) was added to a stirred solution of **54** (20.0 mg, 0.0675 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (1.4 mg, 0.00135 mmol), and dppf (3.0 mg, 0.00541 mmol) in toluene (2.00 ml), and the resulting solution was stirred at 60 °C for 60 min. After cooling the reaction mixture to room temperature, the mixture was filtered through an SiO_2 pad, and the filtrate was concentrated to afford crude **56**, which was purified with preparative TLC (Hexane/AcOEt=1/1) to afford **56** (26.6 mg, 0.0592 mmol, 88% yield) as a pale yellow amorphous. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.31–5.84 (m, 3H), 4.57 (d, J=7.9 Hz, 1H), 4.35 (m, 1H), 3.97 (m, 1H), 2.94 (m, 1H), 2.15–1.89 (m, 5H), 1.42 (s, 9H), 0.93 (s, 9H), 0.38 (s, 3H), 0.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 155.7, 134.2, 123.5, 114.9, 114.6, 80.1, 67.0, 51.0, 47.1, 45.2, 28.4, 27.2, 25.4, 23.4, 18.3, −4.5, −4.5; IR (neat, cm^{-1}) 3299, 2957, 2932, 2860, 2242, 1698, 1659; ESI-MS: m/z 471.3 $[M+Na]^+$; FAB-HRMS: m/z calcd for $C_{22}H_{36}CsN_4O_4Si$ $[M+Cs]^+$: 581.1555, found: 581.1564. $[\alpha]_D^{25}$ −10.1 (c 1.15, $CHCl_3$).

4.3. *tert*-Butyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2-acetamido-5-((*tert*-butyldimethylsilyloxy)dicyanomethyl)-3,4-dihydroxycyclohexylcarbamate (57)

A 1 M H_2SO_4 aqueous solution (22.3 μl, 0.0223 mmol) was added to a stirred suspension of $NaIO_4$ (35.8 mg, 0.167 mmol) in H_2O (86 μl). The mixture was cooled down to 4 °C, and 0.1 M $RuCl_3$ (5.6 μl, 0.000557 mmol) aqueous solution was added. The mixture was stirred for 5 min at the same temperature, and AcOEt (341 μl) was added. After stirring for 5 min, CH_3CN (341 μl) was added, and the mixture was stirred for an additional 5 min. Then, **56** (50.0 mg, 0.111 mmol) was added, and the resulting mixture was stirred for 80 min at the same temperature. AcOEt, saturated $NaHCO_3$ aqueous solution, and saturated $Na_2S_2O_3$ solution were added at the same temperature, and the mixture was stirred for 10 min at room temperature. The aqueous layer was extracted with AcOEt three times, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford crude **57** (63.4 mg) as a pale yellow film, which was used for the next reaction without further purification.

4.4. *tert*-Butyl (3a*S*,4*R*,5*S*,7*S*,7a*R*)-4-acetamido-7-((*tert*-butyldimethylsilyloxy)dicyanomethyl)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-5-ylcarbamate (58)

2,2-Dimethoxypropane (58.3 μl, 0.474 mmol) and $TsOH \cdot H_2O$ (7.2 mg, 0.0379 mmol) were added to a stirred solution of crude **57** (63.4 mg) in toluene (474 μl) at room temperature, and the resulting mixture was stirred for 30 min at 50 °C. After cooling the mixture to room temperature, AcOEt and saturated $NaHCO_3$ aqueous solution were added. The aqueous layer was extracted with AcOEt three times,

and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford crude **58** (57.1 mg), which was purified with silica gel column chromatography (SiO_2=2.5 g, hexane/AcOEt=1/1 to 1/2) to afford **58** (32.8 mg, 0.0627 mmol, 56% yield for two steps) as a colorless film. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (d, J=8.1 Hz, 1H), 5.13 (d, J=8.1 Hz, 1H), 4.29 (dd, J=7.4, 5.8 Hz, 1H), 4.12–4.05 (m, 2H), 3.70 (m, 1H), 2.60 (m, 1H), 2.02–1.90 (m, 5H), 1.50 (s, 3H), 1.39 (s, 9H), 1.33 (s, 3H), 0.91 (s, 9H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 156.0, 114.6, 114.3, 110.7, 80.1, 77.4, 73.2, 65.5, 52.8, 48.2, 46.1, 28.4, 27.8, 27.6, 25.7, 25.4, 23.5, 18.3, −4.5, −4.5; IR (neat, cm^{-1}) 3302, 2933, 2860, 2362, 2242, 1696, 1662; ESI-MS: m/z 545.2 $[M+Na]^+$; FAB-HRMS: m/z calcd for $C_{25}H_{42}CsN_4O_6Si$ $[M+Cs]^+$: 655.1923, found: 655.1943. $[\alpha]_D^{23}$ +7.2 (c 1.00, $CHCl_3$).

4.5. (3*R*,4*R*,5*S*)-Ethyl 4-acetamido-5-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-1-enecarboxylate (10)

A 0.67 M solution of 3HF·NEt_3 in EtOH (112 μl, 0.0750 mmol) was added to a stirred solution of **58** (28.1 mg, 0.0538 mmol) in EtOH (438 μl) at room temperature, and the resulting solution was stirred for 10 min at the same temperature. DBU (57.8 μl, 0.387 mmol) was then added at room temperature, and the resulting solution was stirred for an additional 36 h at the same temperature. AcOEt and saturated NH_4Cl aqueous solution were added, and the mixture was stirred for 10 min at the same temperature. The aqueous layer was extracted with AcOEt three times, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford crude **10** (17.9 mg), which was purified with silica gel column chromatography (SiO_2=0.40 g, hexane/AcOEt=1/4 to AcOEt) to afford **10** (14.0 mg, 0.0409 mmol, 76% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J=5.5 Hz, 1H), 6.78 (m, 1H), 4.98 (m, 1H), 4.83 (d, J=7.9 Hz, 1H), 4.30–4.26 (m, 1H), 4.21–4.13 (m, 2H), 3.85–3.77 (m, 1H), 3.74–3.66 (m, 1H), 2.84–2.76 (m, 1H), 2.20–2.12 (m, 1H), 1.99 (s, 3H), 1.44 (s, 9H), 1.26 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8, 166.0, 157.8, 139.2, 127.8, 81.1, 73.8, 61.2, 60.8, 48.2, 31.0, 28.4, 23.2, 14.3; IR (neat, cm^{-1}) 3330, 2979, 2933, 1717, 1678; ESI-MS: m/z 365.4 $[M+Na]^+$; FAB-HRMS: m/z calcd for $C_{16}H_{27}N_2O_6$ $[M+H]^+$: 343.1864, found: 343.1877. $[\alpha]_D^{28}$ −11.0 (c 0.91, $CHCl_3$).

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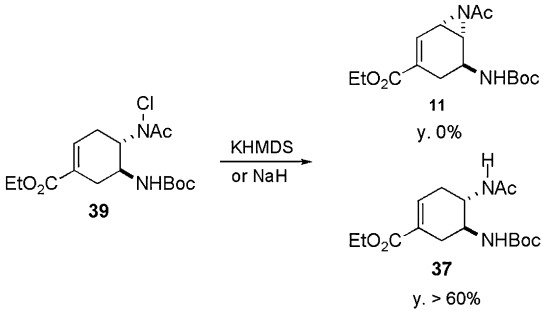

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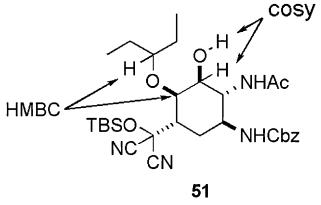

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