VIP Domino Reactions

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One-Pot High-Yielding Synthesis of the DPP4-Selective Inhibitor ABT-341 by a Four-Component Coupling Mediated by a Diphenylprolinol Silyl Ether**

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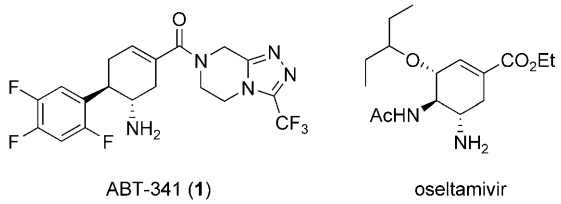
In a "one-pot" reaction, several transformations are carried out to form several bonds in a single flask.[1] Such reactions remove the need for several purification steps, minimize the generation of chemical waste, and save time; thus, they can be viewed as "green" processes. However, there are several challenges to be overcome in a one-pot reaction: 1) There are reactions that are not suitable for a one-pot reaction. The reaction has to be performed in the presence of the products generated in the previous reactions. When A reacts with B to generate C, along with D, the next reaction has to be carried out in the presence of D, which might cause a problem. In the Horner–Wadsworth–Emmons reaction, for example, a phosphoric acid derivative would be generated in an equimolar amount as a side product. 2) As the number of transformations increases, the amount of other compounds present increases. Furthermore, each transformation has to proceed in high yield. 3) There is a limitation in terms of solvent usage. When the best solvents for successive reactions are different, a solvent with a high boiling point cannot be used for the earlier reaction because of the difficulty of its removal under reduced pressure. 4) The reagents that can be employed are limited. If a reactive reagent remains, it might influence the subsequent reaction. The exact stoichiometric amount of the reagent has to be used, or a low-boiling reagent has to be employed, in which case the excess reagent can be removed under reduced pressure. Thus, there are several limitations in a one-pot reaction, and a one-pot reaction is not a simple connection of each optimized reaction.

Dipeptidyl peptidase IV (DPP4, also known as CD26), a 110 kDa serine protease that is ubiquitously distributed in the body, deactivates glucose-regulating hormones, such as GLP-1 and GIP. Thus, DPP4 inhibition has become a useful therapy for type 2 diabetes.[2] ((4*R*,5*S*)-5-Amino-4-(2,4,5-trifluorophenyl)cyclohex-1-enyl)-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8*H*)-yl)methanone (ABT-341 (**1**)) is a highly potent, selective, and orally bioavailable DPP4 inhibitor developed by Abbott Laboratories.[3] Structurally, it possesses an amide part and, on the other side of the carbonyl group, a cyclohexene moiety with a trifluorophenyl and an amino forming two contiguous stereogenic centers. Chiral ABT-341 (**1**) has been synthesized in 11 steps;[3] the key chiral disubstituted methyl cyclohexenecarboxylate was prepared by separation of the enantiomers by preparative HPLC on a chiral phase. Thus, an efficient enantioselective synthesis of ABT-341 (**1**) would be highly desirable.

Our strategy for the synthesis of ABT-341 (**1**) began with the construction of a disubstituted cyclohexenecarboxylate with the correct absolute and relative configurations. The rest of the reactions were transformations of the functional groups and amide-bond formation. Recently, we completed the synthesis of (−)-oseltamivir through two one-pot reactions,[4] which also involved a cyclohexenecarboxylate as a key structure (Scheme 1). Although the synthetic approach to ABT-341 (**1**) was similar to that used for our synthesis of (−)-oseltamivir, the synthesis of ABT-341 (**1**) through a one-pot reaction is more challenging for several reasons. Although a chiral trisubstituted cyclohexene was prepared in the first one-pot reaction in the synthesis of (−)-oseltamivir, not only the preparation of the chiral cyclohexene but also further transformations, such as the formation of the amide bond and functional-group manipulations, have to be performed in one flask in the case of ABT-341 (**1**). That is, after the construction of the chiral cyclohexene framework, several transformations have to be carried out in the same flask in the presence of several products, such as $(EtO)_2P(O)OH$. Control of the relative and absolute configurations at C4 and C5 of the cyclohexene ring is another key issue.



ABT-341 (**1**) oseltamivir

Scheme 1. Structures of ABT-341 (**1**) and oseltamivir.

The one-pot reaction to form ABT-341 (**1**) from four components is summarized in Scheme 2. Thus, an initial enantioselective Michael reaction of acetaldehyde (**3**) and nitroalkene **2** in the presence of the diphenylprolinol silyl ether organocatalyst **4**,[5,6] followed by the successive addition of vinyl phosphonate **5**, trifluoroacetic acid (TFA), amine **6**

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[**] DPPA = dipeptidyl peptidase IV.

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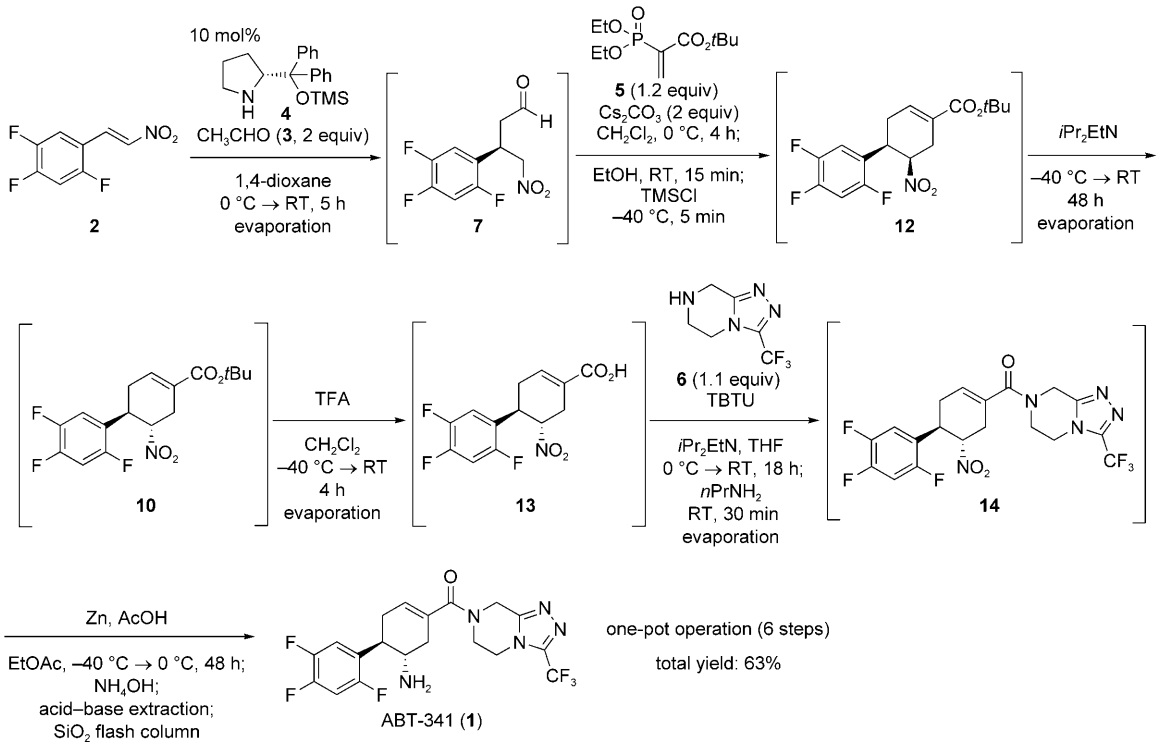
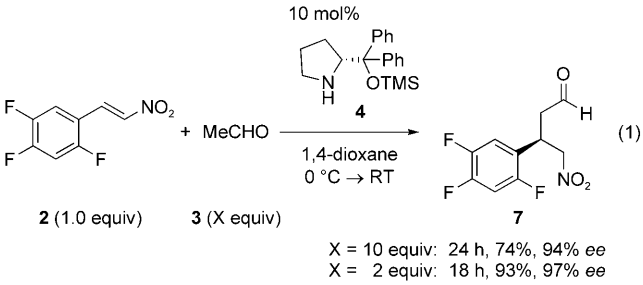


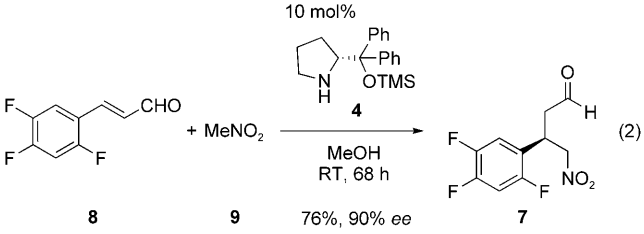
Scheme 2. One-pot reaction for the synthesis of ABT-341 (**1**).

with a coupling reagent, and a reducing agent, provided ABT-341 (**1**) in 63% yield over six steps in a highly diastereoselective and enantioselective manner.

The first step in the one-pot reaction is the Michael reaction of acetaldehyde with a nitroalkene under the catalysis of a diphenylprolinol silyl ether developed independently by our research group[7] and List and co-workers.[8] Our reported procedure with 10 equivalents of acetaldehyde gave the product in good yield (74%) with excellent enantioselectivity (94% *ee*); however, it is not suitable for a one-pot reaction. Because this reaction is the first step, the yield should be quantitative, and the generation of by-products should be avoided as much as possible. Otherwise, by-products will accumulate and interrupt subsequent reactions. We optimized the reaction conditions and found that the use of 2 equivalents of acetaldehyde was the key to improving the yield to 93%; the reaction had to be quenched at this point. The observed enantioselectivity was excellent (97% *ee*). Excess acetaldehyde promotes the self-aldol reaction, and the crotonaldehyde thus generated reacts further with **7** to decrease the yield of **7**. These optimized conditions are suitable for the first step of the one-pot reaction, not only because the yield and selectivity are excellent, but also because the small excess of reactive acetaldehyde can be removed readily under reduced pressure.

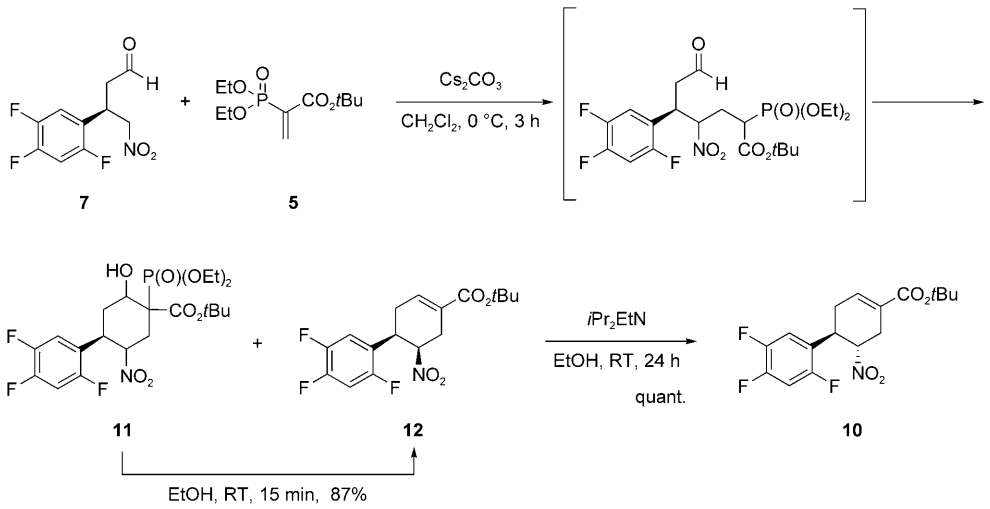
Compound **7** was prepared not only by the Michael reaction of acetaldehyde and nitroalkene **2** [Eq. (1); TMS = trimethylsilyl], but also by the Michael reaction of nitromethane and the α,β-unsaturated aldehyde **8** [Eq. (2)], which was also developed by our research group.[9,10] When **8** and nitromethane (**9**) were treated with the diphenylprolinol silyl ether **4**, the Michael product **7** was obtained in good yield with excellent enantioselectivity, even though the reaction was not optimized.





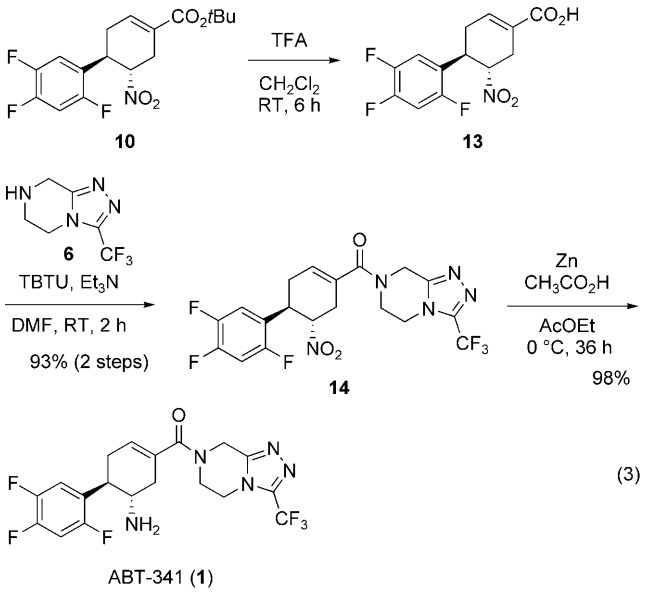
The next step, which involves several reactions, is the preparation of the *trans*-substituted cyclohexenecarboxylate **10** (Scheme 3). When the isolated Michael adduct **7** and vinyl phosphonate **5** were treated with Cs_2CO_3 in CH_2Cl_2 at 0 °C, a Michael reaction of **7** and **5** was followed by an intramolecular Horner–Wadsworth–Emmons reaction to afford two prod-

ucts: the phosphonate ester derivative **11** and the *cis*-substituted cyclohexene **12**. The addition of EtOH to the reaction mixture at room temperature promoted the retro-aldol reaction and the subsequent intramolecular Horner–Wadsworth–Emmons reaction from **11** to **12**. In this way, the *cis*-substituted cyclohexene **12** was obtained in 87% yield. Isomerization of the *cis* isomer **12** to the *trans* isomer **10** did not occur in the presence of Cs_2CO_3. After several experiments, it was found that iPr$_2$EtN promoted complete isomerization at room temperature in 24 h to afford the *trans* isomer **10** quantitatively.



Scheme 3. Synthesis of **10** from **7**.

The transformation of the isolated *tert*-butyl ester **10** into ABT-341 (**1**) was investigated in separate reactions [Eq. (3)]. Carboxylic acid **13**, which was obtained when the isolated ester **10** was treated with TFA, was coupled with amine **6** in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and Et$_3$N in *N*,*N*-dimethylformamide (DMF)[3] to afford amide **14** in 93% yield over two steps. The nitro group was successfully reduced to an amine by treatment of the isolated compound **14** with Zn and CH_3CO_2H in AcOEt at 0 °C to afford ABT-341 (**1**) in 98% yield. In this reaction, the temperature is the key. ABT-341 (**1**) was obtained in low yield when the reaction was performed at room temperature because of overreduction of the triazole moiety.



(3)

Since the separate reactions with isolated compounds proceeded well, we investigated the one-pot reaction (Scheme 2). After the first asymmetric Michael reaction, excess acetaldehyde was removed under reduced pressure, and the next domino[11] intramolecular Horner–Wadsworth–Emmons reaction, a retro-aldol reaction, took place. The reaction to form the *cis*-substituted cyclohexene **12** was successful. Although the isomerization proceeded well for isolated **12**, it did not work with the crude mixture because of the presence of Cs_2CO_3. As Cs_2CO_3 cannot be removed under reduced pressure, we investigated its inactivation. Its conversion into insoluble and neutral CsCl was examined, and the reagent and temperature were found to be crucial. The Nef reaction to afford the cyclohexanone was a major side reaction when 4N HCl was used in 1,4-dioxane at 0 °C. However, a reaction at −40 °C with TMSCl in the presence of EtOH gave a good result. Thus, the reaction of **5** and **7** in the presence of Cs_2CO_3 and the subsequent addition of EtOH afforded **12**. We then added TMSCl at −40 °C, whereupon insoluble CsCl was generated, and the addition of iPr$_2$EtN promoted the isomerization to afford the *trans* isomer **10**. When we isolated **10** at this stage, the yield for the two steps from **7** was 92%.

After removal of the volatile materials from the crude product **10**, the addition of CF_3CO_2H and CH_2Cl_2 transformed the *tert*-butyl ester into the corresponding carboxylic acid **13**. The following coupling reaction of carboxylic acid **13** and amine **6** was expected to be one of the crucial steps. DMF was employed in the reaction in Equation (3), but it cannot be removed under reduced pressure and is not a preferred solvent for the subsequent reduction of the nitro group. Moreover, an equal amount of $(EtO)_2P(O)OH$, which was generated in the Horner–Wadsworth–Emmons reaction, might act as a nucleophile with a coupling reagent. We screened a range of reaction conditions and found that THF can be used as a solvent and that the temperature is important in this coupling reaction. When the reaction was performed initially at 0 °C, and the temperature was then increased to

room temperature, the amide bond formed selectively without formation of the phosphonamide derivative.

The final reaction was the reduction of the nitro group to an amine. The reaction proceeded as well as with the isolated intermediate with Zn and AcOH in AcOEt to provide ABT-341 (**1**). ABT-341 (**1**) was obtained in 63% overall yield from nitroalkene **2** after purification by acid–base extraction followed by column chromatography.

In summary, an efficient, enantioselective total synthesis of ABT-341 (**1**) was completed in a one-pot reaction. This approach demonstrates the power of asymmetric reactions catalyzed by organocatalysts, and especially the diphenylprolinol silyl ether **4**. The present synthesis has several notable features: 1) the total yield is excellent (63% from nitroalkene **2**); 2) the synthesis consists of six reactions, which were conducted in a single flask; 3) four components were combined to afford ABT-341, whereby all of these four components were employed in nearly equimolar amounts, except for inexpensive acetaldehyde (2 equiv); 4) a disubstituted chiral cyclohexene carboxylate with the correct configuration was synthesized from three starting materials by successive reactions, including an asymmetric Michael reaction mediated by a diphenylprolinol silyl ether, as developed by our research group, a domino Michael reaction/Horner–Wadsworth–Emmons reaction combined with a retro-aldol reaction, and a base-catalyzed isomerization; 5) amide-bond formation and functional-group manipulations can also be performed in the same single flask by the appropriate choice of reaction conditions, under which previous reagents and products do not interfere with the desired reaction.

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