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A short synthetic pathway via three-component coupling reaction to tamiphosphor possessing anti-influenza activity

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ABSTRACT

Three-component coupling reaction of (pent-3-oxy)acetaldehyde, (*Z*)-*N*-(2-nitrovinyl)acetamide, and tetraethyl 1,1-diylbis(phosphonate) is performed in a one-pot operation, followed by reduction of the nitro group and hydrolysis of the phosphonate ester, to afford 8.7% overall yield of tamiphosphor as a potent neuraminidase inhibitor with IC_{50} and EC_{50} values of 2.5 and 31.5 nM against wild-type H1N1 influenza virus. The tamiphosphor (5*R*)-epimer is a less active anti-influenza agent with IC_{50} and EC_{50} values of 39 and 117 nM.

1. Introduction

Seasonal influenza is a contagious respiratory illness, and new types of influenza viruses may emerge to cause global infections. The threat of influenza is even more serious due to the cross-species transmission of avian influenza viruses, such as H5N1 and H7N9, to humans in the recent years. Influenza neuraminidase (NA) is a viral surface glycoprotein that is responsible for releasing progeny influenza viruses by cleaving the linkage between the viral hemagglutinin and the sialo-receptor on the host cell.[1,2] Inhibition of NA has been utilized as a very effective strategy for development of anti-influenza drugs.[3] Tamiflu™, as the phosphate salt of oseltamivir (OS, **1a**),[4–7] is an orally available anti-influenza drug, which is hydrolyzed by endogenous esterases to generate the active ingredient oseltamivir carboxylic acid (OC, **1b**) as a potent NA inhibitor.[6,8–11] However, tamiflu-resistant influenza viruses such as the clinically relevant H275Y strain of H1N1 virus have emerged over past years.[12–16] Thus, many scientists have exerted great effort to develop new anti-influenza drugs that are also active to H275Y virus.[17–19]

We have previously explored tamiphosphor (TP, **2**),[17] a phosphonate congener of OC, as a potent NA inhibitor against various avian and human influenza viruses. Strecher's and our research teams have further demonstrated that the TP monoesters also possess remarkable anti-influenza activities based on the enzymatic, cell, and animal assays.[18,20–23] Moreover, the guanidine analogs of TP and its monoesters are potent NA inhibitors against H275Y virus with the IC_{50} values in nanomolar range.[17,18]

As delineated in Fig. 1, only a few methods have been utilized in the syntheses of TP and its derivatives. In the first synthesis of TP (path A),[17] D-xylose (**3**) is utilized as a starting material. After transformation of the 3β-OH group to 3α-NH_2 group, a diphosphorylmethyl substituent is implanted to the C-5 position for the subsequent intramolecular Wittig reaction (in the Horner–Wadsworth–Emmons (HWE) variant)[24,25] to establish the core structure of polysubstituted cyclohexene ring. The pent-3-oxy and amino substituents are then introduced to furnish ~10% yield of the final product of TP in overall 19 synthetic steps. The synthesis of TP was also achieved by using *N*-acetyl-D-glucosamine as another chiral-pool molecule with a preset acetamido group in the desired absolute configuration.[26] In path B,[20,27,28] the *N*-Boc-protected OC (**1c**) is subjected to photochemical Hunsdiecker–Barton halodecarboxylation.[29] A palladium-catalyzed phosphonylation of the halocyclohexene product **6** with diethyl phosphite is carried out to provide TP, after concomitant removal of the ethyl and Boc groups by treatment with Me_3SiBr. The pivotal intermediate **6** can also be prepared from (1*S*,2*S*)-3-bromocyclohex-3,5-diene-1,2-diol (**7**), a fermentation product of bromobenzene,[30,31] by regio- and stereoselective introduction of pent-3-oxy and acetamide groups along with proper manipulation of the desired functional groups (path C).[27] Though the synthesis via paths B and C can provide TP in fewer

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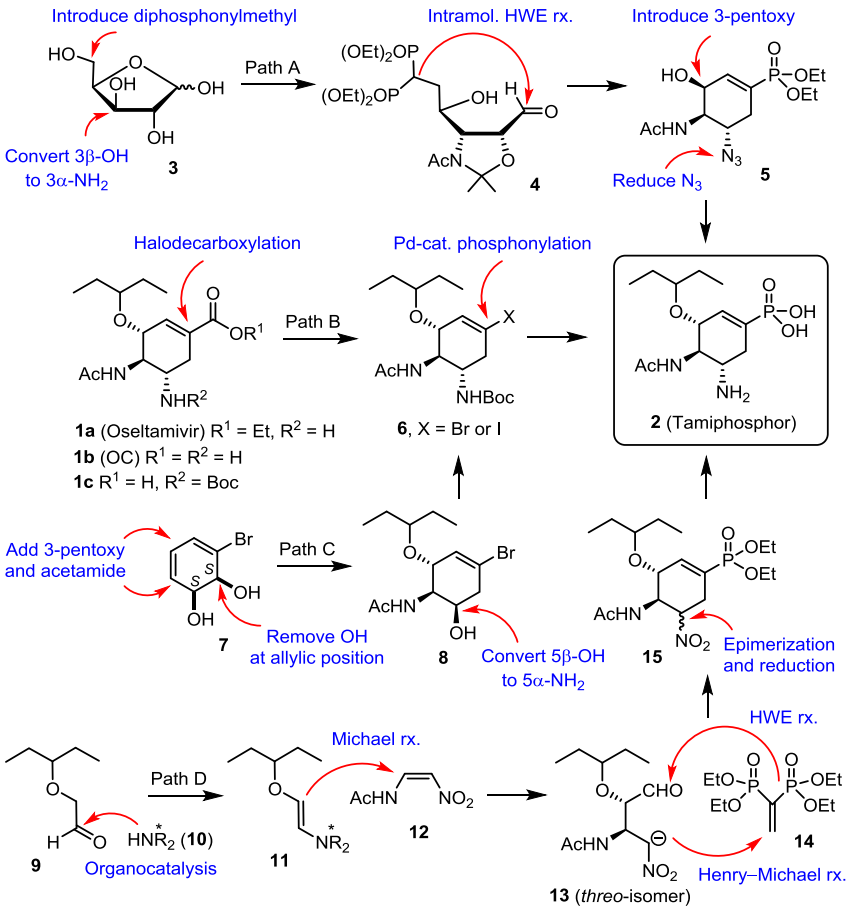

Fig. 1. Methods for the synthesis of tamiphosphor (**2**). (Path A) Carbohydrate molecule, e.g., D-xylose (**3**), is utilized as a chiral pool to construct the core structure of polysubstituted cyclohexene ring via an intramolecular Horner–Wadsworth–Emmons reaction. (Path B) The carboxylic acid in the oseltamivir derivative **1c** undergoes a photochemical Hunsdieker–Barton halodecarboxylation to give a halogen compound **6**, which is converted to the phosphonate ester via a palladium-catalyzed coupling reaction. (Path C) The fermentation product **7** of bromobenzene is sequentially processed to the common intermediate **6**. (Path D) In this study, a one-pot three-component coupling reaction of 2-(pent-3-oxy)acetaldehyde (**9**), (*Z*)-*N*-(2-nitrovinyl)acetamide (**12**), and 1,1-diphosphonylethene (**14**) is devised to construct the polysubstituted cyclohexene-1-phosphonate (**15**) for elaboration to tamiphosphor.

steps, some problems such as the photochemical of **1c** and microbial preparation of chiral diol **7** in large scales remain to be solved.

To develop TP and its derivatives for the therapeutic applications, it is needed to devise practical and large-scale synthetic methods. Inspired by the expedient synthesis of oseltamivir that uses one-pot multiple-component coupling reactions to construct the key intermediate of polysubstituted cyclohexene-1-carboxylate,[32–36] we aimed to investigate whether such straightforward methodology could be applied to synthesize TP? Path D shows our synthetic design to prepare polysubstituted cyclohexene-1-phosphonate **15** in one-pot operation by a sequence of reactions comprising an organocatalytic condensation of 2-(pent-3-oxy)acetaldehyde (**9**) with (*Z*)-*N*-(2-nitrovinyl)acetamide (**12**), a Henry–Michael reaction to trap the anion of the nitro intermediate **13** with tetraethyl ethene-1,1-diylbis(phosphonate) (**14**), and an intramolecular HWE reaction. In comparison with ethyl 2-(diethoxyphosphoryl)acrylate, $H_2C{=}C(CO_2Et)PO(OEt)_2$, used in oseltamivir synthesis,[32–36] 1,1-diphosphorylethene **14** would be a less reactive electrophile in Michael reaction because the sp^2-hybridized C–C double bond is not fully conjugated with the phosphoryl groups in the tetrahedral configuration.

2. Results and discussion

We first validated the asymmetric Michael reaction of aldehyde **9** with nitroalkene **12** using (*S*)-diphenylprolinol trimethylsilyl ether (**11a**) as the chiral organocatalyst to furnish the addition product **13**, predominantly in the *threo*-isomer (Scheme 1).[35] The *threo*-isomer showed the CHO group at δ_H 9.61, whereas the *erythro* isomer displayed the aldehyde proton at δ_H 9.57. We then carried on the reaction of **13** (as a mixture of *threo* and *erythro* isomers) with bisphosphorylethene **14** in the presence of Cs_2CO_3. The ^1H NMR spectrum of the crude product showed a vinyl proton (H-2) at δ_H 6.60 with a large coupling constant (J_{H-P}=21.6 Hz),[17] indicating that cyclohexene-1-phosphonate **15** was formed by tandem Henry–Michael reaction and intramolecular HWE reaction. The elimination species of phosphoric acid diethyl ester, $(OEt)_2P(O)(OH)$ generated from HWE reaction, exhibited the phosphorus(V) signal at δ_P=0 in the ^{31}P NMR spectrum. However, an appreciable amount of the side product **16**, showing a sodiated molecular ion $[M+Na]^+$ at *m*/*z* 729.2616, was also observed. Compound **16** was presumably derived from a second Henry–Michael reaction of **14** with **15**.[33] The NOESY correlation between H-4 (at δ_H 4.58) and the methylene protons (H-1′ at δ_H 2.69) of C5 substituent was consistent with the attack of **14** at the **15**-anion from the less hindered face. There are three phosphorus signals occurring at δ_P 17.2, 23.0, and 23.4 in compound **16**. The characteristic vinyl proton (H-2) appeared at δ_H 6.60 (J_{H-P}=22 Hz), and the methine proton (H-2′) adjacent to the phosphoryl groups exhibited at δ_H 2.57 with a large H–P coupling constant of 25.4 Hz. The NOESY correlation between H-3 (at δ_H 3.84) and NH (at δ_H 6.31) of C4 acetamide group revealed the trans-relationship at C3 and C4.

Our attempts to reduce the formation of **16**, e.g., by conducting the reaction at low temperature (−30 °C) or using less amounts of