Synthetic Methods

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Catalytic Asymmetric *anti*-Selective Nitroaldol Reaction En Route to Zanamivir**

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An influenza virus infection of the respiratory system produces severe coldlike symptoms. Local and global epidemics occur annually and the possibility of an unexpected pandemic is a major health concern worldwide.[1] Neuraminidase, a surface glycoprotein of the influenza virus membrane, plays a crucial role in budding to target new host cells, and its inhibitors, for example, zanamivir (**1**) and oseltamivir (**2**), are widely prescribed for effective treatment and prophylaxis of influenza (Figure 1).[2] Zanamivir (**1**) was first identified as a potent neuraminidase inhibitor in 1989 based

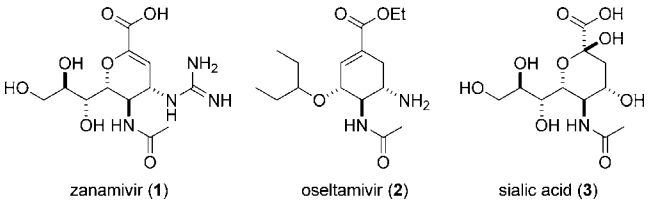
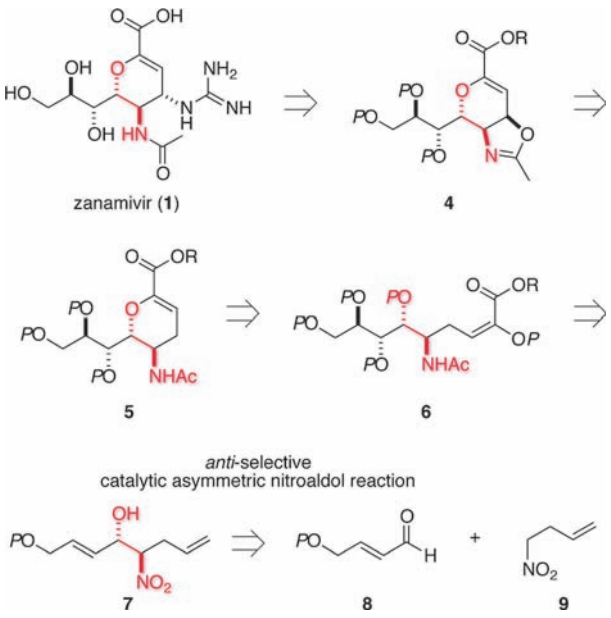


Figure 1. Structures of zanamivir (**1**), oseltamivir (**2**), and sialic acid (**3**).

on the rational design from sialic acid (*N*-acetyl neuraminic acid; **3**) and has been marketed since 1999.[3,4] Although **1** is administered only by intranasal inhalation and has less potential for clinical treatment than orally active **2**, its efficacy toward the oseltamivir-resistant H274T (H1N1) mutant strain particularly highlights the clinical importance of **1**.[1c,5] A number of analogues of **1** has been derived from **3** and some of them exhibit more potency than **1** against the wild-type and mutant influenza strains.[6] In this context, attempts to identify an orally active analogue of **1** and develop a new synthetic strategy to produce analogues against forthcoming zanamivir-resistant mutants[7] are crucially important for confronting potential influenza pandemics.

Zanamivir (**1**) is a densely functionalized dihydropyran entity bearing five consecutive stereogenic centers and a synthetic derivative of sialic acid (**3**). As a result of its molecular complexity and structural similarity to **3**, all the synthetic approaches in the literature are semisyntheses from natural chiral building blocks. Since the original report, continuing efforts toward developing a synthetic approach including analogues of **1** from **3** advanced the synthetic efficiency,[4,6,8] but the inherent problems of limited structural variation in derivatization and cost of **3** still remain.[9] Yao et al. reported an alternative approach from inexpensive D-gluconolactone,[10] but, a de novo enantioselective synthesis of **1** has not been reported. A recent calculation study indicated that H1N1 mutant strains other than H274T could be resistant to **1** as a result of the loss of polar interactions,[11] thus highlighting the importance of developing afresh a synthetic route to produce a wide variety of analogues.[12,13] Herein, we report the enantioselective synthesis of **1** through an *anti*-selective catalytic asymmetric nitroaldol (Henry) reaction.

The retrosynthetic analysis is outlined in Scheme 1. A vicinal *anti* amino alcohol moiety of **1** can be constructed by an *anti*-selective catalytic asymmetric nitroaldol reaction. The requisite guanidine functionality can be installed through the known intermediate oxazoline **4** after constructing the



Scheme 1. Retrosynthetic analysis of zanamivir (**1**). *P* = protecting group.

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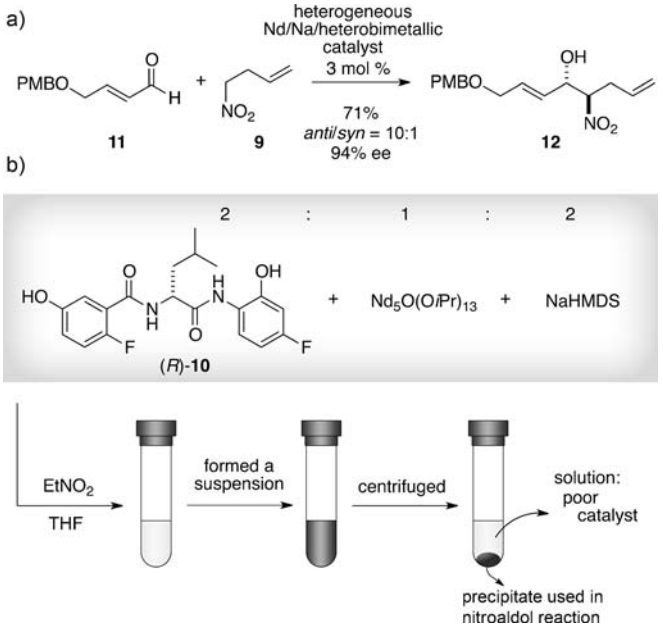
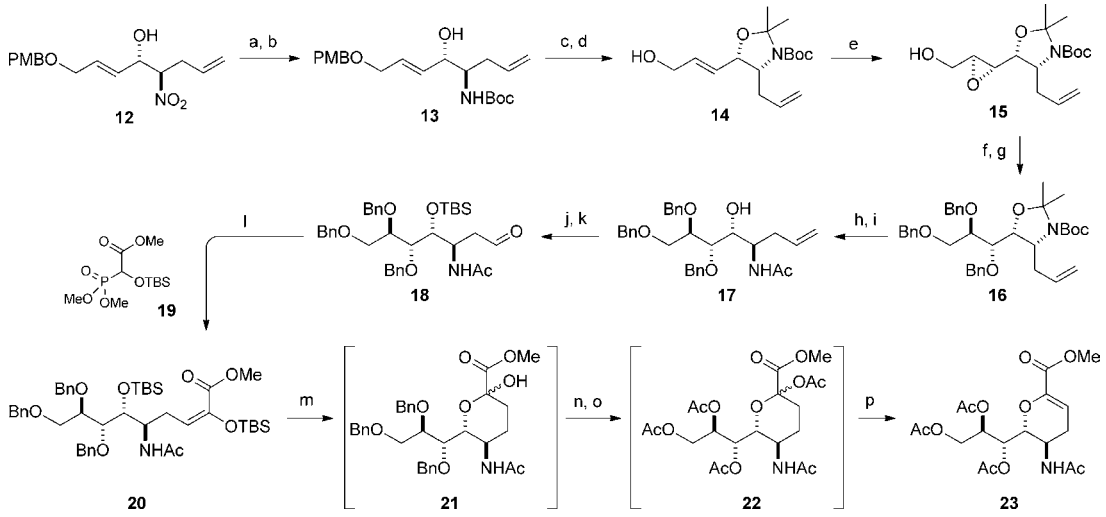
dihydropyran core **5**.[4d] The dihydropyran skeleton of **5** can be furnished by a ketalization/elimination sequence of ε-hydroxy-α-ketoester produced from **6**. Functional groups on **6** can be installed on the unsaturated *anti* vicinal nitroalkanol **7**, which is a nitroaldol product from enal **8** and 4-nitro-1-butene (**9**).[14]

The enantioselective synthesis of **1** commenced with an *anti*-selective catalytic asymmetric nitroaldol reaction[15–18] promoted by the Nd/Na heterobimetallic complex (Scheme 2a). We recently disclosed that the amide-based ligand (*R*)-**10** specifically designed for constructing a heterobimetallic complex allowed us to perform a highly *anti*- and enantioselective nitroaldol reaction with broad substrate generality.[16d,19] The heterobimetallic complex was prepared by mixing (*R*)-**10**, $Nd_5O(OiPr)_{13}$,[20] and NaHMDS in a 2:1:2 ratio in the presence of nitroethane to afford a white suspension (Scheme 2b), which was centrifuged to isolate the precipitate as an active catalyst. Nitroethane was essential for forming the suspension through the self-assembly of Nd and Na cations with the bis(phenol) and diamide platforms of the ligand (*R*)-**10** at the catalyst preparation stage, thus allowing isolation/purification of the active catalyst species. The whole suspension of (*R*)-**10**/Nd/Na or the supernatant exhibited inferior catalytic activity and stereoselectivity. Therefore, the isolation of the precipitate was required to exert maximum catalytic performance in this catalytic system.[16d] The isolated precipitate was washed with dry THF in two cycles of a swell/centrifuge/decantation process to remove the inactive catalyst ingredients and nitroethane in solution.[21] About 3 mol% of the thus-formed active Nd/Na heterogeneous catalyst was subjected to the catalytic asymmetric nitroaldol reaction of functionalized enal **11** and 4-nitro-1-butene (**9**) under heterogeneous conditions in THF at −60 °C. The reaction proceeded in a predominantly 1,2-manner,[22,23] thus delivering the vicinal nitroalkanol **12** in 71% yield with an *anti*/*syn* = 10:1 ratio and 94% *ee* (*anti*). The subsequent synthetic route is delineated in Scheme 3. Reduction of the nitro group of **12** with Zn in acidic medium and subsequent Boc protection gave the alcohol **13** (53%; 2 steps).

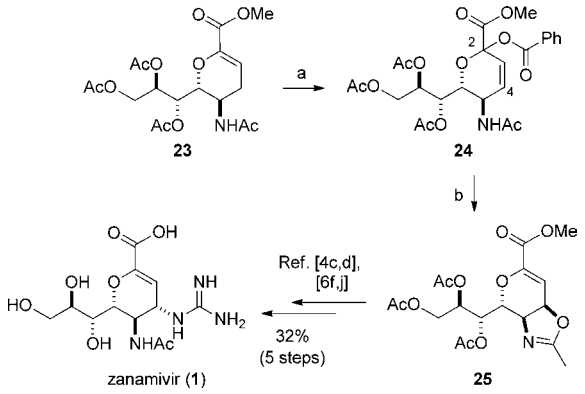


Scheme 2. Catalytic asymmetric nitroaldol reaction promoted by a heterogeneous (*R*)-**10**/Nd/Na heterobimetallic complex.



Scheme 3. Construction of a dihydropyran core. Reagents and conditions: a) Zn (20 equiv), 2 N HCl/MeOH, 0 °C, 1 h; b) Boc_2O (1.0 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 10 h, 53% (2 steps); c) $BF_3{\cdot}OEt_2$ (0.1 equiv), 2,2-dimethoxypropane/acetone (2:5), 0 °C, 1 h, 87%; d) DDQ (1.2 equiv), CH_2Cl_2/H_2O (5:1), 0 °C to RT, 12 h, 85%; e) $Ti(OiPr)_4$ (1.0 equiv), (+)-DET (1.25 equiv), TBHP (2.5 equiv), CH_2Cl_2, −20 °C, 67 h, 95%, d.r. = 3.7:1; f) TBAF aq., MeCN, 50 °C, 91 h, 80%, (2 cycles, 87%); g) NaH (8 equiv), BnBr (5 equiv), DMF, 0 °C, 3 h, 91%; h) 4 N HCl/1,4-dioxane, CH_2Cl_2, 0 °C, 3 h; i) Ac_2O (1.2 equiv), Et_3N (5.5 equiv), EtOAc, 0 °C, 10 min, 84% (2 steps); j) TBSOTf (1.6 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −78 → RT, 30 min, 89%, (oxazoline formation 2%); k) OsO_4 (2 mol%), NMO (2.0 equiv), acetone/H_2O (3:1), 45 °C, 2.5 h, then $NaIO_4$ (2.2 equiv), RT, 2 h, 98%; l) phosphonate **19** (1.5 equiv), LiHMDS (1.05 equiv), THF, −20 °C, 1 h, 96%, *E*/*Z* = 14:1; m) TBAF/AcOH (1:2), 0 °C, 20 min then $BF_3{\cdot}OEt_2$ (2 equiv), CH_3CN, 0 °C, 30 min; n) Pd/C (30 w/w%), MeOH/THF (1:1), RT, under H_2, 3 h; o) Ac_2O (8 equiv), DMAP (0.2 equiv), pyridine, 5.5 h; p) $Ph_3P{\cdot}HBr$ (0.1 equiv), CH_3CN, 55 °C, 5 h, 79% (4 steps). DET = diethyl tartrate, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DMAP = 4-(dimethylamino)pyridine, LiHMDS = lithium hexamethyldisilazide, NMO = *N*-methylmorpholine-*N*-oxide, TBAF = tetrabutylammonium fluoride, TBHP = *tert*-butyl hydroperoxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

The hydroxy group was protected as an acetonide with 2,2-dimethoxypropane and a catalytic amount of $BF_3{\cdot}OEt_2$ (87%), and subsequent removal of the PMB group with DDQ gave the allylic alcohol **14** (85%; 2 steps).[24] Sharpless asymmetric epoxidation using (+)-DET and $Ti(OiPr)_4$ yielded only trace amounts of the corresponding epoxide **15** under catalytic conditions (10 mol%) and 1.0 equivalent of $Ti(OiPr)_4$ was required to attain full conversion with a diastereomeric ratio of 3.7:1 (95%).[25] The use of (−)-DET, however, resulted in the preferential formation of undesired β epoxide. Regioselective ring-opening of the epoxide proceeded with aqueous TBAF to afford the triol with the desired stereochemical orientation (87%),[26] and the triol was then protected with Bn groups by using a conventional method to give **16** (91% diastereomeric ratio 3.4:1). At this stage, the diastereomers could be chromatographically separated. Boc removal and hydrolysis of the oxazolidine were effected by 4N HCl and the resulting amino group was chemoselectively converted into an acetamide to give alcohol **17** (84%; 2 steps). After protection of the hydroxy group with a TBS group (89%), the terminal olefin was transformed into aldehyde **18** by osmium-catalyzed dihydroxylation/oxidative cleavage of a vicinal diol (98%). A Horner–Wadsworth–Emmons reaction with phosphonate **19** delivered the α-siloxy-α,β-unsaturated ester **20** (86%). Removal of the TBS groups with TBAF/AcOH and subsequent treatment with $BF_3{\cdot}OEt_2$ gave rise to tetrahydropyranyl hemiketal **21**.[27] The Bn groups were removed by hydrogenolysis over Pd/C and the resulting tetraol was subjected to Ac_2O/DMAP to afford the tetraacetate **22**, which was converted into the dihydropyran **23** with $PPh_3{\cdot}HBr$ (79%; 4 steps). Installation of a guanidine functionality into the dihydropyran ring was the final task. Dihydropyran **23** was subjected to copper-mediated oxidation conditions with *tert*-butyl perbenzoate (Scheme 4),[28] thus affording the 2-benzoate **24** with the concomitant formation of 4-benzoate,[29] which was converted



Scheme 4. Synthesis of zanamivir (**1**). Reagents and conditions: a) CuBr (2 equiv), BzO_2tBu (4 equiv), CH_2Cl_2, reflux, 3 h; b) H_2SO_4 (1 equiv), Ac_2O/AcOH (1:1), RT, 12 h, 33% (2 steps).

into the known oxazoline **25** by treatment with H_2SO_4/Ac_2O/AcOH at room temperature (33%; 2 steps). NMR data and optical rotation of the synthetic **25** were consistent with those of the reported **25** derived from sialic acid (**3**).[29] Oxazoline **25** was transformed into zanamivir (**1**) by known procedures with slight modifications.[30]

In summary, we describe the enantioselective synthesis of zanamivir (**1**) utilizing an *anti*-selective catalytic asymmetric nitroaldol reaction as the initial C–C bond-forming and chirality introduction step. Based on the fact that the nitroaldol reaction can be performed on a large scale and various aldehydes can be implemented,[16d] scalable synthesis and efficient preparation of analogues bearing different side chains are highly anticipated. Studies toward those aims as well the refinement of the overall synthetic efficiency are underway.

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[22] A trace amount of the 1,4-addition product was observed.
[23] 3 mol% of catalyst based on Nd content was used for catalyst preparation. The actual Nd content in the Nd/Na heterogeneous catalyst was lower than 3 mol%.
[24] Oxazoline formation was accompanied (ca 2%). Reaction at higher temperature (TBSOTf (1.3 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −20 °C to 0 °C, 2 h, 85% yield of **17**) increased the oxazoline formation (ca. 8%).
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[30] See the Supporting Information.

