Asymmetric Synthesis Hot Paper

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Organocatalytic and Scalable Synthesis of the Anti-Influenza Drugs Zanamivir, Laninamivir, and CS-8958**

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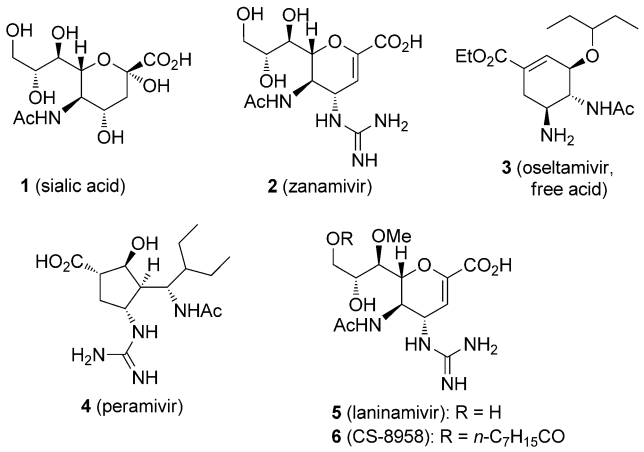
Abstract: *Zanamivir, laninamivir, and CS-8958 are three neuraminidase inhibitors that have been clinically used to combat influenza. We report herein a novel organocatalytic route for preparing these agents. Only 13 steps are needed for the assembly of zanamivir and laninamivir from inexpensive* D*-araboascorbic acid by this synthetic route, which relies heavily on a thiourea-catalyzed enantioselective Michael addition of acetone to tert-butyl (2-nitrovinyl)carbamate and an anti-selective Henry reaction of the resulting Michael adduct with an aldehyde prepared from* D*-araboascorbic acid. The synthetic procedures are scalable, as evident from the preparation of more than 3.5 g of zanamivir.*

Neuraminidase is a validated drug target for therapeutic intervention in influenza.[1] To date, a considerable number of sialic acid analogues that interact with the active sites of this family of enzymes have been discovered as potent neuraminidase inhibitors (Scheme 1).[1–5] Among them, zanamivir was the first agent approved (in 1999) by the FDA for influenza treatment;[2] oseltamivir is a more bioavailable anti-influenza drug that was developed by Roche and has been successfully used to treat millions of patients;[3] peramivir is an experimental antiviral drug that has been authorized by the FDA for the emergency treatment of certain hospitalized patients;[4] and laninamivir and its prodrug CS-8958 (both are long-acting neuraminidase inhibitors) have been launched in Japan.[5] These drugs have proved to be a cost-effective stockpiling option for reducing the impact of a fast-spreading pandemic.[1]



Scheme 1. Structures of sialic acid and related neuraminidase inhibitors.

Although the monocyclic structures of zanamivir, laninamivir, and CS-8958 do not appear particularly complex, their high functional-group density and the five consecutive stereogenic centers make these drugs challenging synthetic targets.[6] Until now, manufacturing processes for these three molecules all rely on the starting material sialic acid (Scheme 1), which can be converted into the target drugs in 9–12 steps and 5–21% overall yield.[6,7] However, the relatively high price of sialic acid[8] and low overall yields make the cost of these processes extremely high. The development of novel neuraminidase inhibitors with the capacity to inhibit oseltamivir-resistant influenza virus sialidases has become an urgent task for the scientific community; however, in recent synthetic approaches from sialic acid, modifications are limited to very particular structures.[9–11] Consequently, a de novo and highly efficient route for assembling zanamivir and related neuraminidase inhibitors is highly desirable. In 2004, Yao and co-workers reported a formal synthesis of zanamivir from cheap D-glucono-δ-lactone as the starting material; they obtained the target molecule in 24 linear steps and 0.2% overall yield.[12] Recently, Shibasaki and co-workers developed a total synthesis of zanamivir from a commercially unavailable functionalized enal by using a catalytic *anti*-selective Henry reaction as the key step (24 linear steps, 1.2% overall yield).[13] Although these achievements are significant, the practicality of these two routes is questionable because of lower overall yields and the requirement for a large number of linear synthetic steps.

During the past two decades, intensive efforts from the chemistry community have been directed toward the development of organocatalytic reactions, which offer additional opportunities for discovering more efficient and less expensive approaches to the assembly of enantiomerically enriched synthetic intermediates.[14] The synthetic use of these newly developed reactions has been preliminarily demonstrated by some short and elegant syntheses of bioactive molecules,[14d] including prostaglandins,[15] oseltamivir,[16] and indoline alkaloids.[17] Herein, we disclose our results in the total synthesis of zanamivir and laninamivir, for which we took advantage of an

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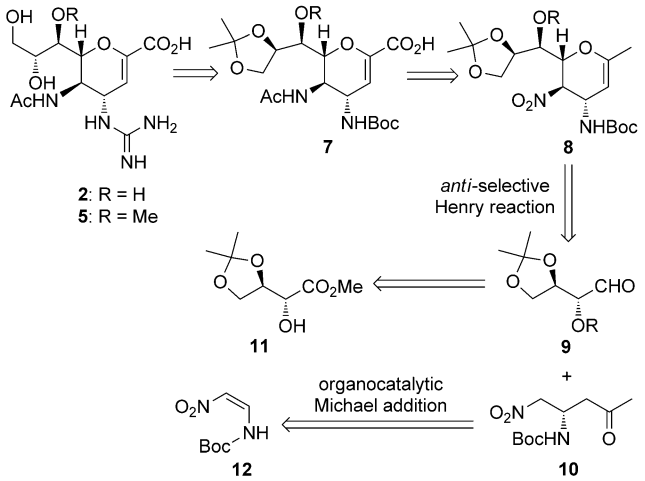
organocatalytic Michael addition of acetone to (*Z*)-*tert*-butyl (2-nitrovinyl)carbamate (**12**)[16a] (prepared from nitromethane in 3 steps and 72% overall yield) and an *anti*-selective Henry reaction of the resultant adduct **10** with aldehydes **9** (prepared from inexpensive D-araboascorbic acid[8] via ester **11** in 5 steps), as outlined in Scheme 2. Only 13 linear steps



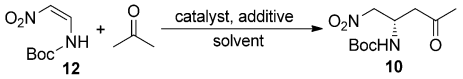
Scheme 2. Retrosynthetic analysis of zanamivir and laninamivir. Boc = *tert*-butoxycarbonyl.

(from D-araboascorbic acid) are required in the presented syntheses, and the overall yields are above 18%. Our study not only provides a promising and inexpensive alternative for the production of these anti-influenza drugs, but also opens a new avenue for the diverse synthesis of zanamivir analogues because intermediates **7** and **8** are both compatible with further tunable transformations.

Since the Michael addition of acetone with less reactive *tert*-butyl (2-nitrovinyl)carbamate (**12**) had not been investigated, we commenced our synthetic study by screening suitable reaction conditions for this particular reaction. Initially, we tried to catalyze the reaction by the activation of acetone with chiral amines. It was found that under the catalysis of L-proline,[18] the reaction reached completion in MeOH in 56 h to provide the desired adduct **10** in 86% yield but with only 28% *ee* (Table 1, entry 1). The addition reaction was accelerated by the use of triamine **B**[19] as the catalyst but still showed poor enantioselectivity (Table 1, entry 2). After failure to obtain **10** in addition reactions catalyzed by imidazolidinone **C**,[20] tetrazole **D**,[21] and cinchona alkaloid **F**[22] (Table 1, entries 3, 4, and 6), we found that an improved result could be obtained with amine **E**[23] (entry 5). Since the enantiomeric purity of adduct **10** was still unsatisfactory, we turned our attention to chiral bifunctional primary amine–thiourea catalysts and were pleased that **10** could be obtained in 96% yield with 82% *ee* by the use of thiourea catalyst **G** described by Huang and Jacobsen (Table 1, entry 7).[24] Further investigations revealed that changes in the solvent and additive could not improve enantioselectivity significantly (Table 1, entries 8–12), whereas the use of amine–thiourea catalysts **H**[25] and **I**[26] led to decreased enantioselectivity (entries 13 and 14). At this stage, we decided to continue our synthesis by using the reaction conditions described in entry 7 of Table 1 to prepare **10** on a large scale. Gratifyingly, this procedure is scalable: A reaction on a scale of 0.69 mol still proceeded smoothly and produced more than 100 g of **10** (Table 1, entry 15). Notably, a reduction in the catalyst loading to 5 mol% did not lead to a decrease in enantioselectivity, and **10** was obtained in 72% yield with 98% *ee* after a single recrystallization of the crude adduct. Further reduction of the catalyst loading to 1 mol% still gave complete conversion, but the enantioselectivity dropped significantly (Table 1, entry 16).

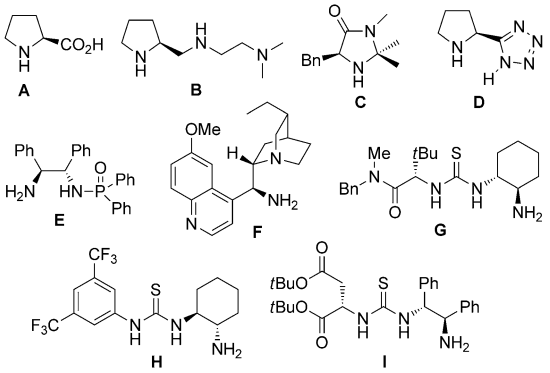
With large quantities of adduct **10** in hand, we attempted its Henry reaction[27] with aldehyde **9a**, which had the desired

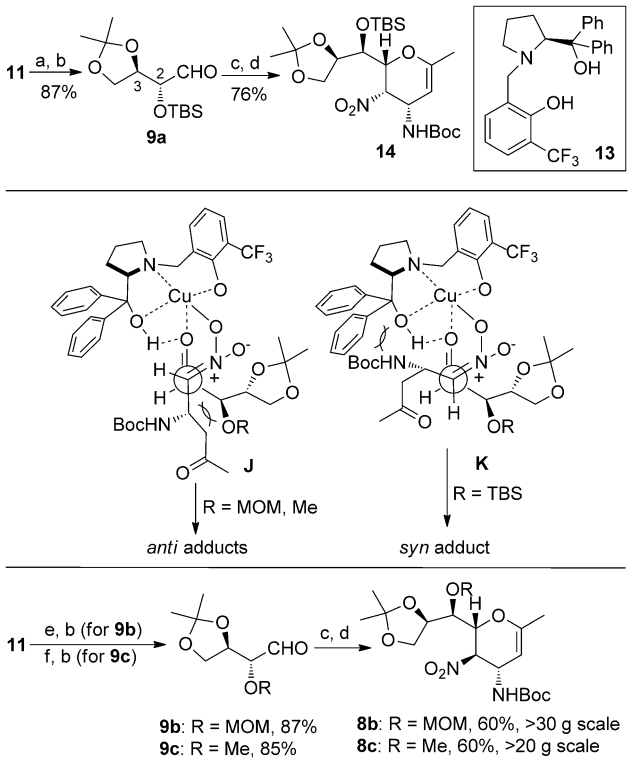
Table 1: Screening of conditions for the organocatalytic Michael addition of acetone with *tert*-butyl (2-nitrovinyl)carbamate.[a]



Entry	Catalyst	Additive	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**A**	–	MeOH	56	86	28
2	**B**	TsOH	DMF	22	76	24
3	**C**	–	$CHCl_3$	72	–	–
4	**D**	H_2O	MeCN	72	–	–
5	**E**	$AcOH/H_2O$	toluene	7	76	42
6	**F**	$PhCO_2H$	–	72	–	–
7	**G**	$PhCO_2H$	toluene	72	96	82
8	**G**	$PhCO_2H$	CH_2Cl_2	72	71	83
9	**G**	$PhCO_2H$	*n*-hexane	72	81	77
10	**G**	$PhCO_2H$	ether	72	81	82
11	**G**	(+)-CSA	toluene	72	77	84
12	**G**	TsOH	toluene	72	64	84
13	**H**	$AcOH/H_2O$	toluene	72	49	51
14	**I**	$PhCO_2H$	toluene	96	87	10
15[d]	**G**	$PhCO_2H$	toluene	16	72[e]	98[e]
16[f]	**G**	$PhCO_2H$	toluene	48	92	71

[a] Reactions were carried out with nitroalkene **12** (1 mmol), acetone (10 mmol), and a catalyst (0.2 mmol) at room temperature, with or without an additive (0.2 mmol). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction was carried out with **12** (0.69 mol), acetone (6.86 mol, 507 mL), catalyst **G** (0.0343 mol), and $PhCO_2H$ (0.137 mol) in toluene (28 mL); an *ee* value of 82% was determined for the crude product. [e] Both the yield and the *ee* value were determined after recrystallization of the crude product from ethyl acetate/petroleum ether (1:10). [f] The reaction was carried out with 1 mol% of catalyst **G**. Bn = benzyl, CSA = camphorsulfonic acid, Ts = *p*-toluenesulfonyl.

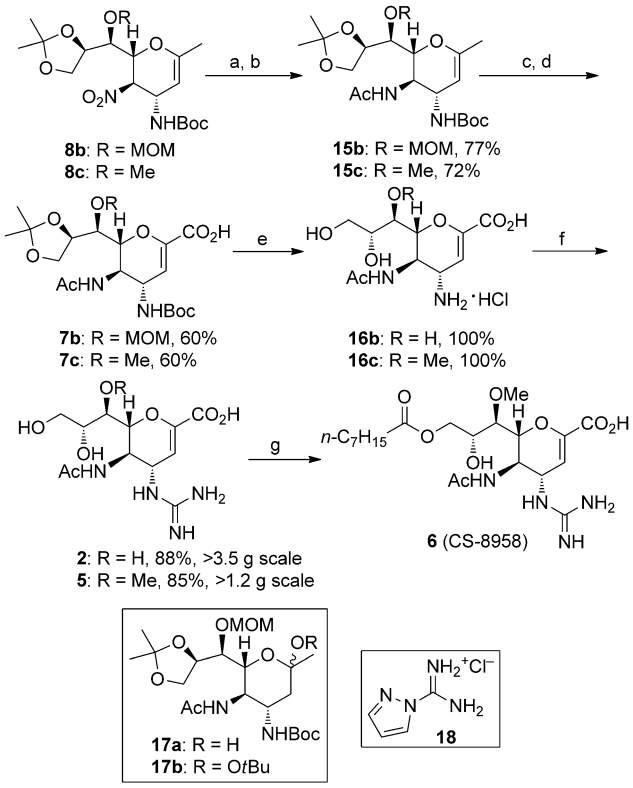




Scheme 3. Reagents and conditions: a) TBSCl, imidazole, DMF, room temperature; b) DIBAL-H, CH_2Cl_2, −78 °C; c) $CuBr_2$, ligand **13**, Cs_2CO_3, 0 °C, THF; d) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C; e) MOMCl/DIPEA; f) MeI, Ag_2O. DIBAL-H = diisobutylaluminum hydride, DIPEA = *N*,*N*′-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, MOM = methoxymethyl.

configuration at the 2- and 3-positions and was synthesized from ester **11**[28] through silyl ether formation and reduction with DIBAL-H (Scheme 3). On the basis of the structural analysis of zanamivir, we envisioned that *anti*-selective Henry reaction conditions[29] should be considered to ensure the formation of the new stereogenic centers with the correct configuration. Recently, Wang and co-workers reported that a combination of $CuBr_2$ and the proline-derived ligand **13** is a powerful catalytic system for *anti*-selective Henry reactions.[29c] Accordingly, we tried our Henry reaction under their reaction conditions, but were surprised to find that the reaction of **9a** with **10** gave the undesired isomer **14** as a single product after spontaneous cyclization and subsequent dehydration with thionyl chloride and pyridine. This result indicated that the Henry reaction had taken place in a *syn*-selective, rather than an *anti*-selective manner. By analyzing the possible transition structures (Scheme 3), we realized that the problem could result from the steric hindrance of the bulky silyl ether group. The large repulsion between this group and the carbamate side chain might force the reaction to proceed via the transition structure **K**, instead of the transition structure **J**, and thereby lead to formation of the undesired *syn* adduct. On the basis of this analysis, we decided to use smaller hydroxy-protecting groups to replace the *tert*-butyldimethylsilyl (TBS) group, and were pleased to observe that under the same conditions, the MOM- and methyl-protected aldehydes **9b** and **9c** were converted into the desired *anti*-selective products **8b** and **8c**, which were isolated in 60% yield together with the corresponding products of a *syn*-selective reaction in about 8% yield.

After reduction of the nitro group of **8b** with Zn/HOAc, acylation afforded amide **15b** (Scheme 4). According to our synthetic plan, next we needed to convert the methyl group on



Scheme 4. Reagents and conditions: a) Zn, HOAc; b) AcCl, Et_3N; c) SeO_2, pyridine, 4 Å molecular sieves, dioxane/THF; d) $NaClO_2$, NaH_2PO_4, 2-methylbutene, *t*BuOH/THF/H_2O; e) HCl, THF; f) **18**, DIPEA, DMF, 50 °C; g) n-$C_7H_{15}C(OMe)_3$, HCl, MeOH, 92%.

the six-membered ring into a carboxy group. Under typical conditions for oxidation with SeO_2 (e.g. SeO_2, dioxane, reflux or SeO_2, *t*BuOOH, CH_2Cl_2, room temperature),[30] the desired acid **7b** was formed after further oxidation with sodium chlorite. However, the overall yields (30–40%) were not satisfactory owing to formation of the side product **17** in the first oxidation step. Since **17a** was generated by the addition of water to **15b**, we decided to prevent its formation by introducing molecular sieves and adding pyridine to maintain neutral reaction conditions. Upon the addition of these two additives, we were pleased that the yield of **7b** could be increased to 60% if the first oxidation reaction was carried out at 50 °C. Finally, the one-pot removal of all three protecting groups of **7b** with 3 N HCl delivered amino acid **16b**, which was subjected to guanidination with **18**[31] in DMF at 50 °C to provide zanamivir (**2**) in 88% yield with 97% purity after a single recrystallization. Notably, only a moderate yield was observed if aminoiminomethanesulfonic acid[32] was used as the guanidination agent. In this case, incomplete

conversion and the formation of more side products were observed. By following the same procedure, we assembled laninamivir (**5**) from **8c** in 34.3% overall yield. The esterification of **5** with n-$C_7H_{15}C(OMe)_3$ in 1N methanolic hydrochloride provided CS-8958 (**6**) in 92% yield. To our delight, the present synthetic procedures are scalable, as evident from the synthesis of more than 3.5 g of **2** and 1.2 g of **5**.

In conclusion, we have developed a short and practical route for assembling the anti-influenza drugs zanamivir, laninamivir, and CS-8958 by using inexpensive D-araboascorbic acid as the starting material. The key transformations include a thiourea-catalyzed Michael addition and a copper-catalyzed *anti*-selective Henry reaction. Our route offers advantages over current routes in terms of cost, ease of execution, and efficiency. This study provides another example of the remarkable influence of new synthetic methodologies in the efficient synthesis of complex molecules. More importantly, our method offers an inexpensive and alternative approach for manufacturing these known anti-influenza drugs and preparing analogues for the development of more effective anti-influenza drugs. Investigations towards these goals are being actively pursued in our laboratory.

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