Azide-Free Synthesis of Oseltamivir from L-Methionine

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This paper is dedicated to Professor Jiro Tsuji.

Abstract: Highly enantioselective synthesis of oseltamivir has been achieved starting from L-methionine, in which Staudinger reaction is utilized for the alignment of three contiguous chiral centers of oseltamivir. The present method would lead to an alternative synthesis of oseltamivir that avoids the use of hazardous azide reagents.

Key words: anti-influenza drugs, tamiflu, Staudinger reaction, hydroformylations, intramolecular aldol condensation

The recent emergence of world-shaking avian flu virus H5N1 has prompted many nations to stock oseltamivir phosphate (**1**·H_3PO_4, Tamiflu™),[2] the potent anti-influenza drug developed by Gilead Science. The present commercial production of **1**, however, relies heavily on the semi-synthesis starting from less available shikimic acid, which would hamper to stock a sufficient amount of Tamiflu. Given the current supply issue of **1**,[3] we have launched our program directed toward the synthesis of **1**[4,5] (Figure 1) using commodity chemicals as the starting material and have disclosed a novel synthetic method for **1**[6] starting from commercially available D-mannitol, which employs the intramolecular condensation of dialdehyde **3** culminating in a successful construction of densely functionalized cyclohexenal **2** without causing any side reactions such as epimerization, elimination, or aromatization.

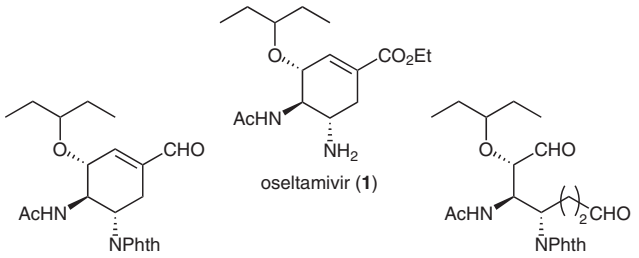
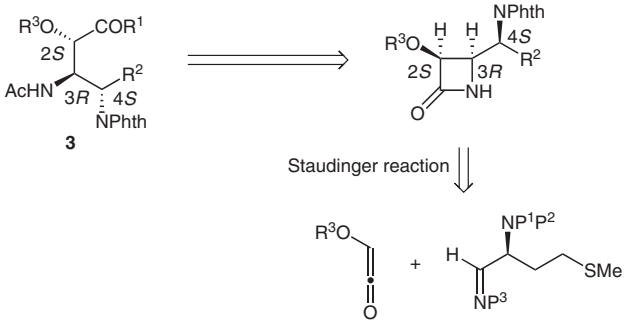


Figure 1 Oseltamivir and key intermediates of our previous synthesis

However, our previous process reluctantly used hazardous sodium azide on delivering two amino groups in **3**. Therefore, we have been exploring a safer approach,[7] having resulted in the development of an alternative access to **3** by taking advantage of a *cis*-β-lactam. As shown in Scheme 1, a *cis*-β-lactam would be a first-rate candidate with the same 2*S*,3*R*,4*S* configuration as that of three contiguous stereogenic centers in **3**. We envisioned that such a *cis*-β-lactam would be constructed in a highly stereoselective fashion[8] by Staudinger cycloaddition reaction[9] between a ketene and an imine.



Scheme 1 Retrosynthetic strategy via β-lactam formation and ensuing ring opening

Thus we commenced with the synthesis of β-lactam **9**[10] as illustrated in Scheme 2. First, 3-pentanol was alkylated with bromoacetic acid[11] to give **4a** followed by treatment with thionyl chloride to furnish 3-pentyloxyacetyl chloride (**4b**, bp 110–118 °C, 20–27 mbar, 94% yield for 2 steps). On the other hand, imine **6b** as a partner was synthesized as follows: hydride reduction (DIBAL-H, PhMe) of ester **5** derived from L-methionine afforded aldehyde **6a** (91% yield), which was treated with *p*-anisidine (0.9 equiv, $MgSO_4$, CH_2Cl_2) to give crude **6b** quantitatively. Staudinger reaction between a ketene derived from **4b** and imine **6b** was performed by the following procedures; slow addition of **4b** (1.5 equiv) in CH_2Cl_2 to a solution of freshly prepared **6b** (1 equiv) and *i*-Pr_2NEt (4.5 equiv) in CH_2Cl_2 led to the desired *cis*-β-lactam **7a**[12] (55% yield based on *p*-anisidine). The enantiomeric purity of **7a** thus obtained was determined to be >99% ee by HPLC analysis.[13]

Then, oxidation of **7a** (NCS, MeCN–EtOH–H_2O) and subsequent thermal desulfinylation of sulfoxide **7b** afforded **8a**[14] (81% yield for 2 steps), whose acid-sensitive Boc group was exchanged for a phthaloyl group to afford **8c**[15] (86% yield for 2 steps) via allylic amine **8b**. Following CAN-mediated oxidative cleavage of *p*-methoxyphenyl group[16] occurred smoothly to generate β-lactam **9** (80% yield) with the phthaloyl group intact.

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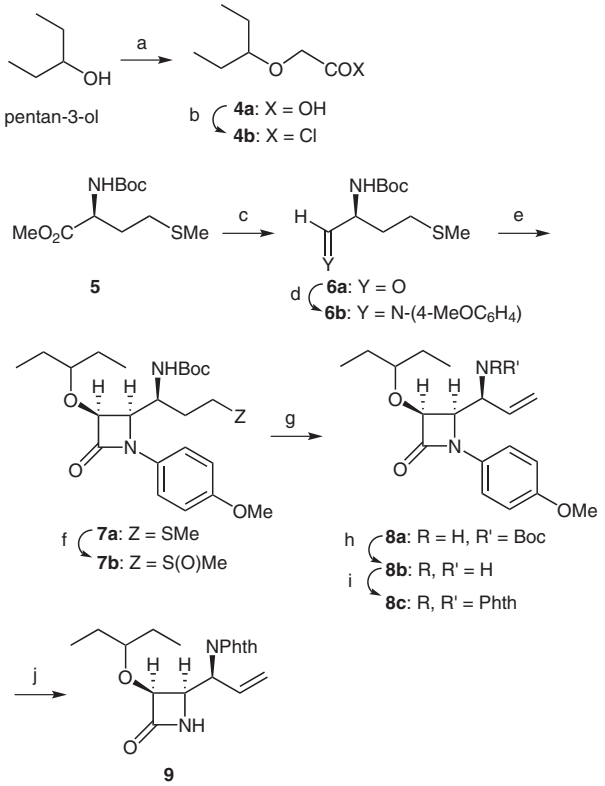
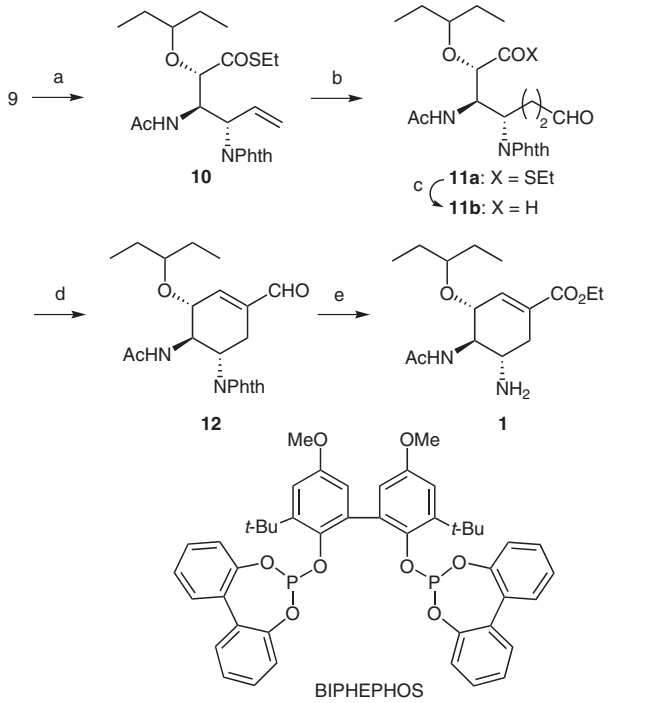


Scheme 2 *Reagents and conditions*: (a) KH (3.3 equiv), bromoacetic acid (2.0 equiv), 60 °C, 20 h, quant.; (b) $SOCl_2$ (4.0 equiv), 80 °C, 10 h, 94% for 2 steps; (c) DIBAL-H (2.0 equiv), toluene, –70 °C, 2.5 h, 91%; (d) *p*-anisidine (0.9 equiv), $MgSO_4$ (10 equiv), CH_2Cl_2 (ca. 0.3 M), 0 °C to r.t., overnight, quant.; (e) *i*-Pr_2NEt (4.5 equiv), **4b** (1.5 equiv), CH_2Cl_2 (ca. 0.5 M), –15 °C to r.t., 2 h, r.t., overnight, 55%; (f) NCS (1.1 equiv), MeCN–EtOH–H_2O (20:20:1), r.t., 40 min, quant.; (g) α-pinene–decalins (1:1), $NaHCO_3$ (10 equiv), 155 °C, 6 h, 81%; (h) TFA–CH_2Cl_2 (3:5), 0 °C to r.t., 1.5 h; (i) $PhthNCO_2Et$ (1.1 equiv), Et_3N (3.0 equiv), THF, 50 °C, 7.5 h, 86% for 2 steps; (j) CAN (3.0 equiv), MeCN–H_2O (1:1), 0 °C, 1 h, 80%.

Next, the ring-opening reaction of **9** was carried out in one-pot operation as shown in Scheme 3; that is, acetylation of **9** (LHMDS, THF, AcCl, –78 °C) followed by treatment with an excess of EtSH and Et_3N (–78 °C to –20 °C) produced thiol ester **10** (94% yield) successfully. Facile hydroformylation[17] of **10** [$Rh(acac)(CO)_2$, BIPHEPHOS,[18] 6 atm of CO/H_2 (1:1), THF] afforded aldehyde **11a** (88% yield) with high regioselectivity (linear/branched >30:1). Transformation of **11a** into dialdehyde **11b** was effected successfully by Fukuyama's protocol (Et_3SiH, 10% Pd/C).[19] The crude aldehyde **11b** underwent the intramolecular aldol condensation employing $Bn_2NH{\cdot}TFA$[20] (1.1 equiv, toluene, 50 °C, 10 h, 62% yield for 2 steps) to yield enal **12**, whose spectroscopic data were in full accord with those of the authentic sample.[6,21] Finally, the conversion of **12** to **1** was accomplished uneventfully according to our reported procedure.[6]

In summary, we have succeeded in developing a new synthetic pathway to oseltamivir (**1**) in 18 steps from abundant L-methionine. The key features of the present method are: (1) ready availability of the starting material, (2) azide-free synthetic route, and (3) highly stereoselective construction of the three contiguous chiral centers by means of Staudinger reaction.



Scheme 3 *Reagents and conditions*: (a) LiHMDS (2.0 equiv), THF, –78 °C, 15 min, AcCl (2.0 equiv), –78 °C, 1 h, then EtSH–Et_3N (5 equiv each), –78 °C to –20 °C, 3.5 h, 94%; (b) $Rh(acac)(CO)_2$ (5 mol%), BIPHEPHOS (10 mol%), CO/H_2 (1:1, 6 atm), THF, 65 °C (autoclave), 7 h, 88%; (c) 10% Pd/C, Et_3SiH (5.0 equiv), CH_2Cl_2, r.t., 1.5 h; (d) $Bn_2NH{\cdot}TFA$ (1.1 equiv), toluene, 50 °C, 10 h, 62% for 2 steps; (e) see the preceding paper.[6]

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References and Notes

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(12) The desired *cis*-β-lactam **7a** was easily purified by trituration in cold MeOH to remove byproducts such as minor stereoisomers (ca. 5%) and *N*-(4-methoxyphenyl)-(3-pentyloxy)acetamide.
Compound **7a**: a white solid; $[\alpha]_D^{22}$ –119 (*c* 0.99 $CHCl_3$); mp 161.6–162.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (br d, *J* = 8.9 Hz, 2 H), 6.87 (br d, *J* = 8.9 Hz, 2 H), 5.09 (br d, *J* = 10.1 Hz, 1 H), 4.78 (d, *J* = 5.5 Hz, 1 H), 4.56 (m, 1 H), 4.40 (dd, *J* = 5.5, 5.8 Hz, 1 H), 3.79 (s, 3 H), 3.61 (tt, *J* = 5.8, 5.8 Hz, 1 H), 2.55 (ddd, *J* = 4.6, 8.6, 13.1 Hz, 1 H), 2.38 (ddd, *J* = 7.9, 8.3, 13.1 Hz, 1 H), 1.93 (m, 1 H), 1.87 (s, 3 H), 1.80 (m, 1 H), 1.72 (m, 2 H), 1.62 (m, 2 H), 1.51–1.43 (two br s, 9 H), 1.94 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 156.6, 155.7, 130.6, 118.4, 114.6, 84.5, 81.1, 79.6, 57.3, 55.5, 48.7, 30.9, 28.8, 28.4, 26.6, 25.5, 15.2, 9.6, 9.4. Anal. Calcd for $C_{24}H_{38}N_2O_5S$: C, 61.77; H, 8.21; N, 6.00. Found: C, 61.87; H, 8.31; N, 6.16.

(13) Daicel CHIRALCEL OD-RH; eluent: MeCN–H_2O (10:1); λ = 254 nm; flow rate: 0.3 mL/min; t_R(**7a**) = 7.8 min; t_R (*ent*-**7a**) = 9.9 min.

(14) A mixture of **7b** (1.55 g, ca. 3.22 mmol), $NaHCO_3$ (2.70 g, 32.2 mmol), α-pinene (10 mL), and decalins (10 mL) was placed into a 100 mL round-bottomed flask fitted with a reflux condenser. The reaction mixture was deoxygenated by alternate evacuation–argon flush cycles (five iterations) and heated with vigorous stirring at 150–155 °C for 6 h under argon atmosphere. After being cooled to r.t., the reaction mixture was partitioned between H_2O (30 mL) and EtOAc (30 mL). The organic layer separated was washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 1:0 to 20:1 to 10:1 to 6:1) to give olefin **8a** as a white solid (1.09 g, 81% from **7a**); $[\alpha]_D^{26}$ –93.6 (*c* 1.03, $CHCl_3$); mp 116.9–117.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.92 (ddd, *J* = 7.6, 10.4, 17.0 Hz, 1 H), 5.30 (d, *J* = 9.5 Hz, 1 H), 5.07 (d, *J* = 10.4 Hz, 1 H), 5.00 (d, *J* = 17.0 Hz, 1 H), 4.94 (m, 1 H), 4.78 (d, *J* = 5.5 Hz, 1 H), 4.38 (dd, *J* = 5.1, 5.5 Hz, 1 H), 3.79 (s, 3 H), 3.60 (tt, *J* = 5.5, 5.5 Hz, 1 H), 1.72 (m, 2 H), 1.62 (m, 2 H), 1.45 (br s, 9 H), 0.95 (t, *J* = 7.5 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 156.4, 133.8, 130.7, 118.6, 114.5, 106.3, 84.4, 81.0, 79.7, 57.5, 55.5, 52.3, 28.4, 26.5, 25.5, 9.6, 9.3. For thermal elimination of a methionine-derived sulfoxide, see: (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071. (b) For our previous protocol of thermal desulfinylation, see also: Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5671.

(15) Compound **8c**: white solid; $[\alpha]_D^{25}$ –14.4 (*c* 0.86 $CHCl_3$); mp 111.6–111.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.55 (br s, 4 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.39 (d, *J* = 8.8 Hz, 2 H), 6.20 (ddd, *J* = 6.1, 10.0, 17.0 Hz, 1 H), 5.33–5.26 (m, 3 H), 5.03 (dd, *J* = 5.2, 10.3 Hz, 1 H), 4.89 (d, *J* = 5.2 Hz, 1 H), 3.65 (tt, *J* = 5.5, 5.5 Hz, 1 H), 3.45 (s, 3 H), 1.72 (m, 2 H), 1.61 (m, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H), 0.92 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 166.0, 156.9, 134.2, 133.5, 131.7, 131.4, 128.1, 123.5, 122.8, 122.7, 119.0, 118.5, 114.5, 113.8, 83.3, 80.3, 57.3, 55.1, 53.0, 26.2, 25.3, 9.4, 9.2. Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63, H, 6.29, N, 6.25. Found: C, 69.25; H, 6.10; N, 6.29.

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(21) Compound **12**: off-white solid; $[\alpha]_D^{23.4}$ –44.0 (*c* 1.05, $CHCl_3$); mp 198–199.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$, data of a mixture of rotamers): δ = 9.56 (s, 0.15 H), 9.54 (s, 0.85 H), 7.86–7.72 (m, 4 H), 6.68 (s, 0.15 H), 6.67 (s, 0.85 H), 5.58 (d, *J* = 7.6 Hz, 0.85 H), 5.26 (d, *J* = 7.6 Hz, 0.15 H), 4.95–4.87 (m, 0.85 H), 4.75–4.71 (m, 0.85 H), 4.50–4.32 (m, 1.15 H), 4.15–4.10 (m, 0.15 H), 3.46–3.33 (m, 1 H), 3.10–2.97 (m, 1 H), 2.76–2.65 (m, 1 H), 2.05 (s, 0.45 H), 1.78 (s, 2.55 H), 1.60–1.50 (m, 4 H), 1.00–0.85 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$, data of a mixture of rotamers): δ = 192.2, 170.3, 168.1, 147.5, 138.8, 134.2, 131.6, 123.4, 82.4, 74.6, 54.3, 47.8, 26.3, 25.7, 25.5, 23.3, 9.6, 9.3. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32, H, 6.58, N, 7.03. Found: C, 66.06; H, 6.72; N, 6.98.