DOI: 10.1002/adsc.200900844

Short Chemoenzymatic Azide-Free Synthesis of Oseltamivir (Tamiflu): Approaching the Potential for Process Efficiency

Lukas Werner,[a] Ales Machara,[a] and Tomas Hudlicky[a,*]

[a] Department of Chemistry and Centre for Biotechnology, Brock University, 500 Glenridge Avenue, St. Catharines, Ontario L2S 3 A1, Canada
Fax: (+1)-905-984-4841; phone: (+1)-905-688-5550 ext. 4956; e-mail: thudlicky@brocku.ca

Received: November 11, 2009; Revised: December 5, 2009; Published online: December 30, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900844.

Abstract: A short chemoenzymatic and azide-free synthesis of oseltamivir was attained with the key steps consisting of a one-pot Dauben–Michno oxidative transposition and amination and a reductive transposition of an acrylate.

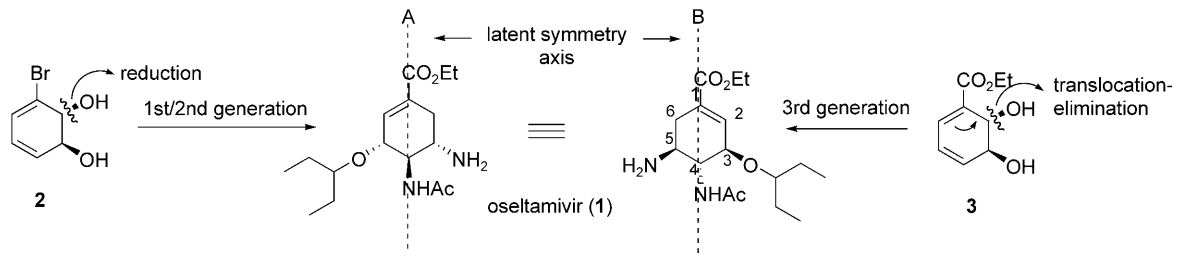
Keywords: antiviral agents; asymmetric synthesis; biotransformations; oxidative transposition; synthesis design; tamiflu synthesis

Recently we have reported a formal chemoenzymatic synthesis of oseltamivir (**1**) from ethyl benzoate in ten steps compressed to just seven operations.[1] While this particular synthesis compared very favorably with most preparations reported to date[2] it still relied on the use of azide as means of introduction of the C-5 amino group. The synthesis represented a third-generation effort that evolved from our previous, and less efficient, attempts, which utilized the *cis*-dihydrodiol **2** derived enzymatically from bromobenzene as shown in Scheme 1.[3]

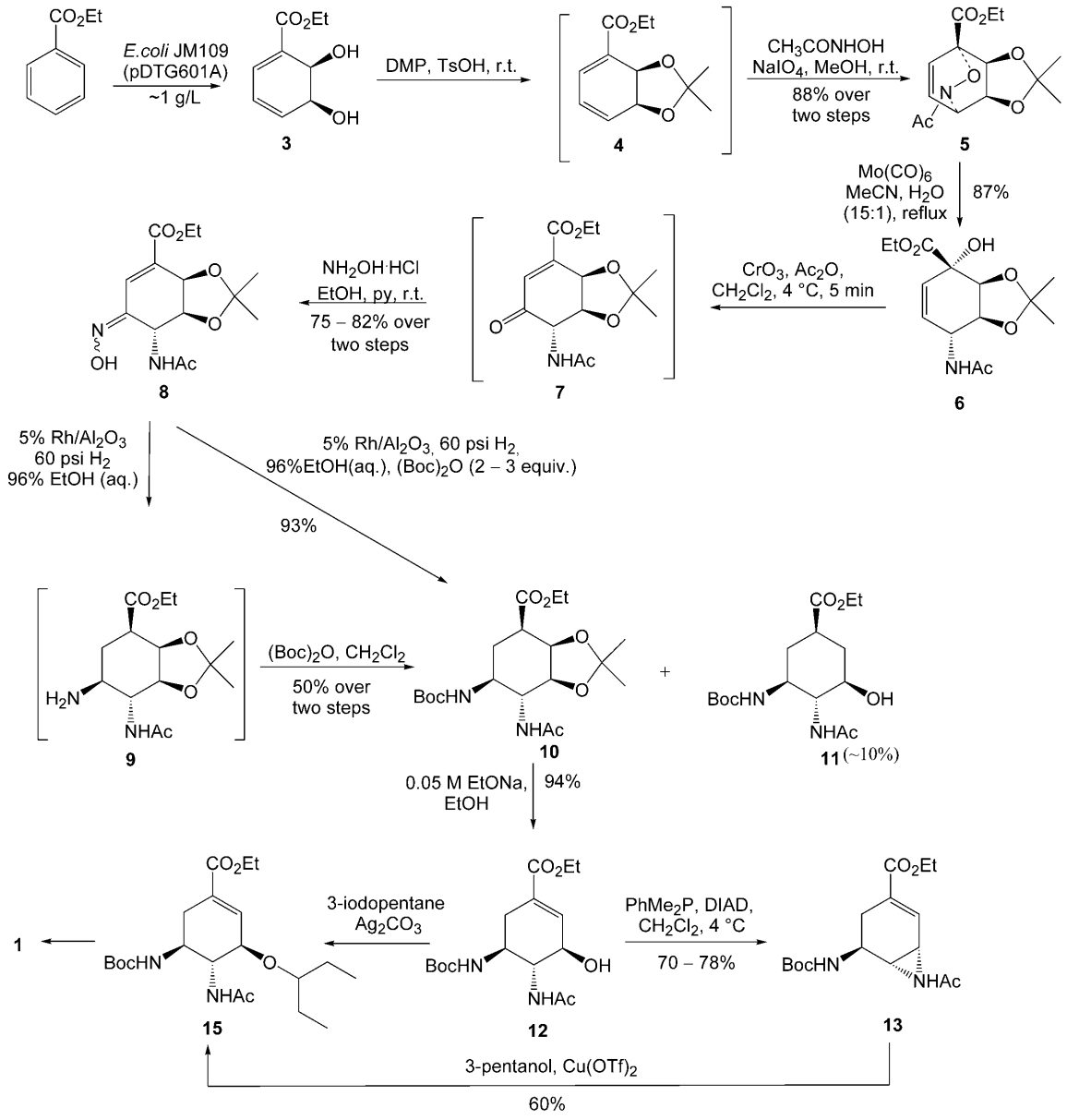
This commercially available homochiral *cis*-dihydrodiol was also used as a starting material in two other syntheses, those of Fang[4p] and Banwell,[4o] respectively. In our first- and second-generation efforts, as well as in the above two preparations, additional transformations were required in order to convert the vinyl bromide functionality in **2** into the acrylate moiety of oseltamivir. Such additional steps, as well as protective and deprotective operations inherent in most of the approaches to oseltamivir published to date,[4] greatly detract from the overall efficiency and hence limit the practicality component essential for a large-scale industrial process.

The efficient and scaleable synthesis of tamiflu and/or related, potentially active, compounds remains a high priority in the event of a pandemic. Herein we report a fourth-generation approach that is among the shortest reported to date and which has the potential for a very efficient process synthesis. The starting material is ethyl benzoate, a commodity chemical containing nine of the sixteen carbon atoms of oseltamivir.

The synthesis begins with the whole-cell fermentation of ethyl benzoate with *E. coli* JM109(pDTG 601), a recombinant organism developed by Gibson.[5] The over-expression of toluene dioxygenase, the enzyme required for the *cis*-dihydroxylation of arenes, facilitates the production of diol **3**, which is isolated by extraction from the fermentation broth in yields of



Scheme 1. Symmetry-based design for oseltamivir.



Scheme 2.

1–2 $g\,L^{-1}$ and immediately converted to its acetonide **4**, Scheme 2.

Without further purification the acetonide is exposed to the *in situ* generated acylnitroso component for the inverse-electron demand Diels–Alder cycloaddition, which provides oxazine **5** as a single isomer in an overall yield of 88% from diol **3**. Reduction of the oxazine yields the allylic alcohol **6** (87%), which has been previously converted to oseltamivir in six steps.

At this point a new protocol was incorporated in order to eliminate the use of azide in the introduction of the remaining nitrogen functionality. The allylic alcohol underwent a [3,3]oxidative rearrangement[6] to enone **7** when exposed to chromium oxide. This type of rearrangement, the Dauben–Michno oxidative transposition, is well known for oxidations of tertiary alcohols containing electron-donating substituents or cycloalkenes[7] but to the best of our knowledge has no precedent for substrates with strong electron-withdrawing groups. We discovered that chromium trioxide dissolved in acetic anhydride (a variation to Fieser's reagent) is very suitable for this transformation while other oxidizing agents such as PDC, PCC, IBX, Dess–Martin periodate or TEMPO derivatives gave only low yields of **7**. Although the oxidative rearrangement proceeds at low temperature (4 °C) it is necessary to prepare a homogeneous solution of the oxidizing agent by heating chromium trioxide in acetic anhydride at 80 °C prior to the reaction. After complete dissolution of chromium trioxide the mix-

ture is cooled to room temperature, diluted with a small amount of dichloromethane, and cooled to 4 °C. At higher temperatures we observed the formation of aromatic by-products or the C-4 epimer of enone **7.** Enone **7** was then converted to oxime **8** without isolation in 75–82% yield over the two steps.

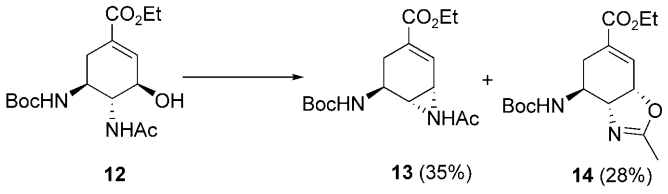
Hydrogenation of the unsaturated oxime isomers produced the saturated amino ester **9**, which was not isolated but converted directly to the Boc carbamate **10** with Boc anhydride in 50% yield over the two steps. However hydrogenation of unsaturated oxime **8** in aqueous ethanol in the presence of 2–3 equivalents of Boc anhydride afforded directly Boc carbamate **10** in 90–93% yield. A small amount (~10%) of the fully saturated ester **11** was also observed probably as a consequence of base-catalyzed elimination of the C-2 ether promoted by the presence of the primary amine.

Exposure of the saturated ester **10** to sodium ethoxide (0.5 equivalents) in ethanol resulted in the elimination of the C-2 ether moiety and generation of the required allylic alcohol **12** in 94% yield. Thus, the entire sequence from ethyl benzoate-derived *cis*-dihydrodiol **3** to alcohol **12** consists of seven chemical steps reduced to *just five operations* and proceeding in an overall yield of 52% from diol **3**.

Attainment of the allylic alcohol constitutes a formal synthesis of oseltamivir as accomplished by Shibasaki[4u] as well as Corey.[4g] The final step in the synthesis requires the introduction of the 3-pentyl ether and this may be accomplished by previously reported procedures, most notably by that of Corey.[4g] Repetition of Corey's procedure produced, in our hands, the Boc-protected oseltamivir **15** in 21% overall yield from the allylic alcohol **12**. Aziridine formation proceeded in 35% yield from **12** at the expense of the formation of the corresponding oxazoline **14** as a by-product in 28% yield, Scheme 3.

However, our repetition of Shibasaki's conditions[4u] provided aziridine **13** in 70–78% yield with only trace amounts of oxazoline **14**. Aziridine **13** was converted to the Boc-protected oseltamivir **15** by copper triflate-catalyzed opening of the aziridine in 60% yield.

Attempts at direct alkylation of the allylic alcohol in **12** with 3-iodopentane in the presence of silver carbonate[8] produced **15** in low yields (<10%). Other methods of direct introduction of the 3-pentyl ether



Scheme 3. Oxazoline formation during the Mitsunobu reaction.

were not successful (oxymercuration, for example) and produced regioisomeric mixtures in low yields.

In summary, we have provided a simplified preparation of the title compound in a manner that compares well in efficiency to all other preparations according to a recent analysis performed by Andraos who provided the green chemistry metrics analysis of most published syntheses for material efficiency.[9] Although our previous synthesis, published after Andraos' review, was not yet subjected to the evaluation, we plan to compare the efficacy of the current procedure with that of other published preparations in the near future. The attainment of alcohol **12** described in this paper represents a substantial improvement over other procedures: the allylic alcohol **12** is obtained from diol **3** in just *five operations* and the entire sequence (**3** to **12**) may be performed without chromatography on a multi-gram scale! The overall yield of **12** from diol **3** is 52% when chromatography is used for purification at key steps (oxime **8** and ester **10**). With the purification of several intermediates by crystallization (oxime **8**, ester **10**, and alcohol **12**) the overall yield is lower as some product remains in the mother liquors. Furthermore, it is possible to use *any* benzoate ester, or even a mixture of esters that are substrates for the enzyme,[10] in the fermentation and to carry such a mixture through the cycloaddition step where all components may easily be transesterified to oxazine **5**. The efficiency of the whole-cell fermentation of benzoate esters with the recombinant organism that over-expresses toluene dioxygenase requires different metrics for evaluation than the synthetic transformations. The space-time yields of *cis*-dihydrodiols are expressed in grams/liter/hour. In the case of diol **3** the amounts obtained from a 15-L fermentor (9–10 L working volume) are reproducibly 1 g L^{-1} hour. The medium-scale procedure for this fermentation has been described in detail[11] and the isolated yields of **3** are currently 9–10 grams per fermentation in which ~20 grams of ethyl benzoate are introduced to the cells grown to maximum density. There are no by-products observed in this fermentation and ~10 grams of ethyl benzoate are recovered. Thus the "chemical yield" of this transformation based on recovered starting material would approach a quantitative conversion. For eventual large-scale commercial application the titers could be improved further by directed evolution of the organism. Finally, the challenge for future generations of oseltamivir synthesis that use the allylic alcohol **12** as an intermediate would certainly be the invention of a new method for introduction of the ether moiety onto the allylic alcohol in **12** (as well as other alcohols not responding well to standard S_N2-type ether formation).

Experimental Section

All non-aqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Dichloromethane was distilled from calcium hydride, THF and toluene were dried over potassium/benzophenone. Analytical thin layer chromatography was performed on Silicycle 60 Å 250 μm TLC plates with F-254 indicator. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer One FT-IR spectrometer. Optical rotation was measured on a Perkin–Elmer 341 polarimeter at a wavelength of 589 nm. ^{1}H and ^{13}C spectra were recorded on a 300 MHz and 600 MHz spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent. Data of proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (δ) relative to solvent resonance as internal standard. Mass spectra and high resolution mass spectra were performed by the analytical division at Brock University.

(3a*R*,7*R*,7a*S*)-Ethyl-7-acetamido-6-(hydroxyimino)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]-dioxole-4-carboxylate (8)

The oxidizing agent was prepared by stirring CrO_3 (835 mg; 8.35 mmol) in Ac_2O (2 mL) at 80 °C. After 7 min the resulting slurry was allowed to cool to room temperature diluted with 6 mL of dichloromethane and cooled in an ice bath. This solution was added over 30 seconds to a cooled (4 °C) solution of tertiary alcohol **6** (1 g; 3.34 mmol) in dichloromethane (20 mL). After 5 min of stirring the reaction was quenched by addition of 8 mL EtOH, pyridine (0.4 mL) and solid $NaHCO_3$ (2 g). The reaction mixture was then stirred for additional 5 min in an ice bath and 30 min at room temperature.

On a preparative scale the intermediate enone *(3aR,7S,7aS)-ethyl-7-acetamido-2,2-dimethyl-6-oxo-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxole-4-carboxylate* (**7**) was not isolated and taken directly to the next step. An analytical sample was purified via flash column chromatography (ethyl acetate) Analytical data for intermediary enone **7**: Colorless oil: R_f 0.6 (ethyl acetate); $[\alpha]_D^{20}$: +19.35 (*c* 1, $CHCl_3$); IR (KBr): ν = 3385, 2988, 1724, 1712, 1662, 1543, 1383, 1253, 1077, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.94 (s, 1H), 6.10 (d, *J* = 5.4 Hz, 1H), 5.13 (d, *J* = 4.8 Hz, 1H), 4.82 (m, 1H), 4.39 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 1H), 2.10 (s, 3H), 1.61 (s, 3H), 1.48 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.0, 170.8, 164.5, 140.7, 134.5, 112.0, 70.3, 62.3, 58.3, 27.7, 26.4, 23.2, 14.0; MS (EI): *m/z* (%) = 297 (M^+), 239 (4), 221 (4), 197 (14), 175 (13), 151 (11), 84 (100), 43 (34); HR-MS: *m/z* = 297.1218, calcd. for $C_{14}H_{19}N0_6$: 297.1212.

The above reaction mixture was again cooled in an ice bath and $NH_2OH{\cdot}HCl$ (2.32 g; 33.43 mmol) was added in one portion. After 1 h of stirring in the ice bath the reaction mixture was allowed to warm to room temperature and stirred for additional 16 h. The mixture was then diluted with ethyl acetate (130 mL) and extracted 4 × 8 mL with saturated $NaHCO_3$ solution. The combined aqueous layers were re-extracted with ethyl acetate (30 mL). The combined organic layer was dried with $MgSO_4$ and evaporated. Chromatography of the residue [hexane-ethyl acetate (1:1)→ ethyl acetate, 30 mL (15 g) silica] afforded oxime **8** as a greenish oil which solidified on trituration with 2-propanol; yield: 860 mg (82%). Recrystallization from 2-propanol-hexane provided **8** as a white solid; mp 106–116 °C; R_f 0.30 (ethyl acetate); $[\alpha]_D^{20}$: −52.63 (*c* 1, $CHCl_3$); IR (KBr): ν = 3367, 2988, 1720, 1659, 1547, 1382, 1246, 1069, 1023 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (bs, 1H), 7.77 (s, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 5.4 Hz, 1H), 5.02 (dd, *J* = 8.4, 8.1 Hz, 1H), 4.32 (m, 1H), 4.30 (m, 2H), 2.06 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 165.4, 148.9, 132.4, 124.8, 111.1, 76.0, 70.6, 61.7, 49.9, 27.9, 26.4, 23.3, 14.1; MS (FAB+): *m/z* (%) = 313 $(M+H)^+$, 255 (73), 195 (76), 150 (16), 43 (38); HR-MS: *m/z* = 313.14056, calcd. for $C_{14}H_{21}N_2O_6$: 313.13996; anal. calcd. for $C_{14}H_{21}N_2O_6$: C 53.84, H 6.45; found: C 54.80,H 7.52; the crystals contain 15 mol% of 2-propanol.

(3a*R*,6*S*,7*R*,7a*S*)-7-Acetylamino-6-*tert*-butoxycarbonylamino-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[1,3]-dioxole-4-carboxylic Acid Ethyl Sster (10)

Procedure A ("stepwise"): A suspension of oxime **8** (400 mg; 1.27 mmol) and 100 mg Rh/Al_2O_3 (5%) in EtOH (96%, 45 mL) was hydrogenated in the Parr apparatus (60 pound/inch^2). After 16 h the reaction mixture was filtered through short bed of celite and evaporated.

On a preparative scale the amine *(3aR,4R,6S,7R,7aS)-ethyl-7-acetamido-6-amino-2,2-dimethylhexahydrobenzo[d]-[1,3]dioxole-4-carboxylate* (**9**) was not isolated but taken directly to the next step. An analytical sample was purified *via* flash column chromatography [dichloromethane-methanol (1:1)] to yield amine **9** as colorless oil: R_f 0.26 (1:1 dichloromethane-methanol); $[\alpha]_D^{20}$: −11.54 (*c* 1, $CHCl_3$); IR (KBr): ν = 3445, 2984, 1733, 1654, 1556, 1384, 1222, 1144, 1049 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 4.8, 4.2 Hz, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 4.05 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.56 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.81 (ddd, *J* = 13.2, 4.2, 4.2 Hz, 1H), 2.76 (m, 1H), 2.06 (s, 3H), 2.04 (m, 1H), 1.85 (ddd, *J* = 13.2, 11.9, 11.9 Hz, 1H), 1.55 (s, 3H), 1.36 (s, 3H), 1.28 (t, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 170.8, 109.7, 77.9, 74.0, 60.9, 59.7, 50.8, 41.4, 30.9, 28.1, 26.2, 23.8, 14.1; MS (FAB): *m/z* (%) = 301 (M^+ + H), 273 (8), 226 (7), 184 (13), 151 (7), 110 (9), 43 (13); HR-MS: *m/z* = 300.1800, calcd. for $C_{14}H_{24}N_20_5$: 300.1685.

Minor over-hydrogenated product *(1R,3S,4R,5R)-ethyl 4-acetamido-3-amino-5-hydroxycyclohexanecarboxylate:* white solid: mp 158–162 °C ($CHCl_3$); R_f 0.10 (1:1 dichloromethane-methanol); $[\alpha]_D^{20}$: dynamic −12 to +7 (*c* 1, $CHCl_3$/MeOH 1:1); IR (KBr): ν = 3444, 3422, 3279, 3093, 2982, 2932, 2900, 2865, 2846, 2798, 1731, 1640, 1592, 1562, 1453, 1383, 1320, 1276, 1244, 1222, 1191, 1155, 1101, 1048, 1031, 977, 956, 855, 744, 609 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.2 Hz, 2H), 3.50–3.42 (m, 2H), 3.33 (dddd, *J* = 4 × ~1.5 Hz, 1H) 2.62 (m, 1H), 2.50 (dddd, *J* = 3.3, 3.3,

12.6, 12.6 Hz, 1H) 2.27–2.16 (m, 2H), 2.05 (s, 3H), 1.57–1.48 (m, 1H), 1.44 (ddd, $J=6.3$, 6.3, 6.3 Hz, 1H), 1.27 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=174.10$, 173.47, 70.35, 60.82, 60.49, 52.01, 38.68, 36.06, 35.11, 21.80, 13.21; MS (FAB+): m/z (%)=245 (100), 168 (12); HR-MS: $m/z=245.15013$, calcd. for $C_{11}H_{21}N_2O_4$: 245.14667.

The crude mixture containing **9** was dissolved in dichloromethane (20 mL) and Boc_2O (800 mg; 3.66 mmol) was added and the mixture stirred at room temperature. The progress of the reaction was monitored by TLC (ethyl acetate-hexane 1:1). After 6 h the reaction mixture was diluted with dichloromethane (45 mL) and washed with a saturated solution of $NaHCO_3$ (5 mL+1 g of solid $NaHCO_3$). The organic layer was dried with $MgSO_4$ and evaporated. Chromatography of the residue [ethyl acetate-hexane (3:1)→ethyl acetate, 15 g silica] afforded protected amide **10** as a white solid (yield: 260 mg, 50%) and ~10% of over-hydrogenated by-product *(1R,3S,4R,5R)-ethyl 4-acetamido-3-(tert-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate* (**11**).

Analytical data for major product 10: white solid; mp 174–175 °C (ethyl acetate-hexane); $R_f=0.3$ (ethyl acetate); $[\alpha]_D^{20}$: −33.51 (*c* 1, $CHCl_3$); IR (KBr): ν=3349, 2978, 2930, 2885, 2360, 2340, 1731, 1682, 1656, 1528, 1459.87, 1384, 1371, 1346, 1289, 1253, 1219, 1166, 1120, 1092, 1064, 1044, 1024, 1008, 988, 969, 958, 929, 905, 870, 800, 781, 755, 715, 696, 653, 624, 586, 545, 514, 464, 431 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=5.63$ (d, $J=9.3$ Hz, 1H), 4.96 (d, $J=8.7$ Hz, 1H), 4.57 (dd, 2 x $J=3.9$, 3.9 Hz, 1H), 4.33–4.18 (m, 2H), 4.00 (ddd, $J=11.4$, 9.3, 9.0 Hz, 1H), 3.86 (dd, $J=4.5$, 9.0 Hz, 1H), 3.38 (m, 1H), 2.83 (ddd, $J=4.2$, 4.2, 8.7 Hz, 1H), 2.12 (ddd, $J=3.9$, 3.9, 9.6 Hz, 1H), 2.01 (s, 3H), 1.92 (ddd, $J=13.2$, 13.2, 13.2 Hz, 1H), 1.43 (s, 9H), 1.36 (s, 3H), 1.28 (s, 3H), 1.27 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=171.27$, 170.40, 109.93, 79.73, 78.66, 73.76, 61.03, 55.22, 50.78, 41.38, 29.71, 28.33, 27.99, 26.23, 23.43, 14.16; MS (EI+): m/z (%)=385 (3) (M^+-CH_3), 341 (11), 329 (15), 311 (20); HR-MS: $m/z=385.19829$, calcd. for $C_{18}H_{29}N_2O_7$: 385.19748; anal. calcd. for $C_{19}H_{32}N_2O_7$: C 56.99, H 8.05, N 7.00; found: C 57.13, H 8.19, N, 6.93.

Analytical data for minor product 11 [(1*R*,3*S*,4*R*,5*R*)-Ethyl 4-Acetamido-3-(*tert*-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate]: gel-like solid; mp 180 °C (ethyl acetate-hexane); $R_F=0.1$ (ethyl acetate); $[\alpha]_D^{20}$: −90.0 (*c* 1, $CHCl_3$); IR (KBr): ν=3357, 2979, 2936, 2871, 1725, 1686, 1654, 1569, 1559, 1526, 1457, 1384, 1340, 1328, 1317, 1284, 1244, 1171, 1129, 1079, 1023, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=6.91$ (bs, 1H), 5.01 (d, $J=7.2$ Hz, 1H), 4.16–4.11 (m, 2H), 3.55 (m, 2H), 3.48 (m, 1H), 2.44 (dddd, $J=12.0$, 12.0, 3.6, 3.6 Hz, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 2.00 (s, 3H), 1.56–1.50 (m, 2H), 1.49 (s, 9H), 1.45 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=173.64$, 173.46, 80.38, 73.35, 62.01, 60.88, 50.61, 38.70, 36.16, 33.58, 28.26, 23.15, 14.14; MS (FAB+): m/z (%)=345 (M^++H), 289 (45), 245 (100), 168 (26); HR-MS: $m/z=345.20256$, calcd. for $C_{16}H_{29}N_2O_6$: 345.20525; anal. calcd. for $C_{16}H_{28}N_2O_6$: C5 5.80, H 8.19, N 8.13; found: C 55.25, H 8.24, N 7.56.

Procedure B ("One-Pot"): A suspension of oxime **8** (73 mg; 0.24 mmol), Boc_2O (0.105 mg; 0.48 mmol) and 20 mg Rh/Al_2O_3 (5%) in EtOH (96%, 2 mL) was hydrogenated in a Parr apparatus (60 pound/inch^2). After 16 h the reaction mixture was filtered through a short bed of celite and concentrated. Chromatography [ethyl acetate, 6 mL silica] afforded the amide **10** as a white solid; yield: 87 mg (93%).

(3*R*,4*R*,5*S*)-4-Acetylamino-5-*tert*-butoxycarbonylamino-3-hydroxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (12)

Acetonide **10** (534 mg; 1.33 mmol) was dissolved in EtOH (10 mL) and 12.4 mL of ethanolic sodium ethoxide solution (0.05 M) were added dropwise over a period of 1 min. After 5 min of stirring at room temperature reaction mixture was quenched by addition of 1 g of silica and then filtered and evaporated. Chromatography [ethyl acetate→ethyl acetate-ethanol (1:1), 5 g silica] of the residue afforded allyl alcohol **12** as a white solid; yield: 432 mg (94%); mp 177–178 °C (ethyl acetate-hexane); $R_f=0.2$ (ethyl acetate); $[\alpha]_D^{20}$: −9.14 (*c* 1, $CHCl_3$); IR (KBr): ν=3341, 2926, 2854, 2360, 2326, 1726, 1680, 1654, 1626, 1530, 1460, 1319, 1295, 1249, 1165, 1127, 1091, 1046, 1025, 992, 946, 908, 863, 782, 755, 735, 644, 607, 590, 571, 543, 491, 460, 437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta=7.35$ (d, $J=5.8$ Hz, 1H), 6.83 (dd, $J=2.4$, 2.4 Hz, 1H), 5.07 (bs, 1H), 4.92 (d, $J=7.9$ Hz, 1H), 4.36–4.29 (m, 1H), 4.27–4.16 (m, 2H), 3.85–3.83 (m, 1H), 3.77–3.73 (m, 1H), 2.84 (dd, 1H, $J=17.4$, 5.1 Hz, 1H), 2.21 (dddd, $J=17.4$, 11.0, 2 x ≈ 3 Hz, 1H), 2.03 (s, 3H), 1.47 (s, 9H), 1.30 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta=173.61$, 165.86, 157.64, 139.05, 127.65, 80.87, 73.60, 61.05, 60.55, 48.05, 30.83, 28.23, 23.09, 14.17; MS (FAB+): m/z (%)=343 (M^++H), 287 (100), 243 (25), 208 (30); HR-MS; $m/z=343.18417$, calcd. for $C_{16}H_{27}N_2O_6$: 343.18691; anal. calcd. for $C_{16}H_{27}N_2O_6$: C 56.13, H 7.65, N 8.18; found: C 56.31, H 7.83, N 8.17.

Supporting Information

Experimental procedures and ^{1}H- and ^{13}C NMR spectra for compounds **3**–**15** are available as Supporting Information.

Acknowledgements

The authors are grateful to the following agencies for financial support of this work: Natural Sciences and Engineering Research Council of Canada (NSERC), (Idea to Innovation and Discovery Grants), TDC Research, Inc., Brock University, Research Corporation, and the Ontario Partnership for Innovation and Commercialization (OPIC).

References

[1] B. Sullivan, I. Carrera, M. Drouin, T. Hudlicky, *Angew. Chem.* **2009**, *121*, 4293–4295; *Angew. Chem. Int. Ed.* **2009**, *48*, 4229–4231.

[2] For the most recent reviews of approaches to Tamiflu see: a) J. Magano *Chem. Rev.* **2009**, *109*, ASAP; b) M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, *11*, 1839; c) V. Farina, J. D. Brown, *Angew. Chem.* **2006**, *118*, 7488; *Angew. Chem. Int. Ed.* **2006**, *45*, 7330.

[3] a) T. Hudlicky, *Processes for the preparation of oseltamivir and analogs thereof. International PCT Applica-*

tion No. PCT/CA2009/000622, **2009**; b) T. Hudlicky, L. Werner, A. Machara, *Process for the preparation of intermediates useful for the manufacture of oseltamivir and analogs. US Provisional Patent Application* 61/254311, **2009**.

[4] For syntheses of oseltamivir or Tamiflu see: a) C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver, R. C. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 681; b) C. U. Kim, W. Lew, M. A. Williams, H. Wu, L. Zhang, X. Chen, P. A. Escarpe, D. B. Mendel, W. G. Laver, R. C. Stevens, . *J. Med.-Chem.* **1998**, *41*, 2451; c) J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545; d) M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi, A. G. Zwahlen *Org. Process Res. Dev.* **1999**, *3*, 266; e) M. Karpf, R. Trussardi, *J. Org. Chem.* **2001**, *66* , 2044; f) P. J. Harrington, J. D. Brown, T. Foderaro, R. C. Hughes, *Org. Process Res. Dev.* **2004**, *8*, 86; g) Y. Sungwoo Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310; h) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312; i) X. Cong, J.-Z. Yao, *J. Org. Chem.* **2006**, *71*, 5365; j) J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-C. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 11892; k) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2007**, *119*, 5836; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; l) K. M. Bromfield, H. Gradén, D. P. Hagberg, T. Olsson, N. Kann, *Chem. Commun.* **2007**, 3183; m) T. Mita, N. Fukuda, F. X. Roca, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 259; n) K. Yamatsugu, S. Kamijo, Y. Suto, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2007**, *48*, 1403; o) M. Matveenko, A. C. Willis, M. G. Banwell, *Tetrahedron Lett.* **2008**, *49*, 7018; p) J.-J. Shie, J.-M. Fang, C.-H. Wong, *Angew. Chem.* **2008**, *120*, 5872; *Angew. Chem. Int. Ed.* **2008**, *47*, 5788; q) N. T. Kipassa, H. Okamura, K. Kina, T. Hamada, T. Iwagawa, *Org. Lett.* **2008**, *10*, 815; r) B. M. Trost, T. Zhang, *Angew. Chem.* **2008**, *120*, 3819 Angew. Chem. Int. Ed. **2008**, 47, 3819; s) U. Zutter, H. Iding, P. Spurr, B. Wirz, *J. Org. Chem.* **2008**, *73*, 4895; t) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304; u) K. Yamatsugu, L. Yin, S. Kamijo, Y. Kimura, M. Kanai, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 1090; *Angew. Chem. Int. Ed.* **2009**, *48*, 1070; v) T. Oshitari, T. Mandai, *Synlett* **2009**, 787; w) B. Carbain, S. R. Martin, P. J. Collins, P. B. Hitchcock, H. Streicher, *Org. Biomol. Chem.* **2009**, *7*, 257; x) K. Yamatsugu, M. Kanai, M. Shibasaki, *Tetrahedron* **2009**, *65*, 601; y) R. Resende, C. Glover, A. G. Watts, *Tetrahedron Lett.* **2009**, *50*, 4009; for commercial syntheses see: Refs.[4a,4c,4d] and z) S. Abrecht, M. C. Federspiel, H. Estermann, R. Fischer, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi, U. Zutter, *Chimia* **2007**, *61*, 93.

[5] G. J. Zylstra, D. T. Gibson, *J. Biol. Chem.* **1989**, *264*, 14940.

[6] See, for example: a) F. A. Luzzio, *Org. React.* **1998**, *53*, 1; b) W. G. Dauben, D. M. Michno, *J. Org. Chem.* **1977**, *42*, 682.

[7] See, for example: a) M. Hudlicky, in: *Oxidations in Organic Chemistry*, ACS Monograph 186, American Chemical Society (Washington, D.C.), **1990**, pp 86–87; b) P. A. Wender, M. A. Eissenstadt, M. P. Filosa, *J. Am. Chem. Soc.* **1979**, *101*, 2196.

[8] A. F. Morel, E. L. Larghi, M. M. Selvero, *Synlett* **2005**, *18*, 2755.

[9] J. Andraos, *Org. Process Res. Dev.* **2009**, *13*,161–185.

[10] F. Fabris, J. Collins, B. Sullivan, H. Leisch, T. Hudlicky, *Org. Biomol. Chem.* **2009**, *7*, 2619.

[11] M. A. Endoma, V. P. Bui, J. Hansen, T. Hudlicky, *Org. Process Res. Dev.* **2002**, *6*, 525.

