Formal Synthesis of (–)-Oseltamivir Phosphate

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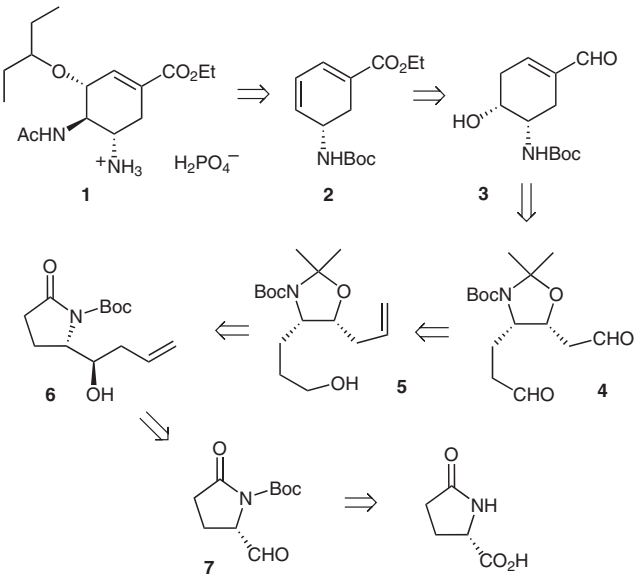
Abstract: The formal synthesis of (–)-oseltamivir phosphate (Tamiflu™) was accomplished starting from (*S*)-pyroglutamic acid. The synthesis comprised two carbon–carbon bond forming reactions, the first one being a diastereoselective, indium-mediated allylation of a pyroglutamic aldehyde derivative. However, attempts to effect the second carbon–carbon bond formation – cyclohexene ring closure – using an enol-*exo* aldolization of a dialdehyde resulted in the formation of a product with the opposite regioselectivity. This shortcoming could be overcome by using a reaction sequence of Mannich methylenation/ring-closing metathesis, which provided the desired regioisomer in high yield.

Key words: antiviral agents, allylation, cyclization, metathesis, total synthesis

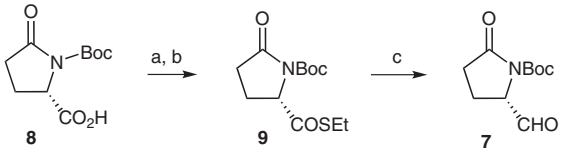
As the most important therapeutic agent against the avian flu, oseltamivir (Tamiflu™) has attracted considerable attention from the synthetic community. While the commercial production still relies on the semi-synthetic route reported by Gilead and Roche scientists,[1,2] a number of total syntheses have been developed.[3,4] Whereas the synthesis by Hayashi[3aa] will hardly be surpassed in terms of efficiency, numerous synthetic studies and ingenious synthetic approaches to this small, but densely functionalized molecule enable access to structural analogues, which may also be of interest to medicinal chemists; in addition, these studies contribute to the development of synthetic methodology.

Our approach to the enantioselective synthesis of Tamiflu™ (**1**) targeted optically pure amine **2** – a key intermediate in the syntheses of Tamiflu™ by Corey[3a] and by Kann.[3f] Retrosynthetic simplification of this compound, delineated in Scheme 1, proceeds via the unsaturated aldehyde **3**, which is in turn obtainable by an intramolecular aldol reaction. The suitable precursor for the latter reaction – dialdehyde **4** – could be formed by a double oxidation of the unsaturated alcohol **5**. Indium-mediated allylation of pyroglutamic aldehyde **7**, followed by reductive opening of the intermediary amide **6**, should produce alcohol **5** in optically pure form.

N-Boc-protected pyroglutamic aldehyde **7** was prepared according to a three-step procedure, comprising the conversion of *N*-Boc-protected pyroglutamic acid[5] into the corresponding ethyl thioester **9**, which was then reduced to aldehyde **7** (Scheme 2). The palladium-mediated reduction of thioesters into aldehydes was developed by Fukuyama,[6] and we have shown previously that it can be successfully applied to the synthesis of optically enriched amidoaldehydes, such as the Garner aldehyde.[7] In the present case, aldehyde **7** was obtained in 85% yield (over three steps) and with an optical purity of 95.5% ee.[8]



Scheme 1 Retrosynthetic analysis of Tamiflu™



Scheme 2 *Reagents and conditions*: a) *i*-BuOCOCl, Et_3N, THF, 0 °C; b) EtSH, Et_3N, 0 °C to r.t., 14 h (90%); c) Et_3SiH, Pd/C, acetone, r.t., 30 min (94%).

The formation of the carbon skeleton commenced with an indium-mediated allylation of aldehyde **7** under aqueous conditions, which produced homoallylic alcohol **6** stereoselectively (82%, *anti*/*syn* = 9:1; Scheme 3). Reductive opening of the lactam ring with aqueous sodium borohydride afforded unsaturated diol **10** (86%), which was protected as aminal **5** upon treatment with 2,2-dimethoxypropane (95%). A NOESY experiment on this cyclic derivative **5** confirmed its *cis*-configuration, and hence the *anti*-stereochemical outcome of the allylation reaction. The original synthetic plan now called for the

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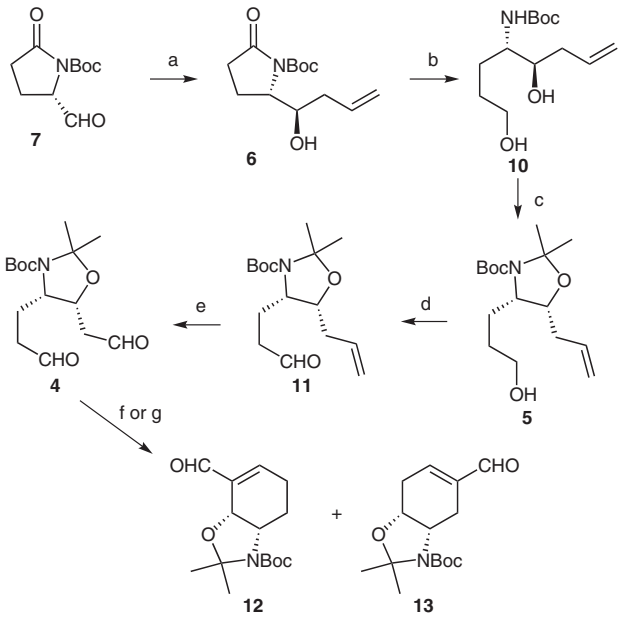
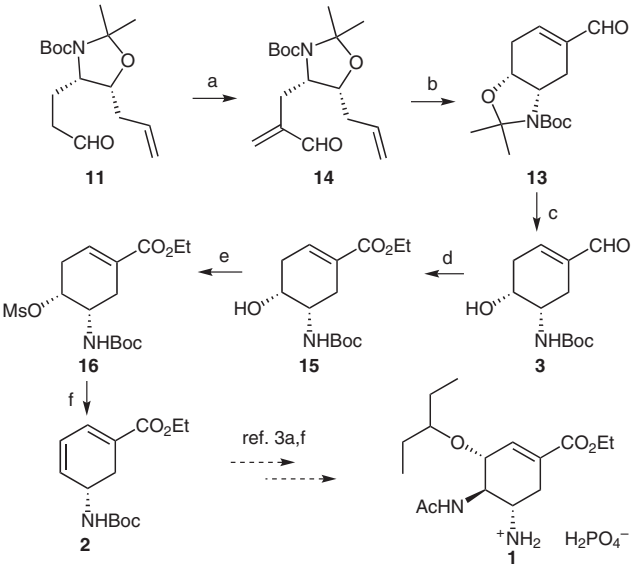
double oxidation of alkenol **5** into dialdehyde **4**. The first step – oxidation of the primary alcohol into aldehyde **11** – was accomplished by treatment of **5** with Dess–Martin periodinane[9] in 85% yield. Subsequent alkene cleavage was effected with osmium tetroxide/sodium periodate. Dialdehyde **4** was too unstable to be purified by chromatography; therefore, crude **4** was directly exposed to conditions for cyclization. Unfortunately, the base-catalyzed cyclization produced regioselectively the undesired isomer **12**; similar results were obtained by enamine catalysis.



Scheme 3 *Reagents and conditions*: a) In, allyl bromide, THF, r.t., 15 h, 82%; b) $NaBH_4$, THF, H_2O, r.t., 15 h; c) 2,2-dimethoxypropane, *p*-TsOH (cat.), CH_2Cl_2, 95%; d) DMP, CH_2Cl_2, r.t., 15 min, 85%; e) OsO_4 (cat.), $NaIO_4$, THF, H_2O; f) DBA·TFA (cat.), toluene, r.t., 15 h, 27% from **11**, **12**/**13** = 5.5:1; g) KOH, CH_2Cl_2, H_2O, TEBA (cat.), r.t., 32% from **11**, **12**/**13** = >10:1.

Therefore, in order to circumvent this regioselectivity problem, a modification of the original synthetic plan was needed. Thus, we resorted to the ring-closing metathesis as a suitable method for the regioselective ring closure. The aldehyde **11** was not oxidatively fragmented, but exposed to Eschenmoser's salt instead, to give enal **14** (87%; Scheme 4). Although the methylenation reaction under these conditions worked well, an organocatalyzed variant was also tried. In the presence of catalytic amounts of pyrrolidine and propanoic acid, in aqueous formaldehyde, the starting aldehyde was smoothly converted into enal **14**.[10] Upon treatment with second generation Grubbs' metathesis catalyst,[11] **14** was converted into cyclohexenecarbaldehyde **13** in high yield (92%). The remaining steps for the conversion of **13** into **2** were straightforward: after deprotection of the aminal with lithium chloride in acetic acid,[12] the aldehyde functionality in **3** was oxidized into carboxylic ester **15**. After some experimentation, we found that this transformation was best accomplished by treatment with Oxone® in DMF,[13] followed by esterification under basic conditions (46% over two steps, i.e., from **3**; in our hands, direct oxidation of aldehyde to the ester did not work). Mesylation of the hydroxyl group in **15**, followed by DBU-induced elimination, could be accomplished as a one-pot procedure, to give the required intermediate **2** (51% over two steps); however, better yields were obtained when mesylation (89%) and elimination (87%) steps were performed separately. Intermediate **2** thus obtained was identical to the compound reported in the literature in all respects,[3a,f] thus completing the formal synthesis of (–)-oseltamivir phosphate.



Scheme 4 *Reagents and conditions*: a) $Me_2N{=}CH_2I$, Et_3N, CH_2Cl_2, r.t., 15 h, 87%; or aq CH_2O, propanoic acid (cat.), pyrrolidine (cat.), *i*-PrOH, r.t., 66%; b) Grubbs 2nd generation Ru-catalyst (cat.) CH_2Cl_2, 35 °C, 1 h, 92%; c) LiCl, AcOH, H_2O, r.t., 3 h, 70%; d) 1. Oxone®, DMF, r.t., 1 h; 2. EtI, K_2CO_3, DMSO, r.t., 40 h, 46% from **3**; e) MsCl, Et_3N, CH_2Cl_2, 89%; f) DBU, CH_2Cl_2, 87%.

To summarize, a formal synthesis of (–)-oseltamivir phosphate was achieved starting from the pyroglutamic aldehyde derivative as a chiral synthon. Characteristic features of the synthesis are the indium-promoted diastereoselective allylation of the amidoaldehyde and the application of the methylenation/ring-closing metathesis reaction sequence as a means to effect the regioselective closure of the cyclohexene ring, which could not be accomplished under conditions of the aldol reaction.

All chromatographic separations were performed on silica gel, 10–18, 60 Å (dry-flash) and 100–200 60Å (column chromatography), ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. Petroleum ether (PE) refers to the fraction boiling at 70–72 °C. NMR spectra were recorded on Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) and Varian Gemini 200 spectrometers (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz). Chemical shifts are expressed in ppm (δ) using TMS as the internal standard. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Microanalyses were performed using the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme

GmbH, Hanau, Germany. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotation was determined on a Rudolph Research Analytical AUTOPOL IV Automatic Polarimeter.

tert-Butyl (_S_)-2-(Ethylthiocarbonyl)-5-oxopyrrolidine-1-carboxylate (9)

Isobutyl chloroformate (0.89 g, 0.85 mL, 6.50 mmol) and Et_3N (0.76 g, 1.05 mL, 7.53 mmol) were added to a cold (0 °C) solution of (*S*)-1-(*tert*-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid (**8**;[5] 1.14 g, 4.95 mmol) in THF (17 mL), under an argon atmosphere. The reaction mixture was vigorously stirred for 30 min at 0 °C; then ethanethiol (0.70 g, 0.85 mL, 11.36 mmol) and Et_3N (0.76 g, 1.05 mL, 7.53 mmol) were added. The resulting solution was stirred for 30 min at 0 °C and 45 min at r.t. The mixture was diluted with CH_2Cl_2 (25 mL) and the organic layer was washed with H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (SiO_2; eluent: PE–EtOAc, 7:3) to give 1.22 g (90%) of the title compound **9** as colorless crystals; mp 53–56 °C (Lit.[8] mp 58.7–60.9 °C); R_f = 0.47 (SiO_2, PE–EtOAc, 7:3); $[\alpha]_D^{20}$ –45.9 (*c* 1.05, $CHCl_3$) {Lit.[8] $[\alpha]_D^{20}$ –47.4 (*c* 1.02, $CHCl_3$)}.

IR (ATR): 2974, 2931, 2874, 1797, 1707, 1678, 1369, 1309, 1257, 1160, 1025, 992, 842 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.72 (dd, *J* = 9.6, 2.6 Hz, 1 H), 3.03–2.90 (m, 2 H), 2.66 (ddd, *J* = 17.6, 10.2, 9.8 Hz, 1 H), 2.49 (ddd, *J* = 17.6, 9.5, 3.1 Hz, 1 H), 2.40–2.28 (m, 1 H), 2.09–1.99 (m, 1 H), 1.50 (s, 9 H), 1.29 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.1 (C), 173.3 (C), 148.8 (C), 83.7 (C), 65.2 (CH), 30.7 (CH_2), 27.8 (CH_3), 23.1 (CH_2), 22.2 (CH_3), 14.5 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}NO_4S$ $[M + Na]^+$: 296.0927; found: 296.0933.

Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.63; H, 6.99; N, 5.12; S, 11.57.

tert-Butyl (_S_)-2-Formyl-5-oxopyrrolidine-1-carboxylate (7)

Et_3SiH (1.46 g, 2.0 mL, 12.52 mmol) was added over 30 min to a suspension of thioester **9** (1.15 g, 4.21 mmol) and 10% Pd/C (220 mg, 0.21 mmol) in acetone (40 mL) at r.t. under an argon atmosphere. The reaction mixture was stirred for an additional 15 min, then filtered, and concentrated under reduced pressure. The residue was purified by dry-flash chromatography (SiO_2; eluent: PE–EtOAc, 1:2) to give 0.84 g (94%) of the aldehyde **7** as a colorless oil;[8] R_f = 0.25 (SiO_2, PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –42.4 (*c* 1.11, $CHCl_3$).

IR (ATR): 3460, 2980, 2936, 1786, 1741, 1714, 1459, 1368, 1313, 1256, 1155, 1024, 847 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 2.0 Hz, 1 H), 4.59 (ddd, *J* = 9.5, 4.8, 2.0 Hz, 1 H), 2.61–2.47 (m, 2 H), 2.30–2.22 (m, 1 H), 2.10–2.03 (m, 1 H), 1.51 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 196.9 (CH), 173.0 (C), 149.3 (C), 84.2 (C), 64.2 (CH), 31.1 (CH_2), 27.8 (CH_3), 18.2 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{15}NO_4$ $[M + Na]^+$: 236.0893; found: 236.0888.

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.00; H, 7.16; N, 6.51.

tert-Butyl (_S_)-2-[(_R_)-1-Hydroxybut-3-enyl]-5-oxopyrrolidine-1-carboxylate (6)

Allyl bromide (1.34 g, 0.96 mL, 11.09 mmol) and In powder (460 mg, 4.00 mmol) were added to a solution of aldehyde **7** (790 mg, 3.70 mmol) in H_2O–THF (36 mL, v/v = 3:1). The reaction mixture was vigorously stirred for 16 h, diluted with H_2O (25 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was and purified by dry-flash chromatography (SiO_2, eluent: PE–EtOAc, 1:2) to give 775 mg (82%) of alcohol **6** as colorless crystals; mp 152–154 °C; R_f = 0.54 (SiO_2, PE–EtOAc, 1:2); $[\alpha]_D^{20}$ –78.5 (*c* 1.03, $CHCl_3$).

IR (ATR): 3437, 3075, 2975, 2936, 1787, 1695, 1638, 1393, 1320, 1292, 1255, 1162, 1027, 910, 856 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.82 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1 H), 5.20–5.12 (m, 2 H), 4.14 (dt, *J* = 9.2, 1.6 Hz, 1 H), 4.11–4.07 (m, 1 H), 2.75 (dt, *J* = 17.7, 10.1 Hz, 1 H), 2.38 (ddd, *J* = 17.7, 10.2, 2.5 Hz, 1 H), 2.31 (d, *J* = 4.0 Hz, 1 H), 2.30–2.20 (m, 2 H), 2.09 (ddt, *J* = 12.2, 9.9, 2.3 Hz, 1 H), 2.03–1.93 (m, 1 H), 1.53 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.3 (C), 150.2 (C), 134.0 (CH), 118.4 (CH_2), 83.0 (C), 71.4 (CH), 61.3 (CH), 38.4 (CH_2), 32.6 (CH_2), 28.1 (CH_3), 17.5 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{21}NO_4$ $[M + Na]^+$: 278.1363; found: 278.1363.

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.83; H, 8.00; N, 5.61.

tert-Butyl (4_S_,5_R_)-1,5-Dihydroxyoct-7-en-4-ylcarbamate (10)

A mixture of $NaBH_4$ (452 mg, 11.95 mmol) and alcohol **6** (750 mg, 2.94 mmol) in THF–H_2O (25 mL, v/v = 4:1) was stirred for 18 h at r.t. The reaction mixture was quenched by the addition of sat. aq NH_4Cl (20 mL) and stirred until excess $NaHB_4$ completely decomposed. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2, PE–EtOAc, 1:4) afforded 657 mg (86%) of the title compound **10** as colorless crystals; mp 96–100 °C; R_f = 0.33 (SiO_2, PE–EtOAc, 1:4); $[\alpha]_D^{20}$ –25.6 (*c* 1.10, $CHCl_3$).

IR (ATR): 3352, 2981, 2935, 2875, 1686, 1531, 1446, 1368, 1342, 1303, 1252, 1174, 1044, 976, 911 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.89–5.81 (m, 1 H), 5.18–5.10 (m, 2 H), 4.90 (d, *J* = 8.8 Hz, 1 H), 3.67 (t, *J* = 6.0, 2 H), 3.66–3.62 (m, 2 H), 2.79 (s, 1 H), 2.44 (s, 1 H), 2.32–2.27 (m, 1 H), 2.23–2.17 (m, 1 H), 1.75–1.53 (m, 3 H), 1.44 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.4 (C), 134.8 (CH), 118.0 (CH_2), 79.5 (C), 73.5 (CH_2), 62.4 (CH_2), 54.5 (CH), 38.2 (CH_2), 28.9 (CH_2), 28.4 (CH_3), 25.9 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{25}NO_4$ $[M + Na]^+$: 282.1676; found: 282.1680.

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 59.89; H, 9.89; N, 5.68.

tert-Butyl (4_S_,5_R_)-5-Allyl-4-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (5)

A solution of 2,2-dimethoxypropane (0.72 g, 0.85 mL, 6.91 mmol), *p*-TsOH (23.7 mg, 0.12 mmol) and diol **10** (600 mg, 2.31 mmol) in CH_2Cl_2 (23 mL) was stirred for 45 min at r.t., and then concentrated under reduced pressure (when it turned red). Purification of the crude product by dry-flash chromatography (SiO_2, PE–EtOAc, 7:3) afforded 599 mg (86%) of the title compound **5** as a colorless viscous oil; R_f = 0.42 (SiO_2, PE–EtOAc, 7:3); $[\alpha]_D^{20}$ +5.6 (*c* 1.13, $CHCl_3$).

IR (ATR): 3448, 3079, 2979, 2933, 2869, 1697, 1456, 1395, 1255, 1179, 1130, 1072, 917 cm^{-1}.

^1H NMR (500 MHz, 65 °C, DMSO-d_6): δ = 5.82 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H), 5.15 (dq, *J* = 17.3, 1.6 Hz, 1 H), 5.06 (dq, *J* = 10.3, 1.3 Hz, 1 H), 4.14 (s, 1 H), 4.07 (ddd, *J* = 7.3, 6.3, 5.1 Hz, 1 H), 3.81 (s, 1 H), 3.41 (dd, *J* = 11.7, 6.1 Hz, 2 H), 2.34–2.28 (m, 2 H), 1.66–1.59 (m, 1 H), 1.52–1.36 (m, 3 H), 1.48 (s, 3 H), 1.46 (s, 3 H), 1.43 (s, 9 H).

^{13}C NMR (126 MHz, 65 °C, DMSO-d_6): δ = 151.1 (C), 134.3 (CH), 116.4 (CH_2), 91.4 (C), 78.5 (C), 75.5 (CH), 60.7 (CH_2), 58.0 (CH), 32.4 (CH_2), 29.2 (CH_2), 27.8 (CH_3), 26.7 (CH_3), 25.8 (CH_2), 23.4 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{29}NO_4$ [M + Na]$^+$: 322.1989; found: 322.1993.

Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.25; H, 9.68; N, 4.80.

tert-Butyl (4*S*,5*R*)-5-Allyl-2,2-dimethyl-4-(3-oxopropyl)oxazolidine-3-carboxylate (11)

Dess–Martin periodinane (DMP; 1.17 g, 2.76 mmol) was added to a solution of aminoacetal **5** (550 mg, 1.84 mmol) in CH_2Cl_2 (18.5 mL) and the reaction mixture was stirred for 15 min at r.t. The mixture was diluted with CH_2Cl_2 (30 mL). The organic layer washed with 10% aq $Na_2S_2O_3$ (25 mL) and sat. aq $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2, PE–EtOAc, 8:2) afforded 465 mg (85%) of the title compound **11** as a colorless viscous oil; R_f = 0.46 (SiO_2, PE–EtOAc, 8:2); $[\alpha]_D^{20}$ –2.4 (*c* 1.01, $CHCl_3$).

IR (ATR): 3079, 2980, 2937, 2874, 2825, 2722, 1726, 1695, 1645, 1389, 1254, 1178, 1132, 1072, 918 cm^{-1}.

^{1}H NMR (500 MHz, 65 °C, DMSO-d_6): δ = 9.68 (s, 1 H), 5.83 (ddt, *J* = 17.0, 10.3, 6.5 Hz, 1 H), 5.16 (dq, *J* = 17.2, 1.7 Hz, 1 H), 5.08 (dq, *J* = 10.3, 1.3 Hz, 1 H), 4.13–4.03 (m, 1 H), 3.83 (br s, 1 H), 2.53–2.38 (m, 2 H), 2.34–2.27 (m, 2 H), 1.95–1.82 (m, 1 H), 1.67–1.59 (m, 1H), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.43 (s, 9 H).

^{13}C NMR (126 MHz, 65 °C, DMSO-d_6): δ = 201.9 (CH), 151.2 (C), 134.1 (CH), 116.7 (CH_2), 91.7 (C), 78.9 (C), 75.2 (CH), 57.3 (CH), 39.4 (CH_2), 32.3 (CH_2), 27.7 (CH_3), 26.8 (CH_3), 24.2 (CH_3), 21.4 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}NO_4$ [M + Na]$^+$: 320.1832; found: 320.1838.

Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.42; H, 9.35; N, 4.78.

tert-Butyl (3a*S*,7a*R*)-7-Formyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*]oxazole-3(2*H*)-carboxylate (12) (Organocatalyzed Cyclization)

*tert-Butyl (4S,5R)-2,2-Dimethyl-5-(2-oxoethyl)-4-(3-oxopropyl)oxazolidine-3-carboxylate (**4**)*: $NaIO_4$ (27.0 mg, 0.126 mmol) and a 2.5% solution of OsO_4 (1.25 mg, 50 μL, 0.05 mmol) were added to a solution of aldehyde **11** (7.0 mg, 0.024 mmol) in H_2O–THF (1.05 mL, v/v = 1:2). The reaction mixture was stirred for 3 h at r.t., quenched with $NaHSO_3$ (100 mg), and stirred for an additional 30 min at r.t. The mixture was diluted with EtOAc (15 mL) and H_2O (15 mL). The organic layer was washed with 10% aq $Na_2S_2O_3$ (15 mL), sat. aq $NaHCO_3$ (15 mL), and H_2O (15 mL). The organic extract was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was used in the next step without further purification.

*tert-Butyl (3aS,7aR)-7-Formyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (**12**)*: A solution of dialdehyde **4** (~7 mg, 0.024 mmol) and dibenzylamine trifluoroacetate (DBA·TFA; 9.1 mg, 0.031 mmol) in toluene (0.26 mL) was stirred at r.t. for 18 h. The mixture was diluted with CH_2Cl_2 (10 mL), the organic layer washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; eluent: benzene–EtOAc, 7:3) afforded 1.8 mg (27%, over two steps, i.e., from aldehyde **11**) of a mixture of compounds **12** and **13** (in a molar ratio **12**/**13** = 5.5:1, as determined by ^{1}H NMR analysis) as a colorless viscous oil.

Spectral Data for 12

IR (film): 2978, 2936, 2876, 2814, 1693, 1391, 1254, 1215, 1174, 1147, 1089, 1022, 886 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 7.12 (s, 1 H), 4.70 (s, 1 H), 3.95–3.74 (m, 1 H), 2.55–2.50 (m, 1 H), 2.35–2.11 (m, 2 H), 1.67–1.45 (m, 17 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.3 (CH), 154.9 (CH), 152.3 (C), 138.2 (C), 93.5 (C), 80.3 (C), 65.3 (CH), 55.0 (CH), 28.5 (CH_3), 27.4 (CH_3), 25.2 (CH_3), 24.2 (CH_2), 23.6 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{21}NO_4$ [M + Na]$^+$: 304.1519; found: 304.1509.

tert-Butyl (3a*S*,7a*R*)-7-Formyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*]oxazole-3(2*H*)-carboxylate 12 (KOH-Catalyzed Cyclization)

*tert-Butyl (4S,5R)-2,2-Dimethyl-5-(2-oxoethyl)-4-(3-oxopropyl)oxazolidine-3-carboxylate (**4**)*: $NaIO_4$ (43.0 mg, 0.201 mmol) and a 2.5% solution of OsO_4 (0.5 mg, 20 μL, 0.02 mmol) were added to a solution of aldehyde **11** (10.4 mg, 0.035 mmol) in H_2O–THF (1.6 mL, v/v = 1:2). The reaction mixture was stirred for 3 h at r.t., quenched with $NaHSO_3$ (100 mg), and stirred for an additional 30 min at r.t. The mixture was diluted with EtOAc (15 mL) and H_2O (15 mL). The organic layer was washed with 10% aq $Na_2S_2O_3$ (15 mL), sat. aq $NaHCO_3$ (15 mL), and H_2O (15 mL). The organic extract was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was used in the next step without further purification.

*tert-(3aS,7aR)-Butyl 7-Formyl-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d]oxazole-3(2H)-carboxylate (**12**)*: A solution of dialdehyde **4** (10.5 mg, 0.035 mmol), Et_3BnCl (TEBAC; 8.0 mg, 0.035 mmol), CH_2Cl_2 (0.21 mL), and 10% solution of KOH (0.21 mL) was vigorously stirred at 35 °C for 16 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with sat. aq NH_4Cl (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: PE–EtOAc, 7:3) afforded 3.2 mg (32%, over two steps, i.e., from aldehyde **11**) of a mixture of compounds **12** and **13** (in a molar ratio **12**/**13** = 8:1, as determined by ^{1}H NMR analysis) as a colorless viscous oil, whose physical data were identical to those of the sample prepared using DBA·TFA (see, above).

tert-Butyl (4*S*,5*R*)-5-Allyl-4-(2-formylallyl)-2,2-dimethyloxazolidine-3-carboxylate (14) (Using the Eschenmoser's Salt)

A solution of Eschenmoser's salt (208 mg, 1.12 mmol), Et_3N (145.2 mg, 0.2 mL, 1.43 mmol), and aldehyde **11** (62.2 mg, 0.21 mmol) in CH_2Cl_2 (10.5 mL) was stirred for 18 h at r.t. Without workup and concentration, the reaction mixture was purified by dry-flash chromatography (by pouring the CH_2Cl_2 solution directly onto the column; SiO_2, PE–EtOAc, 85:15) to give 56.5 mg (87%) of the title compound **14** as a colorless viscous oil; R_f = 0.41 (SiO_2, PE–EtOAc, 85:15); $[\alpha]_D^{20}$ –0.6 (*c* 1.07, $CHCl_3$).

IR (ATR): 2981, 2935, 2872, 1740, 1695, 1644, 1386, 1246, 1178, 1133, 1078, 1050, 947 cm^{-1}.

^{1}H NMR (500 MHz, 65 °C, DMSO-d_6): δ = 9.52 (br s, 1 H), 6.41–5.91 (m, 2 H), 5.81 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1 H), 5.16 (ddd, *J* = 17.3, 3.5, 1.6 Hz, 1 H), 5.09 (ddd, *J* = 10.3, 3.2, 1.3 Hz, 1 H), 4.13–4.07 (m, 1 H), 4.04 (br s, 1 H), 2.54 (dd, *J* = 13.4, 4.3 Hz, 1 H), 2.33–2.24 (m, 2 H), 2.12 (dd, *J* = 13.3, 9.3 Hz, 1 H), 1.55 (s, 3 H), 1.46 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 193.9 (CH), 151.1 (C), 146.2 (C), 135.5 (CH_2), 133.8 (CH), 116.8 (CH_2), 91.7 (C), 78.8 (CH), 75.3 (C), 56.6 (CH), 32.3 (CH_2), 28.1 (CH_2), 27.6 (CH_3), 24.5 (CH_3), 23.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{27}NO_4$ [M + Na]$^+$: 332.1832; found: 332.1817.

Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.84; H, 8.79; N, 4.56.

***tert*-Butyl (4*S*,5*R*)-5-Allyl-4-(2-formylallyl)-2,2-dimethyloxazolidine-3-carboxylate (14) (Organocatalyzed Reaction)**

A solution of 38% aq formaldehyde (0.34 g, 0.31 mL, 4.28 mmol), propionic acid (24.8 mg, 25 μL, 0.34 mmol), pyrrolidine (21.3 mg, 25 μL, 0.30 mmol), and aldehyde **11** (381.5 mg, 1.28 mmol) in *i*-PrOH (4.5 mL) was stirred for 18 h at r.t. The mixture was diluted with EtOAc (50 mL) and the EtOAc layer was washed with H_2O (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2, PE–EtOAc, 85:15) afforded 261 mg (66%) of the title compound **14** as a colorless viscous oil, whose physical data were identical to those of the sample prepared using the Eschenmoser salt (see above).

***tert*-Butyl (3a*S*,7a*R*)-5-Formyl-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*]oxazole-3(2*H*)-carboxylate (13)**

A solution of the 2nd generation Grubbs catalyst[10] (26.1 mg, 0.03 mmol) and aldehyde **14** (299.1 mg, 0.97 mmol) in CH_2Cl_2 (16.1 mL) was stirred at 35 °C for 1 h under an argon atmosphere. The reaction mixture was concentrated and purified by dry-flash chromatography (SiO_2, PE–EtOAc, 8:2) to afford 250 mg (92%) of the title compound **13** as a pale yellow viscous oil; R_f = 0.26 (SiO_2, PE–EtOAc, 8:2); $[\alpha]_D^{20}$ +85.2 (*c* 1.01, $CHCl_3$).

IR (ATR): 3449, 2979, 2936, 1693, 1455, 1394, 1372, 1257, 1175, 1097, 1034, 867 cm^{-1}.

^1H NMR (500 MHz, 65 °C, DMSO-d_6): δ = 9.49 (s, 1 H), 6.98–6.93 (m, 1 H), 4.40 (td, *J* = 5.7, 2.0 Hz, 1 H), 3.88 (dd, *J* = 12.7, 6.6 Hz, 1 H), 2.76 (dqd, *J* = 19.5, 3.9, 1.8 Hz, 1 H), 2.67 (dd, *J* = 16.6, 7.0 Hz, 1 H), 2.58 (ddt, *J* = 19.6, 4.3, 1.9 Hz, 1 H), 1.99 (ddq, *J* = 16.6, 6.8, 1.9 Hz, 1 H), 1.50–1.40 (m, 15 H).

^{13}C NMR (126 MHz, 65 °C, DMSO-d_6): δ = 192.2 (CH), 150.9 (C), 147.7 (CH), 138.4 (C), 91.8 (C), 78.8 (C), 70.0 (CH), 53.3 (CH), 28.2 (CH_2), 27.8 (CH_3), 26.7 (CH_3), 23.5 (CH_3), 23.2 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}NO_4$ $[M + Na]^+$: 304.1519; found: 304.1507.

***tert*-Butyl (1*S*,6*R*)-3-Formyl-6-hydroxycyclohex-3-enylcarbamate (3)**

A solution of aldehyde **13** (53.7 mg, 0.19 mmol) and LiCl (29.0 mg, 0.50 mmol) in AcOH–H_2O (0.65 mL, v/v = 9:1) was stirred for 1 h at r.t., and then diluted with EtOAc (10 mL). The EtOAc layer was washed with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO_2, PE–EtOAc, 1:1) afforded 32.1 mg (70%) of the title compound **3** as a colorless viscous oil; R_f = 0.33 (SiO_2, PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –28.1 (*c* 0.88, $CHCl_3$).

IR (ATR): 3372, 2978, 2831, 2820, 2724, 1682, 1646, 1519, 1393, 1367, 1284, 1249, 1167, 1077, 1045, 1022, 914, 875 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 6.71 (br t, *J* = 3.7 Hz, 1 H), 4.88 (br s, 1 H), 4.16–4.13 (m, 1 H), 3.91–3.79 (m, 1 H), 3.09 (br s, 1 H), 2.74–2.69 (m, 1 H), 2.64–2.49 (m, 2 H), 2.34–2.21 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.8 (CH), 156.3 (C), 146.9 (CH), 138.9 (C), 80.2 (C), 67.6 (CH), 49.3 (CH), 33.5 (CH_2), 28.3 (CH_3), 24.4 (CH_2).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}NO_4$ $[M + K]^+$: 280.0946; found: 280.0939.

Ethyl (4*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-4-hydroxycyclohex-1-enecarboxylate (15)

(4R,5S)-5-(tert-Butoxycarbonylamino)-4-hydroxycyclohex-1-enecarboxylic Acid: A mixture of aldehyde **3** (13.0 mg, 0.054 mmol), Oxone® (82.8 mg, 0.269 mmol), and DMF (0.3 mL) was stirred at r.t. for 4.5 h. The reaction mixture was diluted with EtOAc (10 mL), the organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), concentrated under reduced pressure. The crude product was used in the next step without further purification.

*Ethyl (4R,5S)-5-(tert-Butoxycarbonylamino)-4-hydroxycyclohex-1-enecarboxylate (**15**)*: A solution of the crude acid from the previous step (~14 mg, 0.054 mmol) and K_2CO_3 (22.8 mg, 0.165 mmol) in EtOH–H_2O (0.3 mL, v/v = 5:1) was stirred for 30 min at r.t. The solvent was removed under reduced pressure and the solid residue was dissolved in DMSO (0.3 mL). To this was added EtI (97 mg, 0.05 mL, 0.622 mmol) and the resulting solution was stirred for 40 h at r.t. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). Aq 1.5 M HCl was added till pH reached ~3, and the organic layer was washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, PE–EtOAc, 6:4) afforded 7.1 mg (46% calculated on the bases of starting aldehyde **3**) of the title compound **15** as a colorless oil; R_f = 0.33 (SiO_2, PE–EtOAc, 8:2); $[\alpha]_D^{20}$ –9.3 (*c* 0.74, $CHCl_3$).

IR (film): 3377, 2979, 2933, 1705, 1513, 1390, 1369, 1250, 1171, 1087, 1047 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.90–6.85 (m, 1 H), 4.83 (br d, *J* = 7.4 Hz, 1 H), 4.19 (q, *J* = 7.1, 2 H), 4.06 (br s, 1 H), 3.88 (br s, 1 H), 2.77 (br s, 1 H), 2.71–2.63 (m, 1 H), 2.62–2.54 (m, 1 H), 2.42–2.31 (m, 2 H), 1.45 (s, 9 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.3 (C), 156.4 (C), 135.9 (CH), 128.0 (C), 80.0 (C), 67.4 (CH), 60.6 (CH_2), 49.6 (CH), 32.7 (CH_2), 28.3 (CH_3), 27.6 (CH_2), 14.2 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{23}NO_5$ $[M + Na]^+$: 308.1468; found: 308.1454.

Ethyl (4*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-4-(methylsulfonyloxy)cyclohex-1-enecarboxylate (16)

A solution of MsCl (2.37 mg, 1.60 μL, 0.021 mmol), Et_3N (3.63 mg, 5.00 μL, 0.036 mmol), DMAP (0.33 mg, 0.003 mmol), and alcohol **15** (3.8 mg, 0.013 mmol) in CH_2Cl_2 (0.16 mL) was stirred for 30 min at r.t.. The mixture was diluted with EtOAc (10 mL) and the EtOAc layer was washed with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, PE–EtOAc, 6:4) afforded 4.3 mg (89%) of the title compound **16** as colorless crystals; mp not determined (unstable).

^1H NMR (200 MHz, $CDCl_3$): δ = 6.83 (br s, 1 H), 5.13 (br s, 1 H), 4.86 (br d, *J* = 7.3 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.05–3.81 (m, 1 H), 3.04 (s, 3 H), 2.78–2.67 (m, 3 H), 2.40–2.15 (m, 1 H), 1.45 (s, 9 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

Ethyl (*S*)-5-(*tert*-Butoxycarbonylamino)cyclohexa-1,3-dienecarboxylate (2)

DBU (4.45 mg, 4.37 μL, 0.029 mmol) was added to a solution of mesylate **16** (4.3 mg, 0.012 mmol) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 5 min at r.t. and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, PE–EtOAc, 85:15) afforded 2.9 mg (92%) of the title compound **2** as a colorless oil; R_f = 0.4 (SiO_2, PE–EtOAc, 6:4); $[\alpha]_D^{20}$ –219.7 (*c* 0.20, $CHCl_3$) {Lit.[3f] –217, *c* 1.10, $CHCl_3$)}.

IR (film): 3351, 2978, 2929, 1708, 1514, 1367, 1255, 1169, 1097, 1048, 1024, 718 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.07–7.03 (m, 1 H), 6.20–6.10 (m, 2 H), 4.63 (br s, 1 H), 4.44 (br s, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 2.74 (dd, *J* = 17.7, 6.5 Hz, 1 H), 2.66 (dd, *J* = 18.6, 7.9 Hz, 1 H), 1.44 (s, 9 H), 1.31 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9 (C), 154.8 (C), 132.5 (CH), 131.7 (CH), 127.0 (C), 124.8 (CH), 79.7 (C), 60.6 (CH_2), 43.4 (CH), 28.9 (CH_2), 28.4 (CH_3), 14.3 (CH_3).

HRMS (ESI) *m*/*z* calcd for $C_{14}H_{21}NO_4$ $[M + K]^+$: 306.1102; found: 306.1112.

Ethyl (*S*)-5-(*tert*-Butoxycarbonylamino)cyclohexa-1,3-diene-carboxylate (2) (One-Pot Procedure)

MsCl (3.45 mg, 2.33 μL, 0.030 mmol), Et_3N (6.32 mg, 8.70 μL, 0.062 mmol), and DMAP (0.50 mg, 0.004 mmol) were added to a solution of alcohol **15** (5.0 mg, 0.018 mmol) in CH_2Cl_2 (0.16 mL). The reaction mixture was stirred for 30 min at r.t., then DBU (15.27 mg, 15.0 μL, 0.100 mmol) was added and the resulting solution was stirred for an additional 15 min at r.t. The mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, PE–EtOAc, 85:15) afforded 2.4 mg (51%) of the title compound **2** as a colorless oil. The physical and spectral data for the product were identical with the sample obtained by the two-step procedure (see above).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (b) Rohloff, J. C.; Kent, K. M.; Postish, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545. (c) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044.

(2) For review articles on the development of the industrial synthesis, see: (a) Abrecht, S.; Federspiel, M. C.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia* **2007**, *61*, 93. (b) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621. For improvements and more detailed accounts on industrial synthesis, see: (c) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86. (d) Federspiel, M.; Fisher, R.; Henning, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266. For other semi-syntheses from shikimic acid, see: (e) Nie, L.-D.; Shi, X.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 124. (f) Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970. (g) Karpf, M.; Trussardi, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 5760. (h) Nie, L.-D.; Shi, X.-X.; Quan, N.; Wang, F.-F.; Lu, X. *Tetrahedron: Asymmetry* **2011**, *22*, 1692. (i) Nie, L.-D.; Ding, W.; Shi, X.-X.; Quan, N.; Lu, X. *Tetrahedron: Asymmetry* **2012**, *23*, 742. (j) Kim, H.-K.; Park, K.-J. J. *Tetrahedron Lett.* **2012**, *53*, 1561.

(3) (a) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310. (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (c) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (d) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734. (e) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403. (f) Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183. (g) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259. (h) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815. (i) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895. (j) Matveenko, M.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2008**, *49*, 7018. (k) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5788. (l) Trost, B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759. (m) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304. (n) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1070. (o) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783. (p) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787. (q) Sun, H.; Lin, Y.-J.; Wu, Y.-L.; Wu, Y. *Synlett* **2009**, 2473. (r) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 4229. (s) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60. (t) Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125. Synthesis of racemic Tamiflu™: (u) Kamimura, A.; Nakano, T. *J. Org. Chem.* **2010**, *75*, 3133. (v) Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006. (w) Wichienukul, P.; Akkarasamiyo, S.; Kongkathip, N.; Kongkathip, B. *Tetrahedron Lett.* **2010**, *51*, 3208. (x) Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem. Eur. J.* **2010**, *16*, 4533. (y) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4656. (z) Werner, L.; Machara, A.; Hudlicky, T. *Adv. Synth. Catal.* **2010**, *352*, 195. (aa) Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem. Eur. J.* **2010**, *16*, 12616. (ab) Trost, B. M.; Zhang, T. *Chem. Eur. J.* **2011**, *17*, 3630. (ac) Raghavan, S.; Babu, V. S. *Tetrahedron* **2011**, *67*, 2044. (ad) Tanaka, T.; Tan, Q.; Kawakubo, H.; Hayashi, M. *J. Org. Chem.* **2011**, *76*, 5477. (ae) Werner, L.; Machara, A.; Sullivan, B.; Carrera, I.; Mosher, M.; Adams, D. R.; Hudlicky, T.; Andraos, J. *J. Org. Chem.* **2011**, *76*, 10050. (af) Trajkovic, M.; Ferjancic, Z.; Saicic, R. N. *Org. Biomol. Chem.* **2011**, *9*, 6927. (ag) Gunasekara, D. S. *Synlett* **2012**, *23*, 573. (ah) Chuanopparat, N.; Kongkathip, N.; Kongkathip, B. *Tetrahedron* **2012**, *68*, 6803. (ai) Rawat, V.; Dey, S.; Sudalai, A. *Org. Biomol. Chem.* **2012**, *10*, 3988. (aj) Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 8792.

(4) For review articles on synthetic strategies to oseltamivir, see: (a) Magano, J. *Tetrahedron* **2011**, *67*, 7875. (b) Magano, J. *Chem. Rev.* **2009**, *109*, 4398. (c) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839. (d) Farina, V.; Brown, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 7330.

(5) Suaifan, G. A. R. Y.; Arafatb, T.; Threadgilla, M. D. *Bioorg. Med. Chem.* **2007**, *15*, 3474.

(6) (a) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121. (b) For a review article on this reaction, see: Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87.

(7) Trajkovic, M.; Ferjancic, Z.; Saicic, R. N. *Tetrahedron: Asymmetry* **2012**, *23*, 602.

(8) (a) Recently, aldehyde **7** was prepared by essentially the same procedure: Hoye, A. T.; Wipf, P. *Org. Lett.* **2011**, *13*, 2634. (b) However, the aldehyde **7** was not purified, nor has its optical purity been determined; instead, it was immediately methylenated in a Wittig reaction, to give the product of 70% ee. According to our results, the reported decrease in optical purity of the product is not a consequence

of the aldehyde's inherent instability, but most probably of basic conditions used in the cited work. The optical purity of the aldehyde was determined by its oxidation to acid **8** with Oxone® and comparison of the optical rotation data. Reduction to the corresponding alcohol proved unsuitable, due to side reactions, such as the migration of Boc group during reduction with $NaBH_4$. (c) For the side reaction, see: Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.* **2001**, *3*, 433. (d) For ^1H and ^{13}C NMR spectra of aldehyde **7**, see: Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 167.

(9) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(10) Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.
(11) [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)rutheniu m: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(12) Blot, V.; Jacquemard, U.; Reissig, H.-U.; Kleuser, B. *Synthesis* **2009**, 759.
(13) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

