Supporting Materials: Application of Heterogeneous Catalysts in the First Steps of the Oseltamivir Synthesis

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Materials and Methods

Amberlyst IR-15 (sulfonated polystyrene macroreticular resin, 20% divinylbenzene, 4.7 mmol S/g) was purchased from Alfa Aesar. Deloxan ASP I/9 (polysiloxane supported alkyl sulfonic acid 0.1-0.4 mm particle size, 0.80 mmol S/g) was a gift from Degussa (currently not commercially available). SAC-13 (nafion-silica composite, 13% wt nafion content, 0.17 mmol S/g) was a gift from Dupont (currently not commercially available).

Sulfonated hydrothermal carbon (SHTC, 0.80 mmol S/g) was prepared in two steps from D-glucose, first a hydrothermal synthesis at 195°C and then sulfonation with concentrated sulfuric acid at 150°C, as previously described [1]. Amberlite IRA-400 (trimethylbenzylammonium substituted gel type polystyrene resin, 8% divinylbenzene, basic form, 3.8 mmol/g) was purchased from Carlo Erba. TBD-PS (1,5,7-triazabicyclo[4.4.0]dec-5-ene supported on gel type polystyrene, 1% divinylbenzene, 3.0 mmol/g) and TBD-SiO2 (1,5,7-triazabicyclo[4.4.0]dec-5-ene supported on silica gel, 0.7 mmol/g) were purchased from Aldrich. All the catalysts were dried at 100°C under vacuum overnight prior to use.

Solvents were dried following standard procedures and all the reactions were carried out under argon atmosphere.

3,4-O-Isopropylidenequinic acid 1,5-lactone (2a) [2,3]. To a solution of quinic acid (192 mg, 1 mmol) in acetone (4 mL) was added SHTC (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 µL, 3.5 mmol). The mixture was stirred at 56 ºC for 3h, then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/ETOAc = 6:4, Rf 0.3), affording the compound 2a (179 mg, 84 %). 1H NMR (400 MHz, CDCl3) δ: 1.32 (3H, s, CH3exo), 1.51 (3H, s, CH3endo), 2.17 (1H, dd, J = 14.7, 2.9 Hz, H2ax), 2.30 (1H, dddd, J = 11.7, 6.2, 2.3, 1.4 Hz, H6eq), 2.36 (1H, ddd, J = 14.7, 7.1, 2.3 Hz, H2eq), 2.64 (1H, d, J = 11.7 Hz, H6ax), 2.97 (1H, br s, OH), 4.30 (1H, ddd, J = 6.5, 2.5, 1.4 Hz, H4), 4.49 (1H, ddd, J = 7.2, 7.0, 3.2 Hz, H3), 4.71 (1H, dd, J = 6.2, 2.5 Hz, H5). 13C NMR (100.6 MHz, CDCl3) δ: 24.4 (CH3exo), 27.1 (CH3endo), 34.4 (C6), 38.4 (C2), 71.7 (C3), 71.7 (C1), 72.2 (C4), 76.0 (C5), 109.9 (Cisoprop), 179.0 (C=O). HRMS (ESI) Calcd for C10H14NaO5: 237.0733. Found: 237.0731.
3,4-O-Pent-2-ylidenequinic acid 1,5-lactone (2b) [4]. To a solution of quinic acid (192 mg, 1 mmol) in pentan-3-one (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 101 ºC for 24 h, then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 6:4, Rf 0.3), affording the compound 2b (230 mg, 95 %). 1H NMR (400 MHz, CDCl3) δ: 0.87 (3H, t, J = 7.5 Hz, CH3exo), 0.97 (3H, t, J = 7.5 Hz, CH3endo), 1.59 (2H, q, J = 7.5 Hz, OCH2CH3exo), 1.75 (2H, q, J = 7.5 Hz, OCH2CH3endo), 2.17 (1H, ddd, J = 14.4, 3.3 Hz, H2ax), 2.32 (1H, dddd, J = 11.8, 6.2, 2.7, 1.3 Hz, H6ax), 2.38 (1H, ddd, J = 14.4, 8.1, 2.7 Hz, H2eq), 2.62 (1H, d, J = 11.8 Hz, H6eq), 3.01 (1H, br s, OH), 4.30 (1H, ddd, J = 6.5, 2.7, 1.3 Hz, H4), 4.47 (1H, ddd, J = 8.1, 6.5, 2.7 Hz, H3), 4.77 (1H, ddd, J = 6.2, 2.7 Hz, H5). 13C NMR (100.6 MHz, CDCl3) δ: 8.1 (CH3endo), 8.7 (CH3exo), 27.8 (CCH2CH3exo), 28.9 (CCH2CH3endo), 34.8 (C6), 39.1 (C2), 71.3 (C3), 71.7 (C1), 72.0 (C4), 76.1 (C5), 114.1 (Cpentylid), 179.0 (C=O). HRMS (ESI) Calcd for C12H18NaO5: 265.1046. Found: 265.1040.
Methyl 3,4-\textit{O}-isopropylidenequinate (3\text{aa}) [2]. To a solution of 3,4-\textit{O}-isopropylidenequinic acid 1,5-lactone (2\text{a}) (214 mg, 1 mmol) in methanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 °C for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 4:6, Rf 0.3), affording the compound 3\text{aa} (226 mg, 92 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.37 (3H, s, CH$_3$\textit{endo}), 1.54 (3H, s, CH$_3$\textit{exo}), 1.89 (1H, dd, $J = 13.7$, 10.7 Hz, H$_2\text{ax}$), 2.08 (1H, dd, $J = 13.7$, 4.2 Hz, H$_2\text{eq}$), 2.26 (2H, m, H$_6$), 2.39 (1H, d, $J = 3.6$ Hz, CHO$_2$H), 3.33 (1H, br s, OH), 3.82 (3H, s, OCH$_3$), 3.99 (1H, dd, $J = 6.4$, 5.7 Hz, H$_4$), 4.14 (1H, dddd, $J = 10.7$, 6.4, 4.2, 3.7 Hz, H$_3$), 4.48 (1H, dt, $J = 5.7$, 3.7 Hz, H$_5$). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 25.8 (CH$_3$\textit{endo}), 28.3 (CH$_3$\textit{exo}), 34.8 (C$_6$), 39.1 (C$_2$), 53.2 (OCH$_3$), 68.2 (C$_3$), 73.5 (C$_5$), 74.0 (C$_1$), 80.0 (C$_4$), 109.3 (C$_{\text{isoprop}}$), 175.7 (C=O). HRMS (ESI) Calcd for C$_{11}$H$_{18}$NaO$_6$: 269.0996. Found: 269.1009.
Ethyl 3,4-O-isopropylidenequinate (3ab). To a solution of 3,4-O-isopropylidenequinic acid 1,5-lactone (2a) (214 mg, 1 mmol) in ethanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 °C for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 4:6, Rf 0.3), affording the compound 3ab (215 mg, 83 %). 1H NMR (400 MHz, CDCl3) δ: 1.30 (3H, t, J = 7.1 Hz, OCH2CH3), 1.36 (3H, s, CH3endo), 1.53 (3H, s, CH3exo), 1.85 (1H, dd, J = 13.6, 11.0 Hz, H2ax), 2.04 (1H, ddd, J = 13.6, 4.3, 1.5 Hz, H6), 2.16–2.27 (2H, m, H6), 2.74 (1H, br s, OH), 3.41 (1H, br s, OH), 3.97 (1H, dd, J = 6.4, 5.7 Hz, H4), 4.13 (1H, ddd, J = 11.0, 6.4, 4.0 Hz, H3), 4.24 (1H, dq, J = 10.6, 7.1 Hz, OCHHCH3), 4.25 (1H, dq, J = 10.6, 7.1 Hz, OCHHCH3), 4.45 (1H, ddd, J = 5.7, 4.2, 3.6 Hz, H5). 13C NMR (100.6 MHz, CDCl3) δ: 14.2 (OCH2CH3), 25.8 (CH3endo), 28.3 (CH3exo), 34.9 (C6), 39.1 (C2), 62.4 (OCHHCH3), 68.3 (C3), 73.5 (C5), 73.8 (C1), 80.1 (C4), 109.3 (Cisoprop), 175.3 (C=O). HRMS (ESI) Calcd for C12H20NaO6: 283.1152. Found: 283.1154.
Ethyl 3,4-O-pent-3-ylidenequinate (3bb). To a solution of 3,4-O-pent-2-ylidenequinic acid 1,5-lactone (2b) (242 mg, 1 mmol) in ethanol (4 mL) was added TBD-PS (33 mg, 0.1 mmol). The mixture was stirred at 0 °C for 48 h, then the catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 3:7, Rf 0.3), affording the compound 3bb (239 mg, 83 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.88 (3H, t, $J = 7.5$ Hz, CCH$_2$CH$_3$endo), 0.95 (3H, t, $J = 7.5$ Hz, CCH$_2$CH$_3$exo), 1.30 (3H, t, $J = 7.1$ Hz, OCH$_2$CH$_3$), 1.62 (1H, dq, $J = 13.5, 7.5$ Hz, CCHHCH$_3$endo), 1.64 (1H, dq, $J = 13.5, 7.5$ Hz, CCHHCH$_3$exo), 1.72 (1H, dq, $J = 14.1, 7.5$ Hz, CCHHCH$_3$endo), 1.76 (1H, dq, $J = 14.1, 7.5$ Hz, CCHHCH$_3$exo), 1.85 (1H, dd, $J = 13.7, 11.0$ Hz, H$_2$exo), 2.03 (1H, ddd, $J = 13.7, 4.3, 1.7$ Hz, H$_2$endo), 2.16 (1H, ddd, $J = 15.3, 4.1, 1.7$ Hz, H$_6$exo), 2.23 (1H, dd, $J = 15.3, 4.8$ Hz, H$_6$endo), 3.99 (1H, t, $J = 6.5$ Hz, H$_4$), 4.14 (1H, ddd, $J = 11.0, 6.3, 4.3$ Hz, H$_3$), 4.24 (1H, dq, $J = 10.6, 7.1$ Hz, OCHHCH$_3$), 4.25 (1H, dq, $J = 10.6, 7.1$ Hz, OCHHCH$_3$), 4.45 (1H, dt, $J = 6.3, 4.4$ Hz, H$_5$). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 8.4 (CCH$_2$CH$_3$exo), 8.8 (CCH$_2$CH$_3$endo), 14.2 (OCH$_2$CH$_3$), 28.5 (CCH$_2$CH$_3$endo), 29.9 (CCH$_2$CH$_3$exo), 35.2 (C$_6$), 39.0 (C$_2$), 62.4 (OCH$_2$CH$_3$), 68.6 (C$_3$), 73.1 (C$_5$), 73.6 (C$_1$), 79.8 (C$_4$), 113.4 (C$_{pentylid}$), 175.5 (C=O). HRMS (ESI) Calcd for C$_{14}$H$_{24}$NaO$_6$: 311.1465. Found: 311.1457.
Methyl quinate (4a) [5-7]. To a solution of quinic acid (192 mg, 1 mmol) in methanol (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 65 °C for 48 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vacuum. The product was crystallized from dichloromethane/methanol affording the compound 4a (165 mg, 80 %). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 1.86 (1H, dd, $J = 13.2, 10.1$ Hz, H$_{6ax}$), 2.00 (1H, ddd, $J = 14.2, 4.7, 2.3$ Hz, H$_{2ax}$), 2.07 (1H, dd, $J = 14.2, 3.4$ Hz, H$_{2eq}$), 2.11 (1H, ddd, $J = 13.2, 4.5, 2.3$ Hz, H$_{6eq}$), 3.41 (1H, dd, $J = 8.6, 3.2$ Hz, H$_4$), 3.73 (3H, s, OCH$_3$), 3.99 (1H, ddd, $J = 10.1, 8.6, 4.5$ Hz, H$_5$), 4.08 (1H, ddd, $J = 4.7, 3.4, 3.2$ Hz, H$_3$). $^{13}$C NMR (100.6 MHz, CD$_3$OD) $\delta$: 38.3 (C2), 41.9 (C6), 52.9 (OCH$_3$), 68.2 (C5), 71.4 (C3), 76.5 (C4), 76.8 (C1), 175.9 (C=O). HRMS (ESI) Calcd for C$_{15}$H$_{20}$NaO$_6$: 229.0683. Found: 229.0687.
Ethyl quinate (4b). To a solution of quinic acid (192 mg, 1 mmol) in ethanol (4 mL) was added SHTC (13 mg, 0.01 mmol). The mixture was stirred at 78 °C for 72 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vacuum. The product was crystallized from dichloromethane/methanol affording the compound 4b (172 mg, 78 %). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 1.29 (3H, t, $J = 7.1$, Hz, CH$_3$), 1.87 (1H, dd, $J = 13.2$, 10.2 Hz, H$_{6\alpha}$), 2.02 (1H, ddd, $J = 14.3$, 4.5, 2.5 Hz, H$_{2\alpha}$), 2.09 (1H, dd, $J = 14.3$, 3.4 Hz, H$_{2\alpha}$), 2.12 (1H, ddd, $J = 13.2$, 4.3, 2.3 Hz, H$_{6\alpha}$), 3.42 (1H, dd, $J = 8.7$, 3.2 Hz, H$_4$), 4.01 (1H, ddd, $J = 10.2$, 8.7, 4.3 Hz, H$_5$), 4.10 (1H, ddd, $J = 4.5$, 3.4, 3.2 Hz, H$_3$), 4.19 (2H, q, $J = 7.1$, Hz, OCH$_2$CH$_3$). $^{13}$C NMR (100.6 MHz, CD$_3$OD) $\delta$: 14.4 (CH$_3$), 38.3 (C2), 42.0 (C6), 62.5 (OCH$_2$CH$_3$), 68.2 (C5), 71.5 (C3), 76.6 (C4), 76.8 (C1), 175.5 (C=O). HRMS (ESI) Calcd for C$_9$H$_{18}$NaO$_6$: 243.0839. Found: 243.0847.
Quinic acid 1,5-lactone (5) [8]. To a solution of quinic acid (192 mg, 1 mmol) in ethanol (4 mL) was added deloxan (13 mg, 0.01 mmol). The mixture was stirred at 78 °C for 24h then the acid catalyst was removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (dichloromethane/MeOH = 9:1, Rf 0.4), affording the compound 5 (33 mg, 19 %). 1H NMR (400 MHz, CD3OD) δ: 1.87 (1H, t, J = 11.6 Hz, H2ax), 2.03 (1H, dddd, J = 11.6, 6.6, 2.9, 0.8 Hz, H2eq), 2.22 (1H, ddd, J = 11.4, 6.0, 2.9, Hz, H6eq), 2.47 (1H, d, J = 11.4 Hz, H6ax), 3.70 (1H, ddd, J = 11.2, 6.6, 4.4 Hz, H3), 3.98 (1H, ddd, J = 4.9, 4.4, 0.8 Hz, H4), 4.71 (1H, dd, J = 6.0, 4.9 Hz, H5). 13C NMR (100.6 MHz, CD3OD) δ: 37.8 (C6), 40.1 (C2), 66.8 (C4), 67.3 (C3), 73.1 (C1), 77.9 (C5), 179.4 (C=O). HRMS (ESI) Calcd for C7H10NaO5: 197.0420. Found: 197.0412.
3,4-\textit{O}-Isopropylidenequinic acid (6). To a solution of quinic acid (192 mg, 1 mmol) in acetone/ethanol 1:1 (4 mL) was added deloxan (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 µL, 3.5 mmol). The mixture was stirred at 78 °C for 24 h, then the acid catalyst was removed by filtration and the filtrate was concentrated under vacuum. The solid residue was washed with dichloromethane affording the compound 6 (37 mg, 16 %). \( ^1 \text{H} \) NMR (400 MHz, CD\( _3 \)OD) \( \delta \): 1.33 (3H, s, CH\( _3 \)endo), 1.48 (3H, s, CH\( _3 \)exo), 1.80 (1H, dd, \( J = 13.5, 11.7 \) Hz, H\( 2ax \)), 1.94 (1H, ddd, \( J = 13.5, 4.4, 2.0 \) Hz, H\( 2eq \)), 2.07 (1H, ddd, \( J = 15.3, 4.1, 1.9 \) Hz, H\( 6eq \)), 2.26 (1H, dd, \( J = 15.3, 5.2, \) Hz, H\( 6ax \)), 3.91 (1H, dt, \( J = 5.4, 4.0 \) Hz, H\( 5 \)), 4.05 (1H, ddd, \( J = 11.7, 7.5, 4.3 \) Hz, H\( 3 \)), 4.44 (1H, dt, \( J = 5.4, 4.0 \) Hz, H\( 5 \)). \( ^{13} \text{C} \) NMR (100.6 MHz, CD\( _3 \)OD) \( \delta \): 26.1 (CH\( 3 \)endo), 28.6 (CH\( 3 \)exo), 36.1 (C\( 6 \)), 40.6 (C\( 2 \)), 69.1 (C\( 3 \)), 74.7 (C\( 1 \)), 74.9 (C\( 5 \)), 81.9 (C\( 4 \)), 109.9 (C\( \text{Isoprop} \)), 178.5 (C=O). HRMS (ESI) Calcd for C\textsubscript{10}H\textsubscript{16}NaO\textsubscript{6}: 255.0839. Found: 255.0849.
7,8-O-Isopropylidene (5S,7R,8S,9R)-7,8,9-trihydroxy-2,2-dimethyl-1,3-dioxaspiro [4.5]decan-4-one (7). To a solution of quinic acid (192 mg, 1 mmol) in acetone (4 mL) was added deloxan (13 mg, 0.01 mmol) and 2,2-dimethoxypropane (364 mg, 430 µL, 3.5 mmol). The mixture was stirred at 56 ºC for 4 h, then TBD-PS (33 mg, 0.1 mmol) and ethanol (4 mL) were added. The mixture was stirred at 0 ºC for 24 h, then the catalysts were removed by filtration, the filtrate was concentrated under vacuum and purified by column chromatography on silica gel (hexanes/EtOAc = 6:4, Rf 0.3), affording the compound 7 (73 mg, 27 %). 

1H NMR (400 MHz, CDCl3) δ: 1.36 (3H, s, CH3endo), 1.52 (3H, s, CH3exo), 1.60 (3H, s, CH3), 1.62 (3H, s, CH3), 1.94 (1H, dd, J = 14.1, 9.3 Hz, H6ax), 2.13 (1H, ddd, J = 14.1, 4.0, 1.2 Hz, H6eq), 2.20 (1H, ddd, J = 15.4, 4.5, 1.2 Hz, H10ax), 2.30 (1H, dd, J = 15.4, 4.7 Hz, H10eq), 2.88 (1H, d, J = 4.2 Hz, OH), 3.98–4.30 (2H, m, H7+H8), 4.48 (1H, dt, J = 5.8, 4.5 Hz, H9). 

13C NMR (100.6 MHz, CDCl3) δ: 25.4 (CH3endo), 28.0 (CH3exo), 28.7 (2×CH3), 35.1 (C10), 37.4 (C6), 67.6 (C7), 71.9 (C9), 78.4 (C8), 78.5 (C5), 109.1 (C2), 111.6 (Cisoprop), 176.2 (C=O). HRMS (ESI) Calcd for C13H20NaO5: 295.1152. Found: 295.1154.
References and Notes


2. The assignment is based on COSY, NOESY, HSQC and HMBC experiments. It differs from that reported in: Sánchez-Abella, L.; Férnandez, S.; Armesto, N.; Ferrero, M.; Gotor, V. Novel and efficient syntheses of


5. This assignment has been reached taking into account the only possible axial-axial arrangement of H4 with H3 or H5, present in the conformation represented in the figure, that explains the $J = 8.6$ Hz detected between H4 and one of the vicinal protons. This value is in agreement with those found for $J_{ax-ax}$ in polyhydroxylated cyclohexanes: Aucktor, J.; Brückner, R. Total Synthesis of quercitols: (+)-allo-, (−)-proto-, (+)-talo-, (−)-gala-, (−)-gala-, neo-, and (−)-epi-quercitol. *Synlett* **2015**, *26*, 250–258, doi:10.1055/s-0034-1379603.


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