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Diasterocontrol Synthesis of Tamiflu Intermediate of *Tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl)carbamate

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A new method for the synthesis of Tamiflu intermediate starting with meso mono-epoxide cyclohexene has been developed. The key synthon *tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl)carbamate was synthesized initially by the asymmetric epoxide ring opening reaction using a salen complex catalyst followed by reduction of the azide, amine protection, allylic hydroxylation, alcoholysis with 3-pentanol and epoxidation.

Key words: Azide reduction; epoxide; epoxidation; ring opening; Tamiflu

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Tamiflu (oseltamivir phosphate) (Figure 1) is a powerful inhibitor of influenza viral neuraminidase in influenza A and B infections. It was developed by Gilead Science and Roche companies and is considered as the best option due ease usage and significant reduced cost [1,2]. Tamiflu is the most prescribed anti-influenza drug in clinical use as its demand increased throughout the years [3]. In year 2009, Tamiflu is the only effective treatment against influenza virus during H1N1 pandemic. This continuous rising demand for Tamiflu is placing strain on the drug's supply and raw materials.

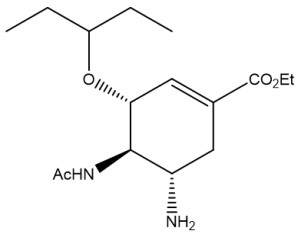

Figure 1. Structure of oseltamivir

Even though the process route has been thoroughly designed and proven to be effective, several researchers reported synthetic approaches [4] which focused on the use of alternative starting materials due to supply issues in the existing manufacturing process [5]. In support of these efforts, this paper embarks on the creation of a new synthetic pathway that uses a low-cost, dependable, and plentiful starting material. Starting precursor materials availability, chromatographic purifications, hazardous reagents, azide chemistry, material efficiency, number of steps, protecting groups, reaction enantioselectivity, catalysts, and overall yield in synthesis are all given special consideration in this work.

Our strategies (Scheme 1) would involve the transformation of cyclohexene epoxide to the key intermediate *tert*-butyl (5-hydroxy-6-(1-ethylpropoxy) -1,2-epoxycyclohex-3-en-1-yl) carbamate to be used for the total synthesis of Tamiflu. Epoxide intermediate as versatile electrophiles have been used by other researchers in subsequent reactions with various amines/nitrogenous nucleophiles and posed significant issues in the progression of the synthesis via the ring opening of the epoxide [6,7]. In this paper, we report the synthesis of Tamiflu intermediate via asymmetric epoxide ring opening reaction, reduction, amine protection, allylic hydroxylation, alcoholises and epoxidation from meso-monoepoxide cyclohexene.

METHODOLOGY

1. General

All the materials and solvents were obtained from commercial suppliers and used without further purification unless stated. All compounds were determined by the thin layer chromatography (TLC) packed with silica gel 60 F254 (Merck KGaA) and were stained with potassium permanganate solution. Fourier Transformed Infrared (FT-IR) spectra were obtained from FT-IR spectrophotometer (1700X

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Perkin Elmer) with neat or KBr pellets and wave-number ($\tilde{\nu}$) in cm^{-1}. NMR spectra for ^1H- and ^{13}C were recorded on Bruker Avance II (300 MHz) instrument. Tetramethylsilane (TMS) was used as the internal standard in chloroform solvent ($CDCl_3$) at ambient temperature, chemical shifts (δ) were reported in ppm, and the *J* values were given in Hz. The molecular weight of the compounds were confirmed by Mass Spectrometry (MS) (GC-7890A, Agilent). High-resolution masses were recorded on a separate mass spectrometer (Thermoquest, Finnigan TSQ 7000).

2. Experimental

*2.1. Synthesis of tert-butyl (1S,6S)-6-(hydroxy) cyclohex-3-enylcarbamate (**3a**) and tert-butyl (1S, 6S)-6-(trimethylsiloxy)cyclohex-3-enylcar bamate (**3b**).*

To a solution of **2** (0.21 g, 1.02 mmol, 1 equiv.) in ethanol (4 mL) was added di-*tert*-butyldicarbonate (BOC_2O; 0.45 g, 2.04 mmol, 2 equiv.), followed by addition of 20% $Pd(OH)_2/C$ (10.2 mg) at room temperature. The reaction proceeded with the addition of triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.). After stirring for 24 h, the resulting mixture was filtered through Celite. After complete removal of ethanol, the crude was purified using silica gel column chromatography (pet ether/ethyl acetate =15: 0.5) to give **3a** (0.18 g ,78%) as a white solid and **3b** (0.032 g, 12%) as a yellowish oily substance. For **3a** (major compound), R_f = 0.25 (SiO_2, hexanes: ethyl acetate 21: 7); m.p. 76-78 °C, ^1H NMR (300 MHz, $CDCl_3$): δ 5.50-5.60 (m, 2H), 4.90 (brs, 1H), 3.60-3.70 (m, 1H), 3.20-3.30 (m, 1H), 2.30-2.50 (m, 1H), 2.00-2.10 (m, 1H), 1.80-1.90 (m, 1H), 1.60-1.70 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 124.9 (2C), 124.5 (2C), 80.1, 70.8, 52.4, 33.9, 31.6, 28.4 (3C); IR (Film): $\tilde{\nu}$; cm^{-1} = 3376 (NH), 3286 (OH), 2977 (CH_2), 1674 (C=O), 1309 (NH), 1245 (CH_3), 1165 (C-O-C), 1071 (C-O), 871 (C=C), 852 (C-N), 742 (CH), 660 (NH). MS [CI, NH_3] m/z (%) = 213.1 (100) [M^+]; Calculated for [$C_{11}H_{19}NO_3$]: 213.14.

Method used for preparation of **3b** (minor product) in the same manner as **3a**. R_f = 0.75 (SiO_2, hexanes: ethyl acetate, 21: 7); ^1H NMR (300 MHz, $CDCl_3$): δ 5.55-5.60 (m, 2H), 4.73 (brs,1H), 3.66-3.72 (m, 1H), 3.27-3.33 (m, 1H), 2.52-2.58 (m, 1H), 2.46-2.48 (m, 1H), 2.12-2.18 (m, 1H), 1.95-2.01 (m, 1H), 1.46 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 157.1, 124.2 (2C), 124.0 (2C), 76.9, 68.9, 51.0, 32.9, 29.9, 28.3 (3C), 0.0 (3C); IR (Film): $\tilde{\nu}$; cm^{-1} = 3340 (NH), 2976 (CH_2), 1689 (C=O), 1366 (Si-$(CH_3)_3$, 1309 (NH), 1249 (CH_3), 1170 (C-O-C), 1102 (O-Si), 1067 (C-O), 881 (C=C), 840 (C-N), 749 (CH), 661(NH). HRMS [CI, NH_3] m/z = 285.24, Calculated for [$C_{14}H_{27}NO_3Si$: 285.1760, found 285.1758].

*2.2. Synthesis of tert-butyl(5,6-dihydroxycyclohex-3-en-1-yl) carbamate (**4**).*

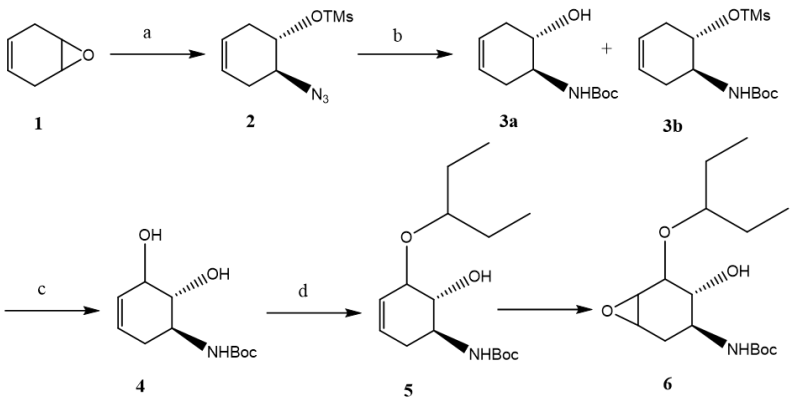
The reagent of SeO_2 (0.091 g, 0.82 mmol, 1 equiv.) was grounded to a powder form and then it was added to 3 mL ethanol containing **3a** (0.165 g, 0.77 mmol, 1 equiv.). The solution was stirred at room temperature for 10 min. *Tert*-butylhydroperoxide (TBHP, 0.025 mL, 1.4 mmol, 2 equiv.) was added and refluxed for 24 h. The solvent was removed under a reduced pressure and the crude product was purified using the silica gel column chromatography (pet ether: ethyl acetate 27: 3) to give 0.09 g (56%) **4** as a white solid. R_f = 0.4 (SiO_2, hexanes: ethyl acetate 21: 7);); m.p. 73-75 °C, ^1H NMR (300 MHz, $CDCl_3$): δ 5.40-5.50 (m, 2H), 4.43-4.60 (brs, IH), 3.66-3.75 (m, 2H), 3.25-3.44 (m, 1H), 2.45-2.63 (d, 1H, *J* = 15.6), 2.15-2.25 (d, 1H, *J* = 12), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 124.5 (2C), 124.4 (2C), 79.3, 69.4, 56.4, 52.1, 31.3, 28.3 (2C); IR (film): $\tilde{\nu}$; cm^{-1} = 3365 (NH), 3284 (OH), 2972 (CH_2), 1671 (C=O), 1307 (N-H), 1246 (CH_3), 1163 (C-O-C), 1056 (C-O), 868 (C=C), 850 (C-N), 742 (CH), 661 (NH). MS [CI, NH_3] *m/z* (%) = 253.01 (75) [M + H+ + Na+], 252.9 (10) [M + Na^+]; HRMS (Cl, NH_3); calculated for $C_{11}H_{19}NO_4$: 229.1314, found 252.1207 [M + Na^+].

*2.3. Synthesis of tert-butyl(5-hydroxy-6-(1-ethylpro poxy) cyclohex-3-en-1-yl) carbamate (**5**).*

$BF_3.OEt_3$ (0.09 mL, 2 equiv.) was added dropwise to a solution of compound 4 (0.112 g, 0.37 mmol, 1 equiv.) in 3-pentanol (mL) resulting mixture was stirred at room temperature. After 24 h, saturated aqueous $NaHCO_3$ was added to quench the reaction. The product was extracted with ethyl acetate (AcOEt) twice and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under pressure and the residue was purified by silica gel column chromatography (pet ether/ethyl acetate, 6:4) to produce 5 (0.059 g, 53%). R_f = 0.69 (SiO_2, hexanes: ethyl acetate 5:5); ^1H NMR (300 MHz, $CDCl_3$): δ 5.52-5.62 (m, 2H), 4.58 (brs, IH), 3.62-3.75 (m, 2H), 3.09-3.04(m, 1H), 2.50-2.52 (d, 2H, *J* = 15.4), 1.87-2.00 (d, 2H, *J* = 15.6), 1.58-1.63 (m, 2H), 1.45 (s, 9H), 0.7-1.4 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 124.9 (2C), 124.3 (2C), 80.0, 74.9, 71.0, 56.5, 52.4, 31.5, 29.8, 28.3 (3C), 24.8, 24.1; IR (Film): $\tilde{\nu}$; cm^{-1} = 3373 (NH), 3283 (OH), 2974 (CH_2), 1675 (C=O), 1552(CH_2CH_3), 1309 (NH), 1247 (CH_3), 1165 (C-O-C), 1054 (C-O), 871 (C=C), 851 (C-N), 743 (CH), 660 (NH). MS [CI, NH_3] m/z (%) = 299.21; found 324.90 [M + Na + 2H]$^+$.

*2.4. Synthesis of tert-butyl(5-hydroxy-6-(1-ethylpro poxy)-1,2-epoxycyclohex-3-en-1-yl) carbamate (**6**).*

A reagent *m*-CPBA (0.049 g, 0.096 mmol, 3 equiv.) was added to ice-cooled mixture of **5** (0.029 g, 0.096



Scheme 1. The synthesis of **6** *tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl) carbamate.

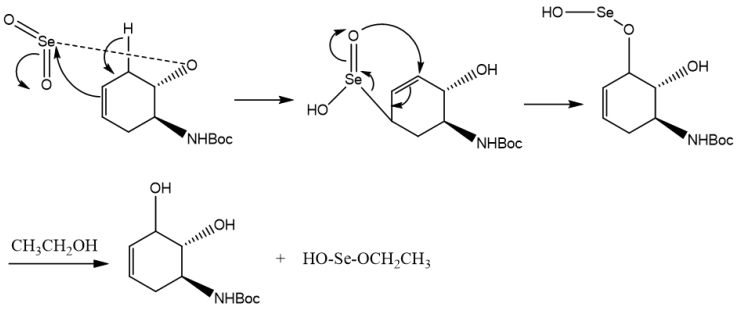
mmol, 1 equiv.) in 5 mL dichloromethane (CH_2Cl_2). The solution was stirred at 0 °C for 1 h and allowed to stir for 48 h. Then an aqueous $Na_2S_2O_3$ solution was added, and the mixture was stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution and brine and dried over Na_2SO_4. The crude product was concentrated under vacuum by using rotary evaporator and was purified using silica gel chromatography (pet ether/ethyl acetate = 6:4) to give **6** (0.017 g, 34 %) as a white solid. R_f = 0.28 (SiO_2, hexanes: ethyl acetate 5:5); m.p. 76-78 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.1 (brs, IH), 3.63-3.79 (m, 2H), 3.16-3.31 (m, 2H), 2.47 (d, 2H, *J* = 15), 1.85 (d, 1H, *J* = 16), 1.64- 1.88 (m, 4H),1.45 (s, 9H), 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 79.7, 75.5, 70.7, 66.1, 51.7, 51.3, 49.3, 30.6 (2C), 29.6, 28.7 (3C), 26.8, 25.0 ; IR (Film): ṽ; cm^{-1} = 3458 (OH), 2942 (CH_2), 1737 (C=O), 1460 (CH_2CH_3), 1300 (NH), 1233 (CH_3), 1097 (C-O-C), 1043 (C-O), 917 (epoxide), 847 (C-N), 786 (CH), 634 (NH). MS [CI, NH_3] m/z (%) = 315.20; found 341.05 [M + Na + 3H]$^+$.

RESULTS AND DISCUSSION

Scheme 1 shows the synthesis of *tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl) carbamate, which is a key intermediate to produce Tamiflu. We started our work in the synthesis of key intermediate of Tamiflu by selecting an enantiopreference ligand, Salen catalyst complex to give *S,S* configurations [8] of **2** azido trimethylsiloxy cyclohexene using **1** meso-monoepoxide cyclohexene as raw material**.** The findings was reported in our previously published article [9].

Reagents and Conditions: (a) (*S*, *S*)-salen complex (2 mol %), $TMSN_3$ (1.05 equiv.), Et_2O, rt., 46 h, (b) BOC_2O, $Pd(OH)_2/C$, Et_3SiH, rt, 24 h, (c) EtOH, SeO_2, TBHP, refluxed, 24 h, (d) 3-pentanol, $BF_3.OEt_2$, rt, 24 h, (e) *m*-CPBA, 0 °C, 1 hr, rt, 48 h.

Protection of azide group of **2** as *N-Boc* was accomplished by its treatment with di-*tert*-butyl dicarbonate in ethanol to afford mixture of **3a** (78%)-(Figure 2 and Figure 3) and **3b** (12%) yield. The mixture was separated by silica gel column chromatography by using pet ether-ethyl acetate (27:3) as eluent. Major product of **3a** was converted to **4** *tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl) carbamate (Figure 4 and Figure 5) via allylic hydroxylation by treatment with SeO_2 and *tert*-butyl hydroperoxide produced 56% yield of product. The proposed mechanism for allylic hydroxylation of **3a** is depicted in scheme 2. The oxidation of **3a** at carbon 6 tend to resist oxidation at the allylic position due to sterically hindered alkenes [10]. Thus, the high conversion to allylic product of **4** was a major compound.



Scheme 2. The proposed mechanism for allylic hydroxylation of **3a**

Alcoholysis reaction at carbon 6 with 3-pentanol and $BF_3.OEt_2$ produced **5** (Figure 6 and Figure 7). Epoxidation of **5** with *m*-CPBA gave a product of *tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl) carbamate that have epoxide moiety as electrophile for nucleophilic reactions. After three subsequent consecutive reactions, the synthesis of Tamiflu will be completed.

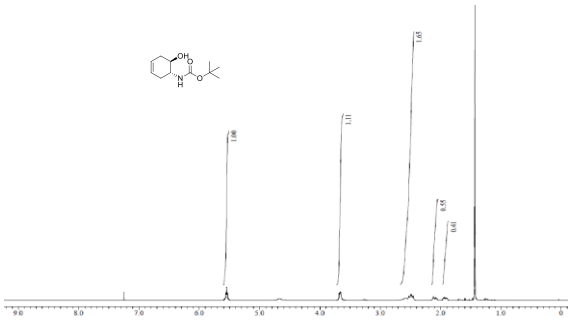


Figure 2. ^{1}H NMR spectrum of **3a**

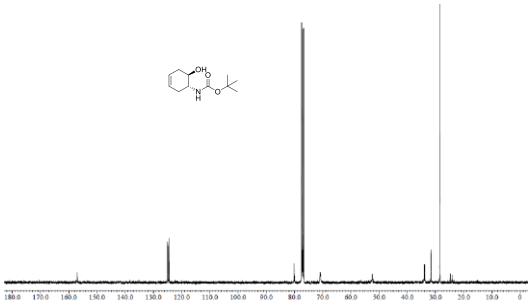


Figure 3. ^{13}C NMR spectrum of **3a**

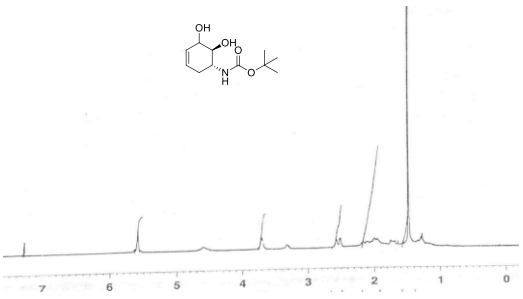


Figure 4. ^{1}H NMR spectrum of **4**

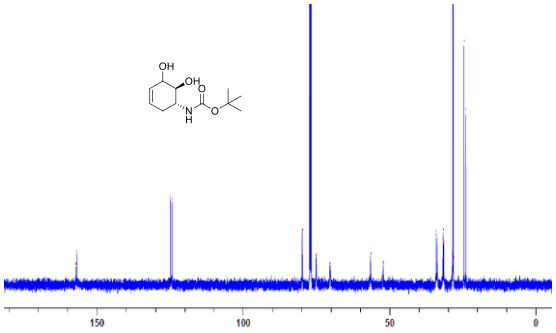


Figure 5. ^{13}C NMR spectrum of **4**

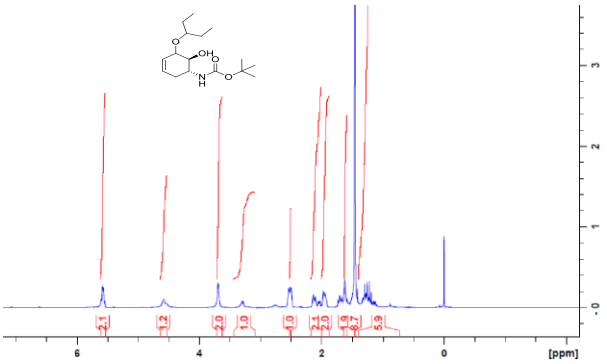


Figure 6. ^{1}H NMR spectrum of **5**

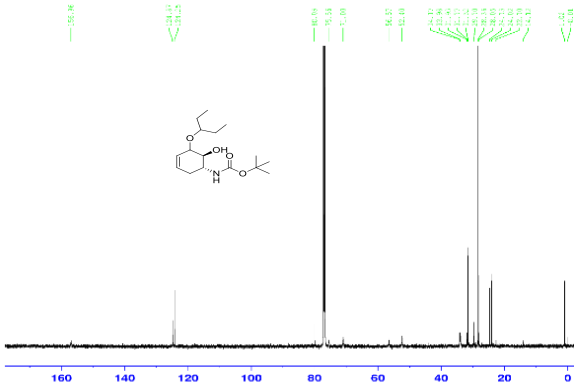


Figure 7. ^{13}C NMR spectrum of **5**

CONCLUSION

In conclusion, the synthesis of *tert*-butyl(5-hydroxy-6-(1-ethylpropoxy)-1,2-epoxycyclohex-3-en-1-yl) carbamate as Tamiflu intermediate, started with cyclohexene epoxide, was accomplished in 5 steps. Our synthetic strategy features asymmetric epoxide ring opening, reduction of the azide, amine protection to give amine moiety, allylic hydroxylation, alcoholysis with 3-pentanol to give *o*-pentane moiety and epoxidation to provide an epoxide that will be modified for ester moiety. Further investigations on few reaction steps are underway in our laboratories to accomplish Tamiflu synthesis.

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