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A practical synthesis of (−)-oseltamivir

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ABSTRACT

Oseltamivir phosphate (Tamiflu®) is a potent inhibitor of neuraminidase, and is used worldwide as a drug for type A or B influenza. The industrial synthesis of oseltamivir uses shikimic acid as a starting material, but the price fluctuates, depending on the supply of star anise. We have developed a practical synthesis of oseltamivir from pyridine, which features an asymmetric Diels–Alder reaction of dihydropyridine using MacMillan's catalyst, a bromolactonization, Hofmann rearrangement with $PhI(OAc)_2$, and a domino transformation of the bicyclo[2.2.2] system into an aziridine compound.

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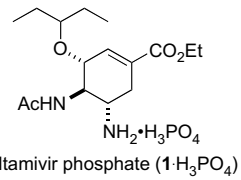
1. Introduction

In 1999, oseltamivir phosphate (**1**·H_3PO_4, Tamiflu®, Fig. 1) was launched as a drug for type A as well as type B influenza.[1] Oseltamivir itself is a prodrug, and the corresponding carboxylic acid, which can be formed by hydrolysis after absorption, displays potent inhibitory activities for influenza neuraminidases. The recent spread of the avian virus H5N1 has prompted governments to stockpile Tamiflu as a precautionary measure against a flu pandemic. Hence, the supplier, Roche, has increased the production of Tamiflu. In addition to its remarkable potency as a drug and the social demand, the structure of oseltamivir, including a *trans*-1,2-diamine moiety, 3-pentyl ether, and α,β-unsaturated ester in the cyclohexene core, has attracted the attention of synthetic chemists. With the goal of establishing a practical route to this densely functionalized compound, synthetic studies toward oseltamivir have been initiated. While numerous syntheses of oseltamivir have been reported to date,[2] we reported in 2007 an efficient synthesis of oseltamivir, which features an asymmetric Diels–Alder reaction of dihydropyridine using MacMillan's catalyst, a bromolactonization, a Hofmann rearrangement with $PhI(OAc)_2$, and a domino transformation of bicyclo[2.2.2] system into aziridine compound.[3] Herein we report our synthetic studies of oseltamivir in detail.



oseltamivir phosphate (**1**·H_3PO_4)

Figure 1. Structure of oseltamivir phosphate.

2. Results and discussion

2.1. Retrosynthesis

Our retrosynthetic analysis of oseltamivir is outlined in Scheme 1. According to a report from Gilead Science, the 3-pentyl ether could be installed by the opening of aziridine **2**, which could be formed from alcohol **3**. The addition of a leaving group X to the β-position of the ester followed by lactam formation would give bicyclo[2.2.2] intermediate **4**. We then envisaged that **4** could be derived from carboxylic acid **5** either by a Curtius rearrangement or by a Hofmann rearrangement of the corresponding amide. Lactone **6**, a precursor of **5**, could in turn be derived from **7** by halolactonization. Finally, bicyclic system **7** could be constructed using an asymmetric Diels–Alder reaction between dihydropyridine **8** and acrylic acid derivative **9**.[4]

2.2. Synthesis of lactone 21

Our synthesis commenced with preparation of dihydropyridine **11**. Thus, the reduction of pyridine (**10**) with sodium borohydride in the presence of benzyl chloroformate at −50 to −35 °C furnished **11** in almost quantitative yield (Scheme 2).[5] Higher reaction temperature caused decomposition of CbzCl, resulting in lower yield of **11**. The Diels–Alder reaction between **11** and acrolein, catalyzed by MacMillan's catalyst **12**,[6] afforded a mixture of aldehydes with more than two aldehydic peaks observed in the ^1H NMR spectrum. Since it was difficult to separate these aldehydes and fully assign the peaks in the ^1H NMR spectrum because of the rotamers about the benzyl carbamate bond, the structure of the

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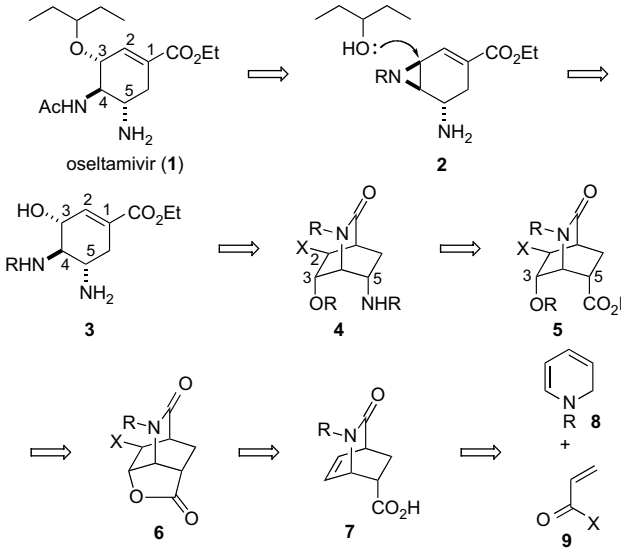
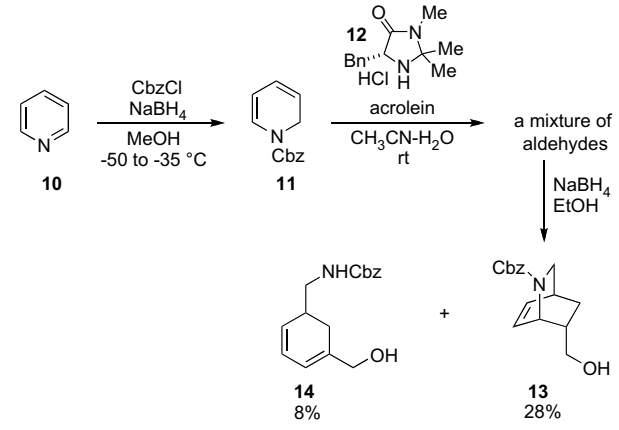


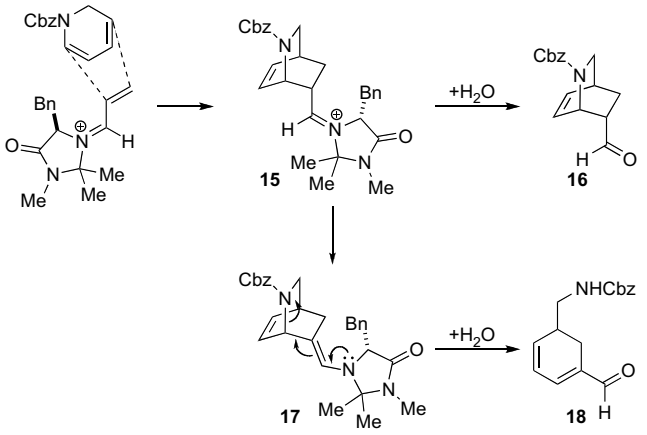
Scheme 1. Retrosynthesis.



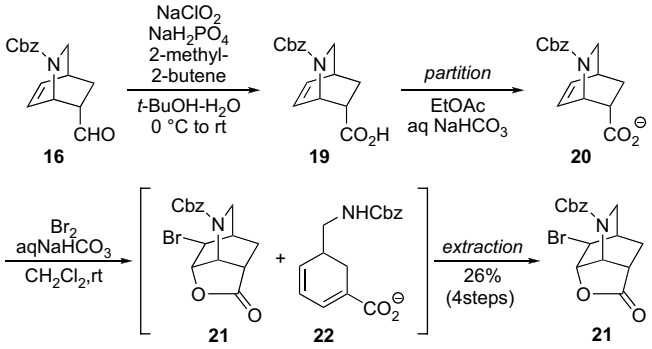
Scheme 2. Asymmetric Diels–Alder reaction.

products was determined by reducing the aldehydes with sodium borohydride. While *endo*-adduct **13** and cyclohexadiene **14** were obtained in 28 and 8% yields, respectively, the *exo*-adduct was not obtained. We could not deny the possibility that a selective decomposition of the *exo*-adduct occurred. The fact that a prolonged reaction time did not change the ratio of the products suggests that cyclohexadiene **18** might be formed via β-elimination of enamine **17** (Scheme 3).

Since chromatographic separation of the aldehydes was tedious and impractical, the crude mixture was subjected to the Kraus oxidation without purification (Scheme 4).[7] The crude reaction mixture, which contained the desired *endo*-carboxylic acid **19**, was taken up in ethyl acetate and washed with dilute HCl to remove the basic impurities. The carboxylic acids were then extracted into an aqueous sodium bicarbonate solution. Upon addition of bromine, a facile bromolactonization proceeded to give the desired bromolactone **21**. Because other acidic by-products, including **22**, remained in the aqueous phase, a simple extraction and subsequent crystallization from methanol afforded practically pure **21** (>99% ee) in 26% yield from benzyl chloroformate. It should be emphasized that neither tedious chromatographic separations nor expensive reagents were needed to prepare bromolactone **21**.



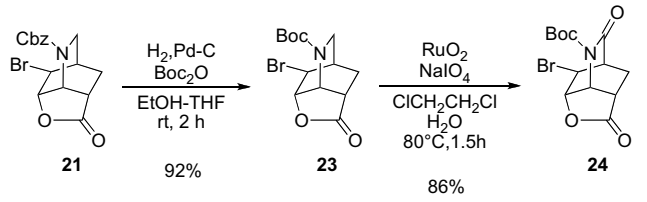
Scheme 3. Plausible reaction pathway of the Diels–Alder reaction.



Scheme 4. Bromolactonization.

2.3. Elaboration of the bicyclic system

Having developed a highly efficient route to the key intermediate, we next focused on oxidation of the methylene group next to the nitrogen in order to cleave the bicyclic skeleton. Since ruthenium oxidation of **21** did not afford any desired product due to the oxidation of the benzyl group, the Cbz group in **21** was converted into a Boc group by hydrogenolysis in the presence of Boc_2O (92% yield, Scheme 5).[8] Oxidation of **23** with a catalytic amount of $RuO_2 \cdot nH_2O$ (10 mol %) and $NaIO_4$ proceeded smoothly to give imide **24** in 86% yield. In addition to rather toxic 1,2-dichloroethane, *n*-propyl acetate, a much safer solvent, proved to be useful for this mild oxidation (85% yield).

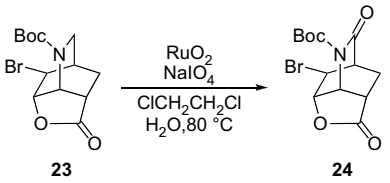


Scheme 5. Ruthenium oxidation.

The relatively expensive ruthenium catalyst could easily be recovered by quenching the reaction with 2-propanol to form a black precipitate of RuO_2, which was collected on filter paper. After drying, the recovered ruthenium catalyst could be used for the same transformation without a loss of activity (Table 1).

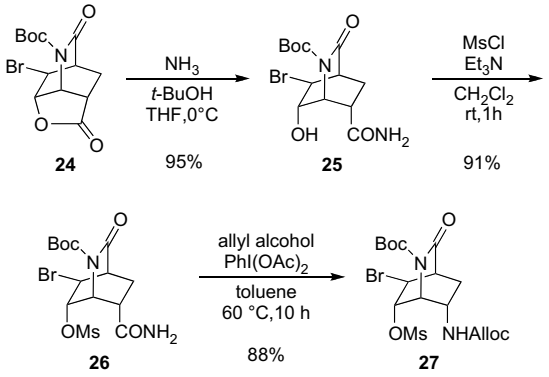
Hence, the next task was to introduce the nitrogen atom at C5. Ammonolysis of the lactone **24** proceeded selectively with the *N*-Boc lactam intact (Scheme 6). The resulting alcohol **25** was

Table 1
Recovery of the ruthenium catalyst



Run	Yield (%)	Recovery of Ru catalyst (%)
1	90	88
2	80	65
3	79	75
4	87	—

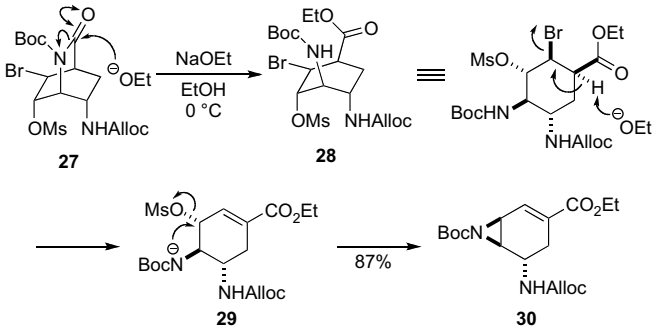
converted into its mesylate **26** to form the aziridine ring at a later stage. Treatment with iodobenzene diacetate and allyl alcohol caused amide **26** to undergo a Hofmann rearrangement to give allyl carbamate **27** in 88% yield.[9]



Scheme 6. Introduction of the amino group via a Hoffmann rearrangement.

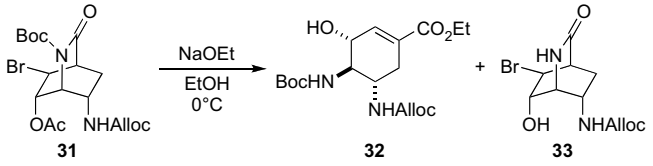
2.4. Transformation into the cyclohexene skeleton and installation of 3-pentyl ether

Having fully arranged the functionalities, we next attempted to cleave the bicyclic system. As initially planned, upon treatment with a slight excess of sodium ethoxide (2.02 equiv) at 0 °C, **27** underwent a series of transformations involving the ethanolysis of the *N*-Boc lactam, a dehydrobromination, and an aziridine formation via an intramolecular S_N2 reaction to provide **30** in 87% yield (Scheme 7). Aziridine **30** turned out to be quite sensitive to nucleophilic attack. Upon exposure to aqueous HCl during partitioning or neutralization, a chloride ion attacked to cleave the aziridine ring at the allylic position.



Scheme 7. Formation of the aziridine ring.

It is worth mentioning that, under the same reaction conditions, acetate **31** gave a mixture of **32** and **33** (Scheme 8). Thus the electron withdrawing nature of the substituent at C3 seemed to affect the reactivity of the *N*-Boc lactam.



Scheme 8.

Installing the 3-pentyl ether moiety proved to be a challenging task. Upon treatment with a Lewis acid in the presence of 3-pentanol, aziridine **30** underwent cleavage to give the desired **34** in moderate to low yields along with oxazolidinone **35**. To suppress the concomitant formation of the undesired **35**, optimization of the reaction conditions was performed.

Since the reactions with 3-pentanol under basic or neutral conditions did not give acceptable results, we screened a variety of acids (Table 2). Brønsted acids such as PPTS preferentially formed oxazolidinone **35** (entry 1). Because chloride ion tended to cleave the aziridine ring, we employed metal triflates or perchlorates as Lewis acids. Among the several Lewis acids, $Sc(OTf)_3$ afforded **34** with a relatively good selectivity in moderate yield (entries 2–8). Although the addition of CH_2Cl_2 as a co-solvent improved the yield, the selectivity was unchanged (entry 9). Moreover, $BF_3\cdot OEt_2$ was confirmed to be a good acid for this transformation.[1] While the addition of a co-solvent did not increase the selectivity (entries 10–15), lowering the reaction temperature improved both the selectivity and the yield (entry 16). Finally, the desired product **34** was obtained in 62% yield after purification by silica gel column chromatography.

2.5. Completion of the synthesis

The final steps of the synthesis were carried out as shown in Scheme 9. Deprotection of the Boc group of **34** with trifluoroacetic acid and subsequent acetylation furnished acetamide **36** in 88% yield. The Alloc group was removed by treatment with palladium on carbon in the presence of triphenylphosphine and 1,3-dimethylbarbituric acid. After complete consumption of **36**, the reaction mixture was filtered and concentrated to afford crude oseltamivir, which was directly subjected to salt formation with phosphoric acid in ethanol to furnish crystalline oseltamivir phosphate ($\mathbf{1}\cdot H_3PO_4$) in 76% yield. The spectroscopic data of oseltamivir phosphate thus obtained were consistent with those reported in the literature.[2a]

3. Conclusion

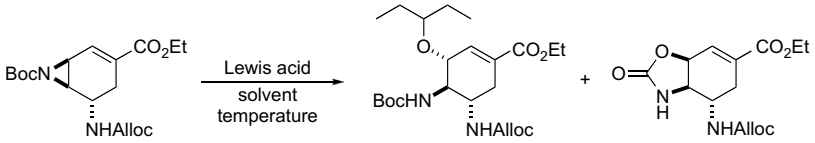
In conclusion, we have successfully synthesized oseltamivir phosphate $\mathbf{1}\cdot H_3PO_4$ in 22% yield from the readily available lactone **21**, featuring an asymmetric Diels–Alder reaction, a bromolactonization, and a Hofmann rearrangement. Finally it should be noted that our synthetic route has the potential to generate a wide range of hitherto inaccessible Tamiflu analogs.

4. Experimental section

4.1. General

Nuclear magnetic resonance (^1H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{31}P NMR (162 MHz)) spectra were determined on

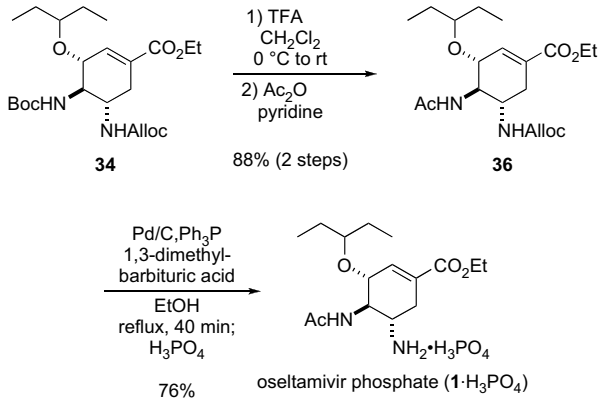
Table 2
Screening of the conditions to install the 3-pentyl ether



30 34 35

Entry	Acid	Temperature (°C)	Solvent	Ratio (**34**:**35**)[a]	Yield (%, **34**)[b]
1	PPTS	rt	3-Pentanol	1.0:7	ND
2	$LiClO_4$	rt to 70	3-Pentanol	1.2:1	ND
3	$Mg(ClO_4)_2$	rt	3-Pentanol	1.0:1	ND
4	$Cu(OTf)_2$	−20 to 0	3-Pentanol	2.3:1	39
5	$In(OTf)_3$	−20	3-Pentanol	1.9:1	46
6	$Sm(OTf)_3$	−20 to rt	3-Pentanol	1.5:1	30
7	$Yb(OTf)_3$	0	3-Pentanol	1.3:1	ND
8	$Sc(OTf)_3$	−20 to 0	3-Pentanol	2.4:1	45
9		−20	3-Pentanol/CH_2Cl_2	2.3:1	54
10	$BF_3{\cdot}OEt_2$	0	3-Pentanol	1.8:1	46
11		0	3-Pentanol/THF	0.5:1	ND
12		0	3-Pentanol/Et_2O	0.7:1	ND
13		0	3-Pentanol/MeCN	1.1:1	ND
14		0	3-Pentanol/CH_2Cl_2	1.5:1	ND
15		0	3-Pentanol/toluene	1.5:1	ND
16		−20	3-Pentanol	2.6:1	62
17		−40	3-Pentanol/CH_2Cl_2	1.0:1	37
18		−40	3-Pentanol/toluene	0.8:1	31

ND: not determined.
[a] The ratio was determined by ^1H NMR.
[b] Isolated yields.



Scheme 9. Completion of the synthesis.

a JEOL-LA400 instrument unless otherwise noted. Chemical shifts for ^1H NMR are reported in parts per million downfield from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). Chemical shifts in D_2O are reported in the scale relative to HOD (4.79 ppm) for ^1H NMR. The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Chemical shifts for ^{13}C NMR were reported in parts per million relative to the center line of a triplet at 77.0 ppm for deuteriochloroform. Chemical shifts in D_2O are reported in parts per million relative to the singlet at 66.5 ppm for 1,4-dioxane. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were recorded on JEOL JMS-GCmate or JEOL JMS-700 under fast atom bombardment (FAB) conditions with polyethylene glycol (PEG) as the matrix. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were made on Merck precoated analytical plates, 0.50 mm thick, silica gel 60 F_{254}. Compounds were eluted from the adsorbent with ethyl acetate. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40–100 mesh). Reagents and solvents were of the commercial grades. All solvents were used after being dried over molecular sieves 3 Å or 4 Å. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

4.2. (1*R*,2*S*,3*S*,6*R*,7*R*)-8-Benzyloxycarbonyl-2-bromo-4-oxa-8-azatricyclo[4,3,1,$0^{3,7}$]decan-5-one (21)

To a stirred solution of pyridine (**10**) (10.0 ml, 124 mmol) in methanol (200 ml) was added sodium borohydride (5.12 g, 135 mmol) at about −40 °C. To this was added benzyl chloroformate (16.1 ml, 113 mmol) dropwise through the dropping funnel over a period of 30 min at such a rate that inner temperature was maintained between −47 and −35 °C. After stirring for 20 min, the resulting solution was gradually warmed to 0 °C. Water (200 ml) was added and the mixture was extracted three times with diethyl ether (200 ml×2 and 100 ml×1). The combined organic extracts were washed with 1 N HCl (200 ml), 1 N NaOH (200 ml), water (100 ml), and brine (100 ml), dried over sodium sulfate, and concentrated under reduced pressure to give the crude dihydropyridine **11** (23.5 g, 109 mmol, 96.4%) as a pale yellow oil, which was used to the next reaction without purification. To a stirred solution of **11** (23.5 g, 109 mmol) and the MacMillan's catalyst **12** (2.80 g, 11.0 mmol) in acetonitrile (114 ml) and water (6 ml) was added acrolein (22.0 ml, 32.9 mmol) at room temperature. After stirring for 14 h, the reaction mixture was diluted with diethyl ether (400 ml), and washed with water (400 ml). The aqueous layer was diluted with water (100 ml) and extracted with diethyl ether (500 ml). The combined organic extracts were washed with water (300 ml), brine (300 ml), dried over sodium sulfate, and concentrated under reduced pressure to give aldehyde **16** as a pale yellow

oil, which was used to the next reaction without purification. To a stirred solution of the aldehyde **16** in *tert*-butyl alcohol (180 ml) and water (60 ml) were added sodium dihydrogenphosphate dihydrate (25.7 g, 165 mmol) and 2-methyl-2-butene (60.0 ml, 566 mmol). To this was added sodium chlorite (29.8 g, 329 mmol) portionwise at 0 °C. After 10 min, the solution was warmed to room temperature and stirring was continued for an additional 1 h. The reaction was then quenched with sodium sulfite, and the reaction mixture was partitioned between ethyl acetate (450 ml) and 3 N HCl (360 ml). The aqueous layer was thoroughly extracted with ethyl acetate (400 ml). The combined organic extracts were washed with water (350 ml), brine (350 ml), and concentrated under reduced pressure. The concentrated solution was diluted with ethyl acetate and extracted four times with a saturated aqueous sodium bicarbonate solution (360 ml×4). To a vigorously stirred mixture of the combined aqueous extracts and dichloromethane (120 ml) was added bromine until the reddish color of bromine persisted. The reaction was quenched with sodium sulfite, and the reaction mixture was extracted three times with ethyl acetate (360 ml×3). The combined organic extracts were washed with water (300 ml), brine (300 ml), dried over sodium sulfate, and concentrated under reduced pressure. The residue was left at room temperature overnight, during which time crystallization took place. The crude product was treated with methanol to promote crystallization and then concentrated to a small volume under reduced pressure. The crystals were filtered and washed with cold methanol three times to afford bromolactone **21** (10.64 g, 29.1 mmol, 25.8% from pyridine, >99% ee). The enantiomeric excess of the bromolactone **21** was determined by HPLC (DAICEL-CHIRALCEL-OD-H, hexane/*i*-PrOH=70:30, flow rate=0.8 ml/min, t_D=22.6 min, t_L=27.9 min). $[\alpha]_D^{23}$ 37.0 (*c* 1.15, $CHCl_3$). Mp 132.9–133.6 °C (methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (5H, m), 5.20 (2H, m), 5.01 ((2/3)1H, t, *J*=5.2 Hz), 4.91 ((2/3)1H, t, *J*=5.2 Hz), 4.86 ((1/3)1H, m), 4.85 ((1/3)1H, m), 4.28 (1H, d, *J*=11.2 Hz), 4.05 (1H, d, *J*=11.2 Hz), 3.33 (1H, d, *J*=11.2 Hz), 2.86 (1H, m), 2.50 ((1/3)1H, br s), 2.44 ((2/3)1H, br s), 2.26 (1H, dd, *J*=13.5, 11.2 Hz), 2.03 (1H, d, *J*=13.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 175.2, 155.4, 154.6, 136.0, 135.7, 128.6, 128.5, 128.4, 128.2, 127.9, 81.5, 81.4, 67.8, 67.6, 49.2, 48.6, 48.4, 48.1, 44.8, 44.7, 36.4, 36.3, 32.6, 32.5, 26.9, 26.9. IR (neat, cm^{-1}): 1795, 1704, 1422, 1354, 1330, 1309, 1118, 998. Anal. Calcd for $C_{16}H_{16}BrNO_4$: C, 52.48; H, 4.40; N, 3.82. Found: C, 52.45; H, 4.35; N, 3.62.

4.3. (1*R*,2*S*,3*S*,6*R*,7*R*)-2-Bromo-8-*t*-butoxycarbonyl-4-oxa-8-azatricyclo[4,3,1,0^{6,7}]decan-5-one (23)

To a stirred solution of **21** (2.52 g, 6.88 mmol) and di-*t*-butyl pyrocarbonate (1.65 g, 7.56 mmol) in ethanol (8 ml) and tetrahydrofuran (8 ml) was added 10% Pd/C (AD wet supplied by Kawaken, 1.00 g). The flask was charged with hydrogen gas (1 atm) at room temperature. The resulting suspension was vigorously stirred for 2 h. The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (dichloromethane) to give **23** (2.42 g, 91.7%) as white crystals. $[\alpha]_D^{23}$ −35.6 (*c* 1.11, $CHCl_3$). Mp 132.8–133.7 °C (methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 ((2/3)1H, t, *J*=5.3 Hz), 4.89 ((2/3)1H, d, *J*=5.3 Hz), 4.86 ((1/3)1H, d, *J*=5.1 Hz), 4.76 ((1/3)1H, t, *J*=5.1 Hz), 4.26 (1H, d, *J*=3.6 Hz), 3.94 (1H, d, *J*=11.2 Hz), 3.25 (1H, d, *J*=11.2 Hz), 2.84 (1H, m), 2.48 ((1/3)1H, br s), 2.42 ((2/3)1H, br s), 2.26 (1H, dd, *J*=14.4, 10.8 Hz), 2.01 (1H, d, *J*=14.4 Hz), 1.50 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 175.6, 154.7, 154.0, 81.7, 81.5, 81.3, 81.0, 49.5, 48.7, 48.3, 48.0, 45.0, 44.3, 36.6, 36.4, 32.8, 32.7, 27.0, 27.0. IR (neat, cm^{-1}): 2978, 1798, 1697, 1412, 1364, 1334, 1313, 1173, 1152, 1123, 999. Anal. Calcd for $C_{13}H_{18}BrNO_4$: C, 47.00; H, 5.46; N, 4.22. Found: C, 46.87; H, 5.41; N, 3.92.

4.4. (1*R*,2*S*,3*S*,6*R*,7*R*)-2-Bromo-8-*t*-butoxycarbonyl-4-oxa-8-azatricyclo[4,3,1,0^{6,7}]decan-5,9-dione (24)

To a solution of **23** (4.50 g, 13.6 mmol) and ruthenium dioxide *n*-hydrate (0.335 g, 1.35 mmol) in dichloroethane (63 ml) were added water (32 ml) and sodium periodate (8.69 g, 40.6 mmol). The resulting solution was stirred at 80 °C for 3 h. Additional sodium periodate (1.45 g, 0.678 mmol) was added to the reaction mixture, which was stirred at 80 °C for another 30 min before quenching with isopropyl alcohol (1 ml). After addition of water (30 ml), the reaction mixture was filtered through filter paper to recover ruthenium dioxide *n*-hydrate. The filtrate was then partitioned between water and dichloromethane. The aqueous phase was extracted once with dichloromethane. The combined organic extracts were washed with aqueous sodium sulfite solution, brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give **24** (4.00 g, 11.6 mmol, 85.3%) as white crystals. The combined aqueous layer containing black precipitate was filtered through filter paper again, and the combined black precipitate was dried in vacuo to give ruthenium dioxide *n*-hydrate (0.313 g, 93.4%), which was reused without further purification to convert **23** (4.20 g, 12.6 mmol) into **24** (3.75 g, 10.8 mmol, 85.6%). $[\alpha]_D^{23}$ −41.8 (*c* 1.14, $CHCl_3$). Mp 160.1–161.4 °C (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (1H, dd, *J*=5.3, 5.0 Hz), 5.05 (1H, dd, *J*=5.3, 0.9 Hz), 4.26 (1H, dd, *J*=3.9, 0.9 Hz), 3.19 (1H, m), 2.88 (1H, ddd, *J*=10.6, 5.0, 0.7 Hz), 2.42 (1H, ddd, *J*=15.4, 10.6, 2.3 Hz), 2.25 (1H, ddd, *J*=15.4, 2.7, 0.7 Hz), 1.58 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 166.9, 150.1, 85.3, 79.9, 53.6, 47.5, 43.4, 34.8, 27.9, 26.2. IR (neat, cm^{-1}): 1799, 1784, 1750, 1722, 1398, 1297, 1285, 1249, 1150, 974. Anal. Calcd for $C_{13}H_{16}BrNO_5$: C, 45.10; H, 4.66; N, 4.05. Found: C, 45.34; H, 4.64; N, 3.79.

4.5. (1*S*,4*R*,5*S*,6*S*,7*S*)-5-Bromo-6-hydroxy-2-*t*-butoxycarbonyl-2-azabicyclo[2,2,2]octan-3-one-7-carboxamide (25)

Ammonia gas was passed through an ice-cold solution of lactone **24** (4.30 g, 12.4 mmol) in tetrahydrofuran (80 ml) and *tert*-butyl alcohol (80 ml) over a period of 2.5 h. After concentration of the reaction mixture under reduced pressure, the crude product was purified by silica gel column chromatography (methanol/dichloromethane=1:9) to give **25** (4.29 g, 95.1%) as white crystals. $[\alpha]_D^{23}$ 8.70 (*c* 1.21, DMF). Mp 137.7–138.7 °C (methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10–5.85 (1H, br s), 5.85–5.60 (1H, br s), 4.91 (1H, m), 4.84 (1H, dd, *J*=3.2, 2.8 Hz), 4.39 (1H, m), 4.08 (1H, t, *J*=3.2 Hz), 3.02 (1H, m), 2.92 (1H, ddd, *J*=14.2, 6.9, 2.0 Hz), 1.56 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 168.5, 149.8, 84.8, 79.0, 55.6, 50.6, 48.5, 41.8, 28.0, 27.5. IR (neat, cm^{-1}): 1772, 1732, 1716, 1668, 1370, 1291, 1255, 1150. Anal. Calcd for $C_{13}H_{19}BrN_2O_5$: C, 42.99; H, 5.27; N, 7.71. Found: C, 42.69; H, 5.33; N, 7.53.

4.6. (1*S*,4*R*,5*S*,6*S*,7*S*)-5-Bromo-6-methanesulfonyloxy-2-*t*-butoxycarbonyl-2-azabicyclo[2,2,2]octan-3-one-7-carboxamide (26)

To a solution of alcohol **25** (1.95 g, 5.37 mmol) and triethylamine (2.25 ml, 16.11 mmol) in dichloromethane (50 ml) was added methanesulfonyl chloride (499 μl, 6.45 mmol) slowly at room temperature. After stirring for 15 min, additional methanesulfonyl chloride (120 μl, 1.55 mmol) was added. The reaction mixture was stirred for an additional 25 min before quenching with aqueous saturated sodium bicarbonate. After the aqueous phase was saturated with sodium chloride, the organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (methanol/

dichloromethane=1:19 to 1:9) to give **26** (2.15 g, 4.87 mmol, 90.7%) as a white solid. $[\alpha]_D^{23}$ −4.4 (*c* 0.91, DMF). Mp 161.9–162.7 °C (methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80–5.50 (1H, br s), 5.75–5.45 (1H, br s), 5.21 (1H, dd, *J*=3.7, 2.8 Hz), 5.14 (1H, dd, *J*=3.7, 3.6 Hz), 4.25 (1H, dd, *J*=3.6, 2.8 Hz), 3.13 (3H, s), 3.04 (1H, m), 2.95 (1H, m), 2.76 (1H, ddd, *J*=14.7, 6.4, 2.8 Hz), 2.17 (1H, ddd, *J*=14.7, 11.0, 3.7 Hz), 1.61 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 167.6, 149.8, 85.4, 83.0, 55.4, 48.1, 45.1, 39.5, 38.3, 28.0, 24.7. IR (neat, cm^{-1}): 3452, 3331, 1776, 1715, 1685, 1372, 1334, 1271, 1171, 1156, 957, 867. Anal. Calcd for $C_{14}H_{21}BrN_2O_7S$: C, 38.10; H, 4.80; N, 6.35. Found: C, 38.01; H, 4.75; N, 6.36.

4.7. (1*S*,4*R*,5*S*,6*S*,7*S*)-5-Bromo-7-allyloxycarbonyl-6-methanesulfonyloxy-2-*t*-butoxycarbonyl-2-azabicyclo[2,2,2]octan-3-one (27)

To a mixture of **26** (2.259 g, 5.118 mmol), allyl alcohol (17.4 ml, 256 mmol), and molecular sieves 4 Å (2.56 g) in 1,2-dichloroethane (33.8 ml) was added diacetoxyiodobenzene (3.297 g, 10.24 mmol). After stirring for 15 min at room temperature, the reaction mixture was heated at 60 °C for 10.5 h. After quenching with saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate, the resulting mixture was filtered through a Celite pad, and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane=1:1) to give **27** (2.233 g, 4.490 mmol, 87.7%) as a white amorphous solid. $[\alpha]_D^{23}$ −2.7 (*c* 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (1H, m), 5.32 (1H, dd, *J*=17.4, 1.4 Hz), 5.29–5.22 (1H, br s), 5.24 (1H, d, *J*=10.8 Hz), 4.97 (1H, s), 4.59 (2H, d, *J*=5.7 Hz), 4.25 (1H, m), 4.22 (1H, dd, *J*=2.8, 1.4 Hz), 3.19 (3H, s), 3.00 (1H, m), 2.76 (1H, m), 1.64 (1H, m), 1.56 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 155.3, 148.8, 132.4, 118.2, 85.2, 84.0, 66.1, 54.7, 47.9, 46.5, 45.9, 38.5, 31.3, 27.9. IR (neat, cm^{-1}): 1781, 1747, 1731, 1710, 1521, 1370, 1294, 1237, 1177, 1148. Anal. Calcd for $C_{17}H_{25}BrN_2O_8S$: 497.0593 ($M+H^+$). Found: 497.0592.

4.8. (1*S*,5*S*,6*R*)-5-Allyloxycarbonylamino-7-*t*-butoxycarbonyl-3-ethoxycarbonyl-7-azabicyclo[4,1,0]heptan-2-ene (30)

To a stirred solution of **27** (2.233 g, 4.490 mmol) in ethanol (8.98 ml) was added portionwise a 1.0 M solution of sodium ethoxide in ethanol (9.05 ml, 9.05 mmol) at 0 °C until TLC (ethyl acetate/hexane=1:2) indicated complete reaction. The resulting solution was diluted with dichloromethane, quenched with acetic acid, and neutralized with aqueous saturated sodium bicarbonate. After the reaction mixture was filtered through a Celite pad, aqueous saturated sodium bicarbonate was added. The aqueous phase was saturated with sodium chloride and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane=1:2) to give **30** (1.438 g, 3.924 mmol, 87.4%) as an off-white amorphous solid. $[\alpha]_D^{23}$ −68.7 (*c* 1.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (1H, dd, *J*=4.6, 3.2 Hz), 5.90 (1H, m), 5.30 (1H, d, *J*=17.4 Hz), 5.22 (1H, d, *J*=10.5 Hz), 4.70–4.50 (1H, br s), 4.61 (2H, s), 4.56 (1H, br d, *J*=4.8 Hz), 4.20 (2H, q, *J*=7.3 Hz), 3.12 (1H, d, *J*=5.6 Hz), 2.99 (1H, dd, *J*=5.6, 4.8 Hz), 2.73 (1H, d, *J*=17.1 Hz), 2.39 (1H, d, *J*=17.1 Hz), 1.45 (9H, s), 1.29 (1H, t, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 160.5, 155.4, 134.0, 132.5, 130.2, 118.0, 82.2, 65.7, 61.0, 42.4, 41.8, 32.4, 27.8, 26.8, 14.1. IR (neat, cm^{-1}): 3330, 2980, 1715, 1530, 1369, 1259, 1156, 1096, 1058. HRMS Calcd for $C_{18}H_{26}N_2O_6$: 366.1791. Found: 366.1788.

4.9. (3*S*,4*S*,5*S*)-5-Allyloxycarbonylamino-4-*t*-butoxycarbonylamino-1-ethoxycarbonyl-3-(3-pentyloxy)-cyclohex-2-ene (34)

Aziridine **30** (442.1 mg, 1.207 mmol) was dissolved in hot 3-pentanol (6.0 ml) and then cooled to −20 °C. To the stirred suspension was added 0.50 M solution of boron trifluoride diethyl ether complex in 3-pentanol (2.88 ml, 1.44 mmol) at −20 °C over 20 min. After stirring for an additional 30 min, the reaction mixture was warmed to 0 °C and quenched with aqueous saturated sodium bicarbonate. The mixture was extracted twice with toluene, and the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane/hexane=1:3) to give **34** (341.0 mg, 0.750 mmol, 62.2%) as a white amorphous solid. $[\alpha]_D^{23}$ −37.7 (*c* 1.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (1H, s), 5.89 (1H, m), 5.63 (1H, d, *J*=8.7 Hz), 5.28 (1H, br d, *J*=17.2 Hz), 5.19 (1H, d, *J*=10.3 Hz), 4.65–4.45 (1H, m), 4.54 (2H, br s), 4.20 (2H, q, *J*=7.1 Hz), 3.94 (1H, m), 3.87 (1H, m), 3.77 (1H, m), 3.41 (1H, quintet, *J*=5.5 Hz), 2.75 (1H, dd, *J*=18.3, 8.3 Hz), 2.34 (1H, dd, *J*=18.3, 8.3 Hz), 1.55 (4H, dq, *J*=7.3, 5.5 Hz), 1.42 (9H, s), 1.28 (3H, t, *J*=7.3 Hz), 0.91 (6H, t, *J*=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 156.3, 137.2, 132.8, 129.3, 117.2, 82.5, 79.5, 75.5, 65.4, 60.8, 54.9, 50.0, 30.6, 28.2, 26.2, 25.9, 14.1, 9.3. IR (neat, cm^{-1}): 3335, 2978, 1716, 1685, 1541, 1283, 1243, 1173, 1058. Anal. Calcd for $C_{23}H_{38}N_2O_7$: C, 60.77; H, 8.43; N, 6.16. Found: C, 60.49; H, 8.41; N, 6.09.

4.10. (3*S*,4*S*,5*S*)-4-Acetamido-5-allyloxycarbonylamino-1-ethoxycarbonyl-3-(3-pentyloxy)cyclohex-2-ene (36)

To a stirred solution of **34** (341.0 mg, 0.750 mmol) in dichloromethane (5.0 ml) was added trifluoroacetic acid (1.11 ml, 15.0 mmol) at 0 °C, and the resulting solution was allowed to warm to room temperature. After stirring for 3 h, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous sodium bicarbonate, and warmed to room temperature. The aqueous phase was saturated with sodium chloride and extracted with dichloromethane three times. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude amine (257.5 mg) as a pale yellow amorphous solid, which was used for the next acetylation without further purification.

To a stirred solution of the amine (257.5 mg, 0.727 mmol) in pyridine (2.6 ml) was added acetic anhydride (1.3 ml) at room temperature. After stirring for an hour, and the reaction mixture was concentrated under reduced pressure. The crude product was recrystallized from isopropyl alcohol–water to give **36** (215.2 mg, 0.543 mmol, 72.4% over two steps) as off-white crystals. The mother liquid was purified by preparative TLC (dichloromethane/hexane=1:1) to give **36** (45.2 mg, 0.114 mmol, 15.2%) as a white solid. $[\alpha]_D^{23}$ −70.3 (*c* 1.21, $CHCl_3$). Mp 153.0–154.3 °C (ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (1H, s), 5.89 (1H, m), 5.56 (1H, d, *J*=11.3 Hz), 5.53 (1H, d, *J*=26.0 Hz), 5.28 (1H, br d, *J*=17.2 Hz), 5.20 (1H, d, *J*=10.3 Hz), 4.54 (2H, m), 4.21 (2H, q, *J*=7.1 Hz), 4.11 (1H, q, *J*=8.7 Hz), 3.99 (1H, br d, *J*=7.1 Hz), 3.86 (1H, m), 3.38 (1H, quintet, *J*=5.7 Hz), 2.77 (1H, dd, *J*=18.1, 4.8 Hz), 2.36 (1H, dd, *J*=18.1, 9.0 Hz), 1.98 (s, 3H), 1.52 (4H, m), 1.29 (3H, t, *J*=7.1 Hz), 0.90 (6H, dt, *J*=8.8, 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 165.9, 156.6, 137.3, 132.7, 129.2, 117.4, 82.1, 75.3, 65.4, 60.9, 54.0, 49.9, 30.6, 26.1, 25.7, 23.2, 14.1, 9.4, 9.2. IR (neat, cm^{-1}): 3299, 3278, 1729, 1685, 1643, 1549, 1248, 1055. Anal. Calcd for $C_{20}H_{32}N_2O_6$: C, 60.59; H, 8.14; N, 7.07. Found: C, 60.36; H, 8.18; N, 7.04.

4.11. (−)-Oseltamivir phosphate (1·H_3PO_4)

A stirred mixture of **36** (566.2 mg, 1.428 mmol), 1,3-dimethylbarbituric acid (272.1 mg, 1.743 mmol), triphenylphosphine (15.0 mg, 0.0571 mmol), and 5% Pd/C (E3, 50% wet, provided by Degussa, 64.0 mg, 0.0143 mmol) in ethanol (11.3 ml) was heated at 80 °C for an hour. The reaction mixture was then filtered and concentrated under reduced pressure. To the solution of the crude product in ethanol (5.80 ml) was added a 1.0 M solution of phosphoric acid in ethanol (1.70 ml, 1.70 mmol). The resulting solution was warmed to 50 °C and seed crystals of **1**·H_3PO_4 were added to initiate the crystallization. The mixture was slowly cooled to room temperature and stirred overnight. The resulting suspension was cooled to −18 °C, stirred for an additional 3 h, filtered and washed successively with acetone (seven times) and hexane (three times) to give **1**·H_3PO_4 (445.1 mg, 1.085 mmol, 76.0%) as white crystals. $[\alpha]_D^{23}$ −31.2 (*c* 1.00, H_2O). Mp 184.0–186.2 °C (ethanol). ^{1}H NMR (400 MHz, D_2O): δ 6.83 (1H, d, *J*=2.1 Hz), 4.32 (1H, m), 4.23 (2H, m), 4.04 (1H, m), 3.55 (2H, m), 2.95 (1H, m), 2.51 (1H, m), 2.07 (3H, s), 1.54 (4H, m), 1.45 (2H, m), 1.37 (1H, ddt, *J*=14.0, 2.3, 1.6 Hz), 0.87 (3H, m), 0.82 (3H, m). ^{13}C NMR (100 MHz, D_2O): δ 175.2, 167.3, 137.8, 84.2, 75.0, 62.3, 52.5, 49.1, 28.1, 25.4, 25.0, 22.3, 13.2, 8.5, 8.4. ^{31}P NMR (162 MHz, D_2O): δ 0.6. IR (KBr, cm^{-1}): 3352, 1718, 1660, 1552, 1375, 1296, 1246, 1128, 1066, 1028, 947. Anal. Calcd for $C_{16}H_{31}N_2O_8P$: C, 46.83; H, 7.61; N, 6.83. Found: C, 46.55; H, 7.36; N, 6.86.

4.12. (1*S*,4*S*,7*S*)-2-Benzyloxycarbonyl-7-hydroxymethyl-2-azabicyclo[2,2,2]octan-7-ene (13) and benzyl 5-(5-(hydroxymethyl)cyclohexa-2,4-dienyl)methylcarbamate (14)

To a stirred solution of pyridine (**10**) (5.00 g, 63.2 mmol) in methanol (50 ml) was added sodium borohydride (2.63 g, 69.5 mmol) at −78 °C. To this was added benzyl chloroformate (10.24 g, 60.0 mmol) dropwise over a period of 90 min at such a rate that inner temperature was maintained under −69 °C. After stirring for 100 min, water (50 ml) and diethyl ether (50 ml) were added to the reaction mixture. The resulting mixture was warmed to room temperature, and the organic layer was separated. The aqueous layer was extracted with ether (50 ml), and the combined organic extracts were washed with 1 N HCl (50 ml), 1 N NaOH (50 ml), water (20 ml), and brine (20 ml), respectively, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude dihydropyridine **11** (9.84 g) as a pale yellow oil, which was used for the next step without further purification. To a stirred solution of **11** (3.00 g) in acetonitrile (14.2 ml) and water (0.75 ml) were added the MacMillan's catalyst **12** (0.36 g, 1.4 mmol) and acrolein (2.8 ml, 42 mmol) at room temperature. After stirring for 16 h, the reaction mixture was diluted with diethyl ether (50 ml), and washed with water (50 ml). The aqueous layer was extracted with diethyl ether (50 ml). The combined organic extracts were washed with brine (50 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give aldehyde **16** (7.77 g) as a pale yellow oil, which was used for the next step without further purification. To a stirred solution of aldehyde **16** (5.00 g) in ethanol (25 ml) was added sodium borohydride (1.40 g, 37.0 mmol). After stirring for 30 min, the reaction was quenched with aqueous HCl (100 ml). The reaction mixture was extracted twice with ethyl acetate, and the combined organic extracts were washed with brine, filtered, and concentrated under reduced pressure to give the crude product (2.42 g). One gram of the crude product was purified by silica gel column chromatography to give **13** (284 mg, 28.1% over three steps) as a colorless viscous oil and **14** (79 mg, 7.8% over three steps) as a white amorphous solid. Compound **13**: $[\alpha]_D^{23}$ 70.2 (*c* 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (5H, m), 6.37 (2H, m), 5.11 (2H, m), 4.90 ((3/5)1H, br s), 4.84 ((2/5)1H, br s), 3.28 (2H, m), 3.18 (1H, m), 3.02 (1H, m), 2.73 (1H, m), 2.36 (1H, m), 1.76 (1H, m), 0.83 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 154.8, 137.0, 136.9, 135.0, 134.6, 130.5, 130.0, 128.4, 128.4, 127.8, 127.7, 127.7, 127.7, 66.7, 66.7, 65.6, 65.5, 47.3, 47.2, 46.9, 46.8, 41.6, 41.6, 30.8, 30.6, 26.1, 26.1. IR (neat, cm^{-1}): 3429, 2935, 2873, 1695, 1419, 1344, 1300, 1113, 1053. HRMS Calcd for $C_6H_{19}NO_3$: 274.1443 ($M+H^+$); Found: 274.1441. Compound **14**: $[\alpha]_D^{23}$ −141 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (5H, m), 5.99 (1H, dd, *J*=9.4, 5.2 Hz), 5.85 (1H, d, *J*=4.4 Hz), 5.64 (1H, dd, *J*=9.4, 5.6 Hz), 5.12 (2H, m), 4.98 (1H, br s), 4.06 (2H, s), 3.21 (1H, m), 3.12 (1H, m), 2.46 (1H, m), 2.31 (1H, m), 2.23 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 137.1, 136.4, 128.5, 128.1, 128.1, 126.7, 125.5, 119.2, 66.8, 66.0, 42.9, 33.9, 26.6. IR (neat, cm^{-1}): 3334, 3033, 2925, 2864, 1699, 1537, 1454, 1259, 1140, 997. Anal. Calcd for $C_6H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.01; H, 6.90; N, 5.08.

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