Formal Synthesis of Tamiflu: Conversion of Tamiflu into Tamiphosphor

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Abstract: A short, enantiomeric, synthesis of Shibasaki's 3rd generation intermediate to form (–)-oseltamivir phosphate (Tamiflu®) has been achieved in eight steps with the use of inexpensive starting materials. A formal synthetic route to convert tamiflu into tamiphosphor via Fang's tamiphosphor intermediate has been accomplished.

Key words: hydrolysis, epoxide, oxidation, amides, enantioselectivity

Influenza is a highly contagious respiratory virus that poses a serious threat to public health. On average, seasonal influenza epidemics cause 36000 deaths and over 200,000 hospitalizations annually in the US.[1] In addition, emergence of novel influenza strains could lead to pandemics resulting in millions of hospitalizations and deaths worldwide.[2,3] Currently, the leading drugs available to treat influenza infections are the neuraminidase inhibitors Relenza® (zanamivir) and Tamiflu® [(–)-oseltamivir phosphate; Figure 1). Since neuraminidases play a key role in the life cycle of all influenza viruses, these drugs represent an efficient molecular weapon to protect humans against epidemic and pandemic influenza.[4] Due to its ability to be administered orally, tamiflu has become the agent of choice for treating severe influenza infections.[4]

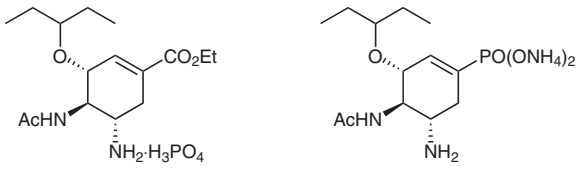

Figure 1 Structures of tamiflu and tamiphosphor

At present, large-scale industrial syntheses of tamiflu require either (–)-shikimic acid or (–)-quinic acid.[5] These processes are time consuming and expensive due to the low natural abundance of these starting materials.[5a,b] Development of alternate syntheses of tamiflu from readily available and less expensive starting materials is mandatory to meet the growing demand for this drug, cost-effectively.[5] In addition, since constant evolutionary pressure could result in the development of novel influenza strains with significant resistance to tamiflu, it is prudent to develop and test additional neuraminidase inhibitors.[6] Recently, Fang et al.[7] synthesized tamiphosphor (**2**; Figure 1), which was reported to be more active than **1** by 19- and 7-folds in NA inhibition and antiflu assays, respectively. The phosphonate group in tamiphosphor has been shown to form strong interactions with three arginine residues of neuraminidase, making it a more potent inhibitor against the wild-type neuraminidases of H1N1 and H5N1 viruses.[8] Moreover, preliminary studies have shown that **2** is also orally bioavailable.[8] Therefore, development of synthetic protocols to convert tamiflu into tamiphosphor would be timely and would reduce costs in the event that a switch between drugs is required.

In Shibasaki's 3rd generation synthesis of tamiflu, the optically active intermediate **8** was obtained by the use of chiral HPLC.[9] Herein, we describe a short enantioselective pathway for the synthesis of **8**, using benzene as an inexpensive starting material. Furthermore, we have shown for the first time, a concise route to convert tamiflu (**1**) into tamiphosphor (**2**) by synthesizing **11**, the key intermediate of Fang's tamiphosphor synthesis.[8] Converting tamiflu (**1**) into tamiphosphor (**2**) might be advantageous if influenza viruses develop resistance to tamiflu (**1**).

Scheme 1 shows the synthetic approach used to construct functionalized Shibasaki's intermediate **8**.[10] While this manuscript was in preparation, Hayashi and co-workers independently reported a similar synthetic approach to **8**.[11] However, our approach is more straightforward, efficient and robust. The synthesis began with the preparation of optically pure epoxide **3** from benzene in 21% yield over three steps.[12,13] Azido alcohol **4** was obtained in moderate yield by cesium chloride promoted ring opening of epoxide **3** using NaN_3–MeCN conditions.[14] A convenient way of transforming azido alcohols to aziridines was reported by Ittah et al.[15] This methodology was successfully applied to obtain N-protected aziridine **5** from **4** in 76% yield. Regioselective ring opening of aziridine **5** was accomplished by the use of tetramethylguanidinium azide (TMGA) to give **6** in excellent yield.[16] Reduction of azide **6** followed by *N*-Boc protection gave diamide **7** in 91% yield. Base hydrolysis of **7**, followed by oxidation using standard Dess–Martin periodinane conditions gave enantiopure Shibasaki's intermediate **8** in 86% yield.[17] Compound **8** proved to be a single stereoisomer as determined by HPLC (OD-H CHIRALCEL column). Shibasaki's intermediate **8** could be easily converted into tamiflu with seven steps.[9] It is worth mentioning that, to date, this ap-

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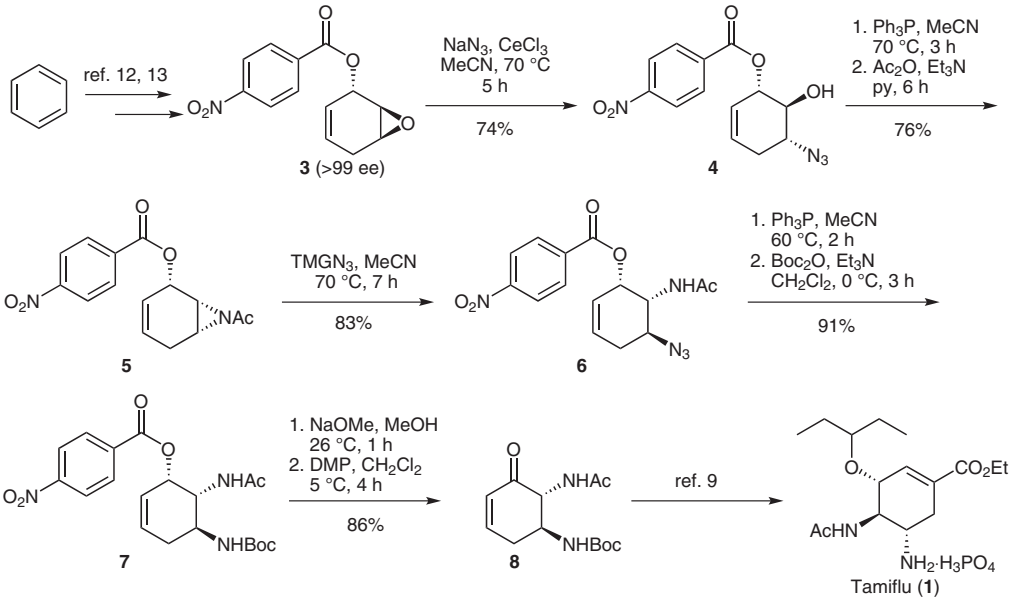
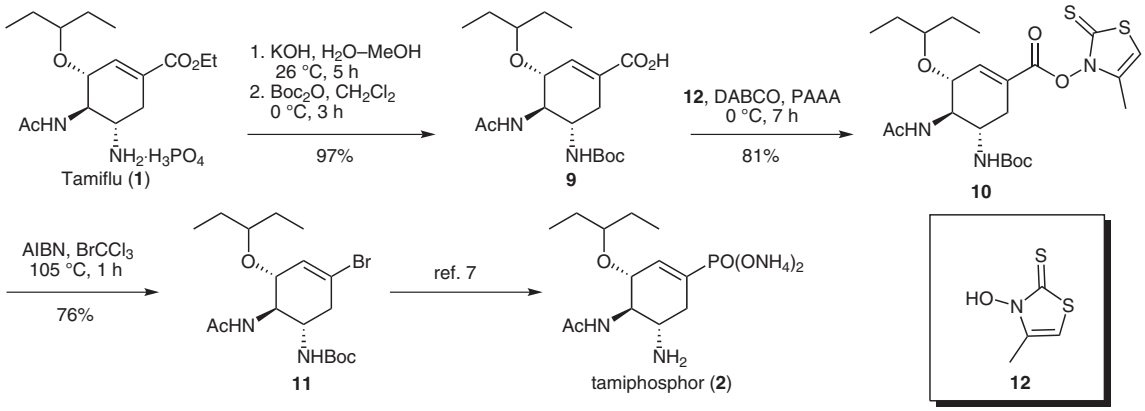


Scheme 1 Enantioselective synthesis of intermediate **8**



Scheme 2 Conversion of tamiflu into tamiphosphor

proach is the shortest synthesis of enantiomerically pure intermediate **8** from benzene.

In order to transform tamiflu to tamiphosphor, we prepared the *N*-Boc-protected acid **9** by hydrolyzing enantiomerically pure (–)-oseltamivir phosphate **1**,[18] as outlined in Scheme 2. Conversion of **9** directly into Fang's tamiphosphor intermediate **11** using Hunsdiecker-type bromodecarboxylation conditions was unsuccessful.[19] However, treatment of **9** with cyclic thiohydroxamic acid **12**, propane phosphonic acid anhydride (PPAA), and 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded **10** in 81% yield.[20] Conversion of **10** into **11** was achieved by slow addition of **10** to a solution of AIBN in bromotrichloromethane to produce **11**, which is the key intermediate of Fang's tamiphosphor synthesis.[21]

In all three transformations, we did not observe any erosion in enantiopurity compared to the starting (–)-oseltamivir phosphate.[22] The intermediate **11** could be converted into tamiphosphor (**2**) in two operations.[8]

In summary, a short (eight steps from benzene, 8% overall yield), and practical synthesis of the intermediate **8** was achieved. This key intermediate **8** could easily be transformed to enantiomerically pure (–)-oseltamivir phosphate.[9] Moreover, we have presented a convenient approach to convert tamiflu into its more potent counterpart tamiphosphor, by synthesizing intermediate **11** in three steps with an overall yield of 59%. The proposed synthetic routes are straightforward, flexible and cost effective.

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

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(17) **(1*S*,5*R*,6*S*)-5-Azido-6-hydroxycyclohex-2-en-1-yl 4-Nitrobenzoate(4)**: $CeCl_3{\cdot}7H_2O$ (1 mmol) and NaN_3 (1.1 mmol) were added to epoxide **3** (1 mmol) in a mixture of MeCN and H_2O (9:1, 10 mL). The reaction mixture was stirred at reflux temperature until the disappearance of starting material as indicated by TLC. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried over anhyd Na_2SO_4, and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (hexane–EtOAc) to provide the pure azidohydrin **4** in 74% yield as a white foam; $[\alpha]^{26}_D$ +27 (*c* = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.33 (m, 4 H), 5.81–5.90 (m, 1 H), 5.62–5.75 (m, 2 H), 3.94 (dd, *J* = 10.4, 7.5 Hz, 1 H), 3.76 (td, *J* = 10.4, 5.9 Hz, 1 H), 2.93 (s, 1 H), 2.61 (dt, *J* = 17.6, 5.5 Hz, 1 H), 2.23 (ddd, *J* = 17.8, 10.3, 2.5 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 164.94, 158.39, 150.93, 135.12, 130.93, 127.81, 124.86, 123.57, 76.79, 74.22, 61.22, 30.39. HRMS (CI): *m*/*z* [M + H] calcd for $C_{13}H_{12}N_4O_5$: 305.0886; found: 305.0883.
(1*S*,2*S*,6*S*)-7-Acetyl-7-azabicyclo[4.1.0]hept-3-en-2-yl 4-Nitrobenzoate (5): A solution of **4** (0.82 g, 2.6 mmol) and triphenylphosphine (0.85 g, 2.9 mmol) in anhyd MeCN (5.2 mL) was refluxed for 2 h. After cooling to r.t., the solvent was removed under reduced pressure, and pyridine (5.2 mL) and Ac_2O (490 μL, 5.2 mmol, 2 equiv) were added at r.t. After 5 h, the reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 3:1 → 1:1) to afford **5** (60 mg, 0.976 mmol) in 76% yield as a pale yellow semisolid; $[\alpha]^{26}_D$ +36 (*c* = 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 4.1 Hz, 4 H), 5.70–5.95 (m, 2 H), 5.50–5.70 (m, 1 H), 3.13–3.38 (m, 1 H), 2.88–3.15 (m, 1 H), 2.64 (dd, *J* = 19.9, 4.4 Hz, 1 H), 2.29–2.54 (m, 1 H), 2.07 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.74, 164.35, 150.96, 135.20, 131.07, 126.69, 123.66, 122.15, 68.22, 37.37, 34.79, 24.51, 23.31. HRMS (CI): *m*/*z* [M + H] calcd for $C_{15}H_{14}N_2O_5$: 303.0981; found: 303.0986.
(1*S*,5*R*,6*S*)-6-Acetamido-5-azidocyclohex-2-en-1-yl 4-Nitrobenzoate (6): To a solution of **5** (2.11 g, 6.98 mmol) in MeCN (4.2 mL), tetramethylguanidinium azide (TMGA; 2.18 g, 13.96 mmol, 2 equiv) was added and the mixture was stirred at 60 °C for 13 h. After completion of the reaction, MeCN was removed under reduced pressure. HCl (5%, 20 mL) was added and the solution was extracted with Et_2O (3 × 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated and purified by column chromatography (hexane–EtOAc) to afford **6** (2.23 g) in 83% yield as a white solid; mp 181–183 °C; $[\alpha]^{26}_D$ +42 (*c* = 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (dd, *J* = 51.0, 8.8 Hz, 4 H), 5.89–6.17 (m, 2 H), 5.66 (d, *J* = 3.3 Hz, 2 H), 4.35–4.73 (m, 1 H), 3.74–4.04 (m, 1 H), 2.71 (dd, *J* = 18.1, 4.0 Hz, 1 H), 2.36 (dd, *J* = 18.1, 9.0 Hz, 1 H), 2.01 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.25, 163.83, 150.74, 135.25, 130.73, 123.73, 70.37, 56.34, 50.82, 30.93, 23.59. HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{15}H_{15}N_5O_5$: 368.0971; found: 368.0974.
(1*S*,5*R*,6*S*)-6-Acetamido-5-*tert*-butoxycarbonylamino-2-en-1-yl 4-Nitrobenzoate (7): To a solution of **6** (1.24 g, 3.6 mmol) in MeCN (6 mL), Ph_3P (1.16 g, 3.96 mmol, 1.1 equiv) was added and the mixture was stirred at 60 °C for 3 h. H_2O (2 mL) was added and the reaction mixture was stirred at 45 °C for 2 h. Solvent was removed under reduced pressure followed by the addition of CH_2Cl_2 (6 mL), Et_3N (1.5 mL, 10.8 mmol), and Boc_2O (1.57 g, 7.2 mmol), and the mixture was stirred at r.t. for 2 h. Deionised H_2O (6 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 1:1) to afford **7** (1.27 g, 3.28 mmol) in 91% yield (2 steps) as a white solid; mp 196–198 °C; $[\alpha]^{26}_D$ +154 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.46 (m, 4 H), 6.38 (d, *J* = 7.7 Hz, 1 H), 5.98 (s, 2 H), 5.59 (s, 1 H), 4.73 (d, *J* = 7.5 Hz, 2 H), 3.89–4.43 (m, 2 H), 2.65 (d, *J* = 18.7 Hz, 1 H), 2.10 (dd, *J* = 17.6, 9.6 Hz, 1 H), 1.91 (s, 3 H), 1.44 (s, 9 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.51, 163.77, 156.90, 150.57, 135.19, 131.99, 130.80, 123.56, 80.08, 70.50, 53.54, 45.56, 32.65, 28.21, 23.13. HRMS (ESI): *m*/*z* [M + H] calcd for $C_{20}H_{25}N_3O_7$: 420.1771; found: 420.1774.
***tert*-Butyl [(1*R*,6*S*)-6-Acetamido-5-oxocyclohex-3-en-1-yl]carbamate (8)**: To a solution of **7** (635 mg, 1.63 mmol) in MeOH (3.26 mL) was added solid NaOMe (44 mg, 0.81 mmol) under argon atmosphere. After stirring at r.t. for 1 h, glacial AcOH (47 μL) was added to quench the reaction. MeOH was removed by rotary evaporation and CH_2Cl_2 (3 mL) was added to the residue. After cooling to 4 °C Dess–Martin periodinane (1.03 g, 2.44 mmol, 1.5 equiv) was added. After 1 h, sat. aq $Na_2S_2O_3$ was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with sat. aq $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure and was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to afford **8** (332.4 mg, 1.4 mmol) in 86% yield as a white solid; mp 143–144 °C; $[\alpha]^{26}_D$ –132 (*c* = 0.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85–7.08 (m, 1

H), 6.38 (d, *J* = 6.4 Hz, 1 H), 6.12 (dd, *J* = 10.1, 3.0 Hz, 1 H), 5.70 (d, *J* = 7.8 Hz, 1 H), 4.59 (dd, *J* = 13.0, 7.1 Hz, 1 H), 3.75–4.03 (m, 1 H), 2.93 (dt, *J* = 18.7, 5.5 Hz, 1 H), 2.29–2.52 (m, 1 H), 2.07 (s, 3 H), 1.40 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.98, 172.50, 156.09, 148.65, 128.51, 79.73, 59.70, 53.49, 34.11, 28.31, 23.11. HRMS (CI): *m*/*z* [M$^+$] calcd for $C_{13}H_{20}N_2O_4$: 268.1423; found: 268.1425.

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(22) **(3*R*,4*R*,5*S*)-4-Acetamido-5-[(*tert*-butoxycarbonyl)-amino]-3-(pentan-3-yloxy)cyclohex-1-enecarboxylic Acid (9)**: Solid **1** (163 mg, 0.413 mmol) was dissolved in sat. $NaHCO_3$ (10 mL) and was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried with Na_2SO_4. After complete removal of the solvent, the residue was dissolved in H_2O–MeOH (1 mL; 1:1) mixture and solid KOH (46.3 mg, 0.826 mmol) was added, and the mixture was stirred at r.t. overnight. After most of the MeOH was removed under reduced pressure, H_2O was removed by azeotropic evaporation with benzene. The residue was dissolved in CH_2Cl_2 (1 mL) and treated with Et_3N (287 uL, 2.06 mmol, 5 equiv), and Boc_2O (180 mg, 8826 mmol, 2 equiv), and the mixture was stirred at r.t. for 4 h. The reaction mixture was quenched with a sat. aq NH_4Cl solution and extracted with EtOAc (3 × 5 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give pure product **9** as a white solid in 97% yield; mp 206–208 °C; $[\alpha]^{26}_D$ –53 (*c* = 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 5.78 (d, *J* = 9.6 Hz, 1 H), 3.86–4.10 (m, 2 H), 3.66–3.84 (m, 1 H), 3.26–3.34 (m, 1 H), 2.69 (dd, *J* = 17.6, 4.7 Hz, 1 H), 2.24 (dd, *J* = 17.4, 10.8 Hz, 1 H), 1.98 (s, 3 H), 1.46 (t, *J* = 6.6 Hz, 4 H), 1.40 (s, 9 H), 0.77 –0.93 (m, 6 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ= 171.36, 169.00, 156.72, 139.30, 128.92, 82.08, 79.65, 76.00, 55.10, 49.27, 30.72, 28.34, 26.15, 25.49, 23.22, 9.63, 9.00. HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{19}H_{32}N_2O_6$: 407.2158; found: 407.2153.

(3*R*,4*R*,5*S*)-4-Methyl-2-thioxothiazol-3 (2*H*)-yl-4-acetamido-5-[(*tert*-butoxycarbonyl)amino]-3-(pentan-3-loxy)cyclohex-1-enecarboxylate (10): DABCO (112 mg, 1.43 mmol) and thiohydroxamic acid (**12**; 84 mg, 0.572 mmol) were added to a cold (0 °C), magnetically stirred solution of **9** (110 g, 0.286 mmoL) in anhyd CH_2Cl_2 (1.43 mL), and the reaction mixture was stirred for 45 min at 0–5 °C, and treated with propane phosphonic acid anhydride [PPAA; 0.5 mL, 50% (w/w) solution of PPAA in DMF]. The reaction mixture was stirred for 5 h at r.t. All volatiles were removed at 20 °C under reduced pressure to afford a residue which was taken up in Et_2O (2 mL) and H_2O (2 mL). The combined ethereal layers were washed with H_2O (2 mL), dried with anhyd Na_2SO_4, filtered, and evaporated. Column chromatography (elution with 25–50% Et_2O and hexane) gave the ester **10** (119 mg, 81%) as a semisolid; $[\alpha]^{26}_D$ –59 (*c* = 0.06, $CHCl_3$). ^{1}H NMR (400 MHz, MeOD): δ = 6.61 (s, 1 H), 4.24 (d, *J* = 7.5 Hz, 1 H), 3.95 (t, 1 H), 3.84 (td, *J* = 10.3, 5.4 Hz, 1 H), 3.40–3.52 (m, 1 H), 2.84 (d, *J* = 17.4 Hz, 1 H), 2.31–2.59 (m, 1 H), 2.19 (s, 3 H), 1.98 (s, 3 H), 1.48–1.63 (m, 6 H), 1.45 (s, 9 H), 0.92 (dt, *J* = 15.4, 7.4 Hz, 6 H). ^{13}C NMR (400 MHz, MeOD): δ = 182.38, 173.72, 157.96, 138.94, 126.34, 104.20, 83.72, 80.41, 77.15, 55.87, 49.99, 31.62, 28.71, 27.22, 26.72, 22.99, 13.14, 9.94, 9.59. HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{23}H_{35}N_3O_6S_2$: 536.1865; found: 536.1873.

***tert*-Butyl-[(1*S*,5*R*,6*R*)-6-acetamido-3-bromo-5-(pentan-3-yloxy)cyclohex-3-en-1-yl]carbamate (11)**: Thiohydroxamic ester **10** (96 mg, 0.187 mmol) and AIBN (1.5 mg) were dissolved in bromotrichloromethane (935 μL) and heated to 70 °C. The reaction was stirred for an additional 1 h, cooled, and chromatographed directly on silica gel (hexane–EtOAc) to give **21** (59 mg, 76%) as a white solid; mp 153–155 °C; $[\alpha]^{26}_D$ –42 (*c* = 0.32, $CHCl_3$). All spectroscopic data was identical to the previously reported data of **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05 (s, 1 H), 5.65 (d, *J* = 9.0 Hz, 1 H), 5.36 (d, *J* = 8.9 Hz, 1 H), 4.08 (q, *J* = 9.2 Hz, 1 H), 3.74–3.92 (m, 2 H), 3.19–3.34 (m, 1 H), 2.76 (dd, *J* = 17.8, 5.2 Hz, 1 H), 2.57 (dd, *J* = 15.7, 8.1 Hz, 1 H), 1.97 (s, 3 H), 1.36–1.53 (m, 13 H), 0.87 (t, *J* = 6.4 Hz, 6 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.66, 155.91, 129.25, 121.57, 81.89, 79.71, 76.37, 52.74, 49.52, 40.41, 28.30, 26.15, 25.87, 23.35, 9.61, 9.43. HRMS (ESI): *m*/*z* [M + H] calcd for $C_{18}H_{31}BrN_2O_4$: 419.1545; found: 419.1550.

