Efficient Asymmetric Synthesis of Oseltamivir from D-Mannitol

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Received 11 December 2008

This paper is dedicated to Professor Jiro Tsuji.

Abstract: A highly practical asymmetric synthesis of oseltamivir has been accomplished in 18 steps from D-mannitol without any chromatographic purification, which features intramolecular aldol condensation of dialdehyde with a 3-pentyl ether moiety in constructing densely functionalized cyclohexene ring of oseltamivir.

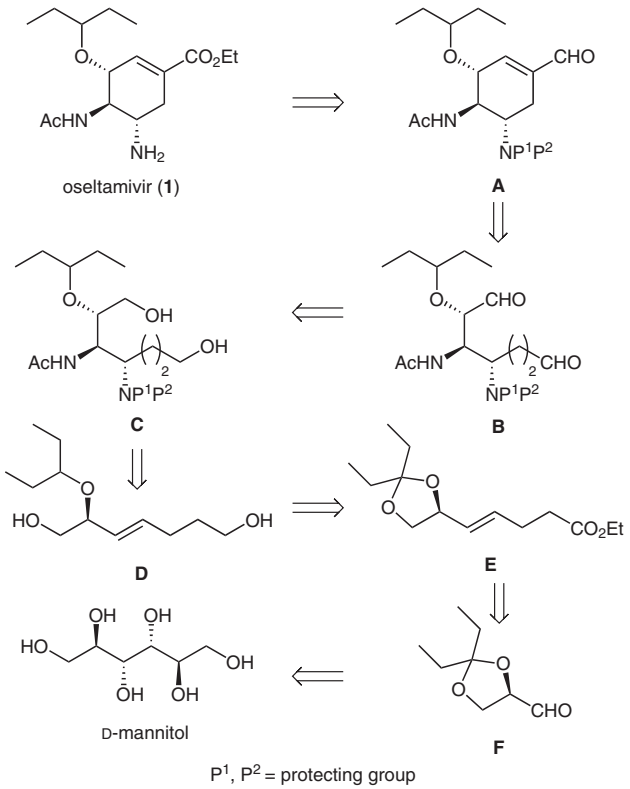
Key words: anti-influenza drugs, Tamiflu, chiral pool, dihydroxylations, intramolecular aldol condensation

The growing epidemics of the avian flu virus H5N1 in Southeast Asia often evoke the pandemic life-threatening influenza caused by the mutated forms thereof. Oseltamivir phosphate (**1**·H_3PO_4, Tamiflu™),[2] the potent anti-influenza neuraminidase inhibitor developed by Gilead Sciences, has been utilized clinically to avert a widespread influenza. However, the current commercial production of **1** depends upon a semisynthesis, starting from less available shikimic acid.[3] To circumvent such a supply problem, it would be crucial to develop new routes to **1** relying upon widely available commodity chemicals. Several research groups have contributed to develop the efficient synthetic methods for **1** starting from easily available chemicals[4,5] through their own original protocols, which prompted us to develop a new access to **1**.

As shown by our retrosynthetic analysis (Scheme 1), we envisioned to construct the densely functionalized cyclohexene framework **A** by an intramolecular aldol condensation of dialdehyde **B** with a 3-pentyl ether moiety, an unprecedented intermediate among the hitherto reported syntheses of **1**.[4]

Compound **B** could be obtained by the oxidation of diol **C** with differently protected vicinal amino groups. Toward the efficient preparation for **C**, we envisaged to deliver two amino groups on alkenediol **D** through highly diastereoselective dihydroxylation and ensuing diazide formation. We envisioned that 3-pentyl ether moiety in **D** could be installed by a cyclic acetal cleavage of ester **E** which could be derived from the well-known aldehyde **F**.

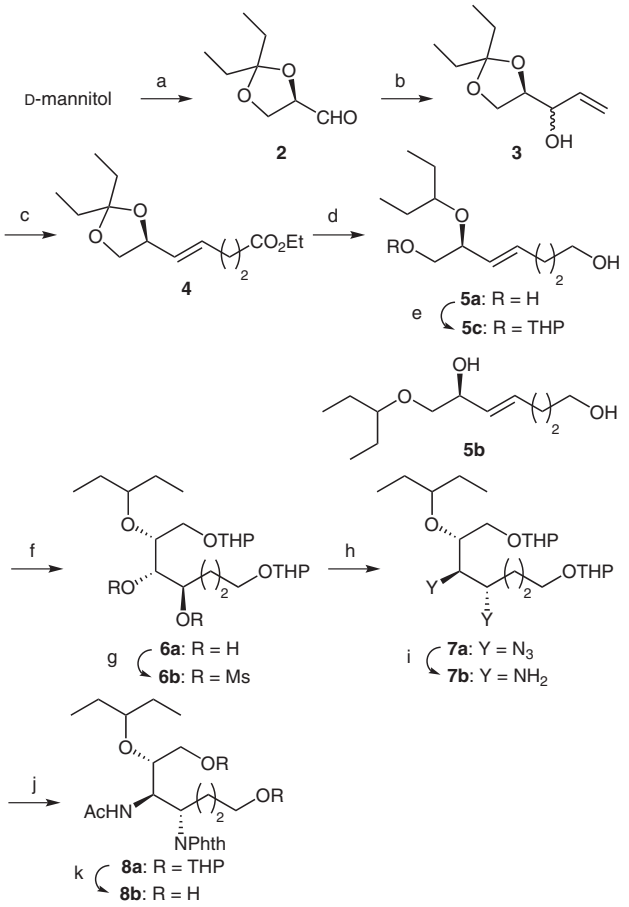
First, we embarked on the preparation of diol **8b** (Scheme 2). Aldehyde **2**,[6] easily prepared from D-mannitol, was transformed into allylic alcohol **3**[7] in 88% yield by treatment with vinylmagnesium bromide. Upon treatment with triethyl orthoacetate in the presence of a catalytic amount of propionic acid (132 °C, 14 h), **3** underwent facile orthoester Claisen rearrangement[8] smoothly to give ester **4**[9] in 95% yield after distillation. Gratifyingly, subsequent tandem acetal cleavage[10] and ester reduction of **4** were effected successfully with DIBAL-H (5 mol equiv) to afford diol **5a** and its regioisomer **5b** as a 10:1 inseparable mixture in favor of **5a**.



Scheme 1 Retrosynthetic analysis of **1**

It is particularly worth noting that the 3-pentyl ether moiety could be installed by this reduction in a highly regioselective manner without use of a strong Lewis acid.[2c] Protection of the crude diols **5a** and **5b** with 3,4-dihydro-2*H*-pyran (DHP) provided di-THP ether **5c**,[11] which, without further purification, was followed by asymmetric dihydroxylation[12] with AD-mix-β to furnish diol **6a** as a sole product.[13] The crude diol **6a** was converted into dimesylate **6b** (MsCl, pyridine) and subsequent azide formation (NaN_3, DMSO) delivered diazide **7a**, which produced diamine **7b** through hydride reduction[14] ($LiAlH_4$, THF). To our delight, highly regioselective protection of the vicinal amino groups of **7b** was realized with much

SYNLETT 2009, No. 5, pp 0783–0786
Advanced online publication: 26.02.2009
DOI: 10.1055/s-0028-1087941; Art ID: U12408ST

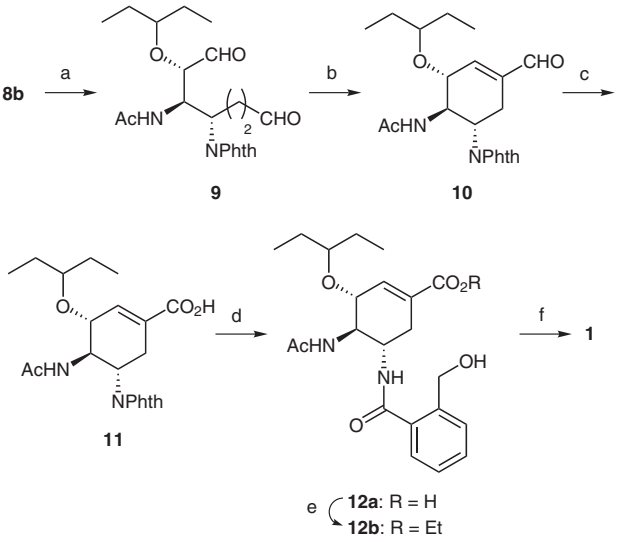


Scheme 2 *Reagents and conditions*: (a) ref. 6, 61%; (b) vinylmagnesium bromide (1.2 equiv), THF, 0 °C, 1 h, 88%; (c) $MeC(OEt)_3$ (5.0 equiv), 2% $EtCO_2H$, 132 °C, 14 h, 95%; (d) DIBAL-H (5.0 equiv), toluene, 0 °C, 2 h, r.t., 3 h; (e) DHP (1.2 equiv), PPTS (2 mol%), CH_2Cl_2, r.t., 24 h; (f) $MsNH_2$ (1.0 equiv), AD-mix-β (1.4 g/mmol), *t*-BuOH–H_2O, 0 °C, 8 h, r.t., 13 h; (g) MsCl (1.2 equiv), pyridine, 0 °C, 2 h, r.t., 8 h; (h) NaN_3 (4 mol equiv), DMSO, 80 °C, 48 h; (i) $LiAlH_4$ (1.1 equiv), THF, r.t., overnight; (j) Et_3N, DMAP, $PhthNCO_2Et$ (0.9 equiv each), THF, 0 °C, 1.5 h, then Ac_2O–pyridine (2.0 equiv each), r.t., 14 h; (k) MeOH, CSA (10 mol%), r.t., 1 h, then recrystallization from toluene, 32% from **4**.

success by the following one-pot procedure. That is, a solution of crude **7b** in THF was reacted with *N*-ethoxycarbonylphthalimide ($PhthNCO_2Et$)[15] in the presence of Et_3N and DMAP.

After the monoprotection of the less hindered amino group had been completed (monitored by TLC), the reaction mixture was treated with Ac_2O–pyridine to provide differently protected diamine **8a**. After usual workup, deprotection of THP groups (MeOH, cat. CSA) furnished a crude diol **8b** as a viscous oil. Fortunately, the pure diol **8b**[16] precipitated from toluene (32% overall yield from **4**).

The latter stage of the synthesis is shown in Scheme 3. Oxidation of diol **8b** delivered dialdehyde **9**[17] quantitatively with a combination of TEMPO, KBr, and NaOCl.[18] It should be noted that **9** was found to be free of a possible eight-membered lactone and byproducts caused by epimerization or elimination. Next, an intramolecular aldol condensation of **9** was successfully accomplished by heating with Bn_2NH·TFA[19] in toluene to provide cyclohexenal **10**[20] as a white solid. Delightedly, the present reaction also proceeded cleanly without formation of any byproducts arising from elimination or aromatization. Then, $NaClO_2$-mediated oxidation[4c,21] of **10** provided carboxylic acid **11**[22] in 86% yield. The transformation of **11** into **1** through esterification followed by deprotection required little ingenuity for a noncolumn chromatographic process. For the solution, **11** was reduced with $NaBH_4$ in wet *i*-PrOH[23] to amide **12a**[24] in 93% yield, which was esterified with a combination of EtI and K_2CO_3 as a base in DMSO, affording ethyl ester **12b**[25] in 85% yield. Finally, **12b** was treated with HCl–EtOH at room temperature for 24 hours followed by back extraction with 5% aqueous Na_2CO_3, giving oseltamivir (**1**)[26] in 83% yield.



Scheme 3 *Reagents and conditions*: (a) TEMPO (10 mol%), KBr (20 mol%), aq NaOCl, $NaHCO_3$ (2.4 mol equiv each), CH_2Cl_2–H_2O (2:1), 5 °C, 15 min; (b) Bn_2NH·TFA (1.1 equiv), toluene, 50 °C, 11 h, 82% for 2 steps; (c) $NaClO_2$–NaH_2PO_4 (3.0 equiv each), 2-methylbut-2-ene (10 equiv), *t*-BuOH–THF–H_2O (4:1:1), 0 °C, 1 h, r.t., overnight, 86%; (d) $NaBH_4$ (5.0 mol equiv), *i*-PrOH–H_2O (6:1), r.t., overnight, 93%; (e) K_2CO_3 (1.1 equiv), EtOH–H_2O (5:1), r.t., 0.5 h; removal of the solvent; then EtI (5.0 equiv), DMSO, r.t., 40 h, 85%; (f) 4 M HCl in 1,4-dioxane (5.0 equiv), EtOH, r.t., 24 h, then back extraction with 5% aq Na_2CO_3, 83%.

In summary, we have succeeded in developing a new method for the synthesis of oseltamivir (**1**) from D-mannitol in 18 steps, which involves intramolecular aldol condensation of dialdehyde as the key reaction to construct cyclohexene ring. Furthermore, it would be of high synthetic value for the reason that no column chromatographic purification is required throughout the whole process. We believe this synthetic protocol would contribute to solve supply problem of **1**.

Acknowledgment

This work was supported financially in part by the Institute of Nippon Chemiphar Co., Ltd.

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(7) The optical purity of **3** was determined as follows. The HPLC analysis [Chiralcel OD; λ = 254 nm; eluent: hexane–EtOH (9:1); flow rate: 1.3 mL/min] of 3,5-dinitrobenzoate of **3** showed the two peaks based on their two diastereomers at t_R = 11.4 min and 22.3 min, respectively. On the other hand, those of racemic **3**, prepared from glycerol via acetalization, Swern oxidation, and Grignard reaction, showed four peaks at t_R = 11.4 min, 14.5 min, 18.7 min, and 22.2 min, respectively. This observation surely indicates that **2** and **3** are formed without racemization throughout the sequential reactions.

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(9) Compound **4**: colorless oil; $[\alpha]_D^{21.6}$ +24.0 (*c* 1.23, $CHCl_3$); bp 110–112 °C/6.66·10^{-4} bar. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80 (dt, *J* = 15.3, 6.4 Hz, 1 H), 5.48 (dd, *J* = 15.3, 7.9 Hz, 1 H), 4.45 (ddd, *J* = 8.25, 7.95, 6.1 Hz, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 4.10 (dd, *J* = 7.95, 6.1 Hz, 1 H), 3.51 (dd, *J* = 8.25, 7.95 Hz, 1 H), 2.43–2.36 (m, 4 H), 1.68–1.60 (m, 4 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 0.95–0.88 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7, 133.3, 128.5, 113.0, 77.3, 69.9, 60.3, 33.5, 29.9, 29.8, 27.4, 14.2, 8.1, 8.0. HRMS (EI$^+$): *m/z* calcd for $C_{14}H_{24}O_4$: 256.1675; found: 256.1655.

(10) A solution of ester **4** in toluene was added dropwise to a solution of DIBAL-H in toluene. As the relevant papers, see: (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

(11) First we prepared a corresponding dibenzyl ether of **5a**, which proved to be cleaved in a later azide-formation step affording a complex mixture.

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(13) The attempted dihydroxylations with OsO_4/NMO and with AD-mix-α provided a 1:1 to 1:2 mixture of diastereomers with respect to the 3-pentyloxy group.

(14) Hydrogenolysis (10% Pd/C, EtOAc, r.t., 48 h) of **7a** also provided **7b** with poor reproducibility probably owing to poisoning by the accumulated contaminations.

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(16) Compound **8b**: $[\alpha]_D^{21.5}$ –19.2 (*c* 1.07, $CHCl_3$); mp 142.1–143.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.70 (m, 4 H), 6.77 (d, *J* = 9.8 Hz, 1 H), 4.77–4.72 (m, 1 H), 4.60–4.54 (m, 1 H), 3.80–3.60 (m, 5 H), 3.25–3.14 (m, 2 H), 2.28–2.18 (m, 1 H), 1.98 (s, 3 H), 1.95–1.86 (m, 1 H), 1.75 (br s, 1 H), 1.55–1.30 (m, 5 H), 1.11–0.98 (m, 2 H), 0.78–0.72 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 169.2, 134.2, 131.6, 123.3, 79.2, 75.3, 61.8, 60.4, 52.5, 51.1, 29.2, 26.1, 25.5, 25.3, 22.9, 9.39, 9.37. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84, H, 7.67, N, 6.66. Found: C, 62.70, H, 7.85, N, 6.65.

(17) Dialdehyde **9** was pure enough to be used for the next step. However, it was labile to purification on silica gel column chromatography for combustion analysis, affording a complex mixture involving cyclized products.

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(20) Compound **10**: obtained as an off-white solid by washing with hot toluene; $[\alpha]_D^{22.5}$ –46.5 (*c* 1.10, $CHCl_3$); mp 202.3–202.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$, data of a mixture of rotamers): δ = 9.55 (s, 0.13 H), 9.53 (s, 0.87 H), 7.86–7.72 (m, 4 H), 6.70 (s, 0.13 H), 6.67 (s, 0.87 H), 5.53 (d, *J* = 7.6 Hz, 0.87 H), 5.26 (d, *J* = 7.6 Hz, 0.13 H), 4.95–4.90 (m, 0.87 H), 4.75–4.71 (m, 0.87 H), 4.45–4.38 (m, 1.13 H), 4.20–4.18 (m, 0.13 H), 3.46–3.37 (m, 1 H), 3.05–2.98 (m, 1 H), 2.75–2.65 (m, 1 H), 2.05 (s, 0.4 H), 1.78 (s, 2.6 H), 1.60–1.50 (m, 4 H), 1.00–0.85 (m, 6 H). ^{13}C NMR (125 Hz, $CDCl_3$, data of a mixture of rotamers): δ = 192.3, 170.3, 168.1, 147.6, 138.8, 134.2, 131.6, 128.5, 123.5, 82.5, 74.6, 54.3, 47.8, 26.3, 25.7, 25.5, 23.3, 9.7, 9.4. Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.15; H, 6.72; N, 7.05. HRMS (FAB$^+$): *m/z* calcd for $C_{22}H_{27}N_2O_5$ [MH$^+$]: 399.1920; found: 399.1925.

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(22) Evaporation of the volatiles and addition of a large excess of H_2O to the residue provided an off-white solid, which was collected by filtration and washed successively with H_2O and MeO*t*-Bu.
Compound **11**: obtained as a white solid (mp >280 °C) with poor solubility in organic solvents such as MeOH or $CHCl_3$: $[\alpha]_D^{25}$ –58.4 (*c* 0.54, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.6 (br s, 1 H), 7.92–7.80 (m, 4 H), 6.69 (s, 1 H), 4.38–4.20 (m, 3 H), 3.42–3.10 (m, 2 H), 2.63–2.50 (m, 1 H), 1.50–1.32 (m, 4 H), 0.86 (t, *J* = 7.3 Hz, 3 H), 0.75 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (125 Hz, DMSO-d_6): δ = 169.1, 167.6, 167.0, 137.5, 134.3, 129.0, 123.0, 81.0, 74.7, 51.5, 48.9, 26.6, 25.8, 25.1, 22.4, 9.5, 8.9. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.45; N, 6.71.

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(24) Crude **12a** deposited efficiently on dilution of the reaction mixture with a large excess of diluted HCl. Filtration and washing with water provided pure **12a** as a white solid: $[\alpha]_D^{22.8}$ –79.2 (*c* 1.07, $CHCl_3$–MeOH = 4:1); mp 180.4–180.8 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.43–7.23 (m, 4 H), 6.73 (br s, 1 H), 4.75–4.50 (m, 2 H), 4.25–3.80 (m, 3 H), 3.37–3.33 (m, 1 H), 2.73–2.65 (m, 1 H), 2.33–2.27 (m, 1 H), 1.50–1.35 (m, 4 H), 0.86–0.77 (m, 6 H). ^{13}C NMR (125 Hz, CD_3OD): δ = 173.9, 172.0, 169.4, 140.9, 139.1, 136.3, 131.7, 130.7, 129.8, 128.7, 128.6, 83.8, 77.3, 63.5, 55.9, 31.5, 27.3, 26.8, 23.0, 9.9, 9.6. Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.89; H, 7.37; N, 6.73.

(25) Dilution of the reaction mixture with a large excess of water deposited a white solid, which was washed successively with H_2O and MeO*t*-Bu to give unmingled **12b** as a white solid: $[\alpha]_D^{23.0}$ –48.0 (*c* 1.11, $CHCl_3$); mp 209.3–210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 4 H), 6.73 (br s, 1 H), 4.75–4.50 (m, 2 H), 4.25–3.80 (m, 3 H), 3.37–3.33 (m, 1 H), 2.73–2.65 (m, 1 H), 2.33–2.27 (m, 1 H), 1.50–1.35 (m, 4 H), 0.86–0.77 (m, 6 H). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 171.5, 169.9, 165.9, 139.8, 137.8, 135.1, 131.2, 130.7, 129.1, 128.1, 127.9, 82.2, 75.7, 64.4, 60.9, 54.3, 48.7, 30.5, 26.2, 25.6, 22.8, 14.1, 9.6, 9.2. Anal. Calcd for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.25; H, 8.03; N, 6.21.

(26) Oseltamivir (**1**), obtained as a white semi-solid: $[\alpha]_D^{25.0}$ –55.8 (*c* 2.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (br s, 1 H), 5.48 (d, *J* = 7.6 Hz, 1 H), 4.25–4.18 (m, 3 H), 3.55–3.48 (m, 1 H), 3.38–3.32 (m, 1 H), 3.27–3.20 (m, 1 H), 2.75 (dd, *J* = 17.9, 5.2 Hz, 1 H), 2.19–2.11 (m, 1 H), 2.04 (s, 3 H), 1.60–1.47 (m, 6 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.95–0.88 (m, 6 H). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 170.9, 166.3, 137.5, 129.5, 81.6, 74.8, 60.8, 58.9, 49.2, 33.6, 26.2, 25.7, 23.6, 14.2, 9.5, 9.3. ^{1}H NMR and ^{13}C NMR spectra and optical rotation value were in full accordance with those of the authentic sample obtained through a basic extraction (sat. aq $NaHCO_3$–5% aq Na_2CO_3–$CHCl_3$) from commercial Tamiflu: $[\alpha]_D^{23.0}$ –56.1 (*c* 1.24, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (br s, 1 H), 5.79 (d, *J* = 7.95 Hz, 1 H), 4.26–4.17 (m, 3 H), 3.57–3.49 (m, 1 H), 3.38–3.32 (m, 1 H), 3.26–3.18 (m, 1 H), 2.75 (dd, *J* = 17.9, 4.9 Hz, 1 H), 2.18–2.10 (m, 1 H), 2.04 (s, 3 H), 1.66–1.60 (m, 2 H), 1.56–1.47 (m, 4 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 0.95–0.87 (m, 6 H). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 170.9, 166.3, 137.5, 129.5, 81.6, 74.8, 60.8, 59.0, 49.2, 33.6, 26.2, 25.7, 23.6, 14.2, 9.5, 9.3.