A concise route to (−)-shikimic acid and (−)-5-*epi*-shikimic acid, and their enantiomers via Barbier reaction and ring-closing metathesis

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ABSTRACT

A simple route for the synthesis of naturally occurring (−)-shikimic acid, (−)-5-*epi*-shikimic acid, and their enantiomers from D-ribose-derived enantiomeric aldehydes **8a** and **8b** by employing Barbier reaction and ring-closing metathesis as key steps has been developed.

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Shikimic acid[1] plays a pivotal role as a key intermediate in the shikimate pathway toward the synthesis of several aromatic amino acids and a variety of secondary metabolites in plants, fungi, and microorganisms.[2] The absence of this pathway in animals, which obtain the required aromatic amino acids through diet, makes the enzymes of this pathway ideal targets for the development of new antimicrobial agents and nontoxic herbicides. For example, glyphosate, besides its wide use as a commercial herbicide,[3] is an effective antiparasitic drug, which inhibits 5-enolpyruvyl shikimate 3-phosphate (EPSP) synthase,[4] the sixth enzyme of this pathway. It is also reported to inhibit the in vitro growth of *Toxoplasma gondii*, *Plasmodium falciparum* (malaria), and *Cryptosporidium parvum*.[5] Besides its bio-significance, shikimic acid, which is a highly functionalized carbocycle, is also an industrially useful[6] chiral compound. More recently, it has emerged as an indispensable starting material for the synthesis of Tamiflu **1** (Fig. 1).[7,8] As a result, development of efficient syntheses for shikimic acid and its analogues has been an active area of research with a view to develop selective enzyme inhibitors[9] which are of relevance as potential antifungal and antibacterial agents.

In addition, epimers of shikimic acid[10] also have attracted great attention as they form the constituents of several natural products and compounds of biological importance. Among the three possible epimers, 5-*epi*-shikimic acid skeleton has its own identity of being a part of antitumor class of natural products pericosines **2** and **3**, (the absolute structure of **2** (pericosine A) has been determined only recently)[11] and also of the glyoxalase inhibitor COTC[12]

4, which was reported to exhibit cytotoxic and cancerostatic activity with low toxicity. Despite its prospective significance, only a limited number of synthetic routes are available for (+)- and (−)-5-*epi*-shikimic acid.

By virtue of its importance, it has been the subject of a few reviews[13] and a number of racemic and chiral syntheses for natural and unnatural shikimic acids are reported in the literature.[13b,14] Synthetic approaches using (i) Diels–Alder reaction, (ii) benzene and its derivatives, (iii) quinic acid, and (iv) carbohydrates as starting materials have been developed.[15,16] Similarly, a few reports are available for the synthesis of both the enantiomers of 5-*epi*-shikimic acid, the notable among which is the synthesis of (−)-methyl 3,4-*O*-isopropylidene-5-*epi*-shikimate, a key intermediate in their synthetic approach to avermectins and milbemycins, with an overall yield of 51%, from (−)-quinic acid.[18,19]

In this context, the realization of different stereoisomers of shikimic acid as chirons for a wide range of target molecules emphasizes the growing stipulation to develop short synthetic routes toward these analogues. In continuation of our interest in the synthesis of carbasugars[20] coupled with the aspiration of exploring the synthetic utility of ring-closing metathesis toward biologically important molecules,[21] herein we report a concise diastereoselective synthesis of four stereoisomers **6a–d** (Fig. 2) of shikimic acid. Our strategy which emanates from the aldehyde **8a** as delineated in the retrosynthetic analysis (Scheme 1) via Barbier reaction with bromomethyl acrylate, followed by ring-closing metathesis, provides a rapid entry into the functionalized cylcohexenes (Scheme 2).

The aldehyde **8a**,[17] derived from D-ribose (Scheme 1), was reacted with ethyl bromomethacrylate under Barbier reaction conditions using zinc to give compound **10** as an inseparable mixture of
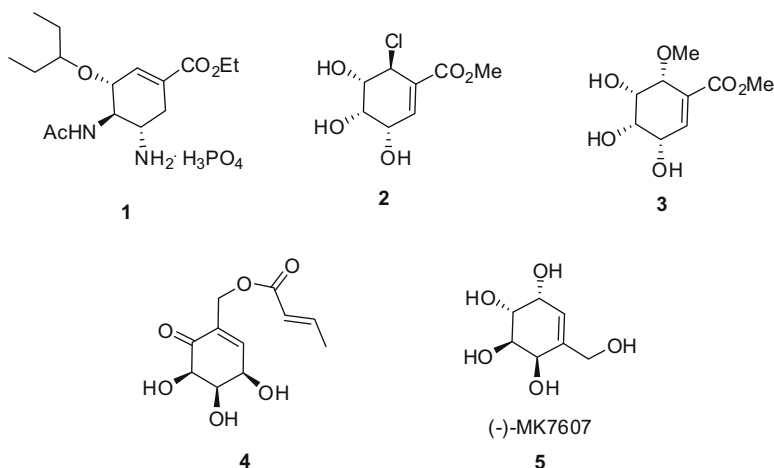
Figure 1. Structures of some biologically important functionalized cyclohexenes.
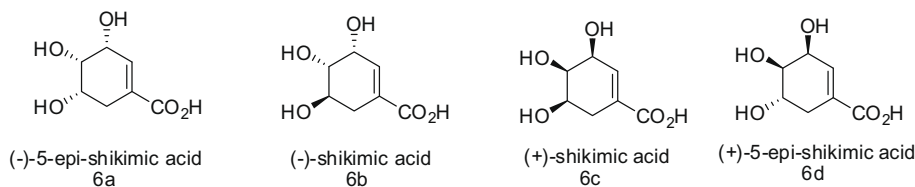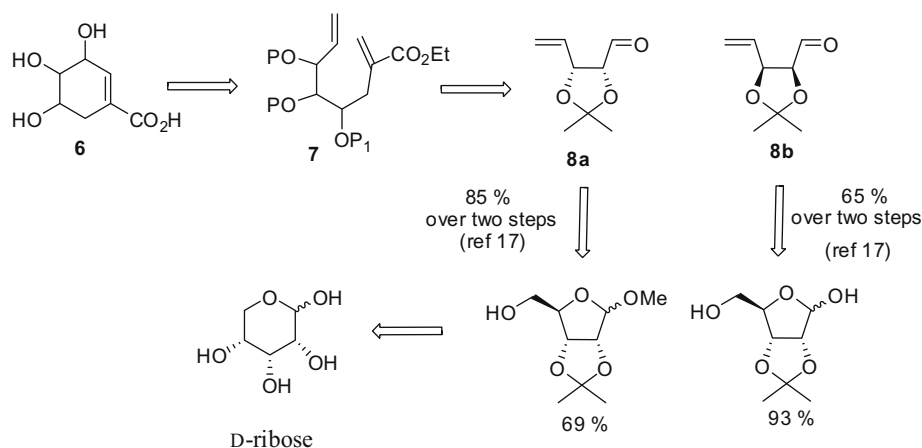

Figure 2. Structures of four stereosiomers of shikimic acid synthesized.

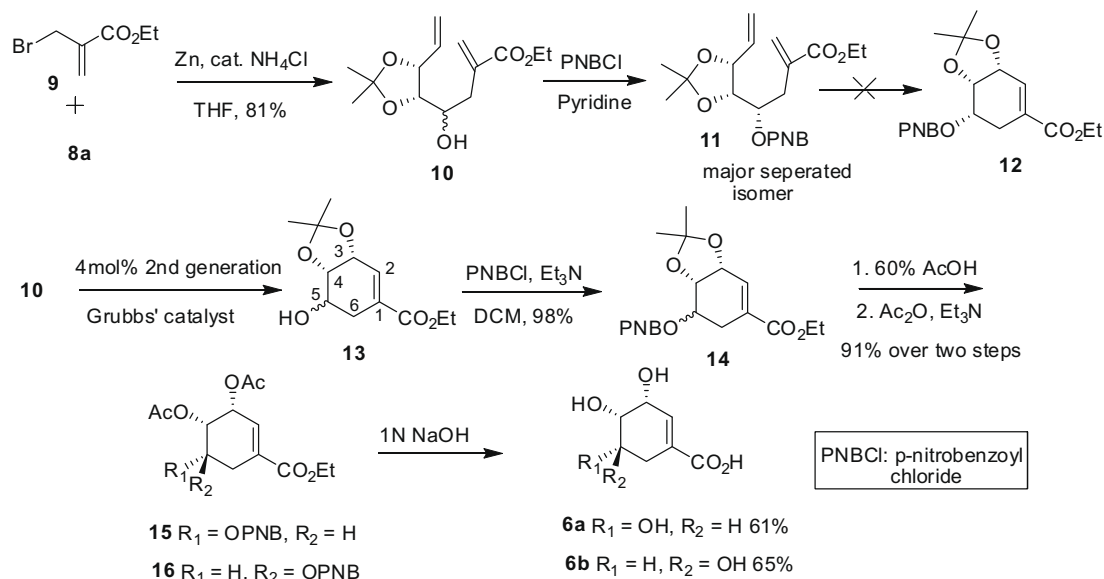**Scheme 1.** Retrosynthesis of Shikimic acid.

two diastereomers in 2:1 ratio. The presence of five olefinic protons for both the diastereomers in the ^{1}H NMR spectrum (δ 6.28–5.27), in addition to other data, confirms the formation of the product. The free hydroxyl group was converted to *p*-nitrobenzoate ester by treating with *p*-nitrobenzoyl chloride and pyridine where the two diastereomers were successfully separated through column chromatography. Various attempts to cyclize the major diastereomer **11** using 1st and 2nd generation Grubbs' catalysts resulted in failure. We, therefore, attempted to cyclize the unprotected diene **10** using 1st generation Grubbs' catalyst, which also met with failure even in refluxing toluene. However, ring-closing metathesis of **10**[22] proceeded smoothly in the presence of 4 mol % of Grubbs' 2nd generation catalyst to yield the shikimic acid skeleton **13** in 80% yield albeit again as an inseparable diastereomeric mixture. The disappearance of the multiplet due to five olefinic protons in the region δ 6.28–5.27 and the appearance of

two new sets of signals at δ 6.93 and δ 6.80 in its ^{1}H NMR spectrum, one for each diastereomer, confirmed that the cyclization had occurred. The appearance of each of the olefinic protons of the endocyclic double bond of each isomer as a multiplet indicates strong allylic coupling with C-6 protons. The diastereomeric mixture was then subjected to esterification with *p*-nitrobenzoyl chloride and triethylamine to obtain the *p*-nitrobenzoate ester in quantitative yield. Cleavage of the acetonide group using 60% acetic acid followed by acetylation provided chromatographically separable mixture of diastereomers **15** and **16**.

The chemical shifts of various protons in the ^{1}H NMR spectra of **15** and **16** were assigned using the COSY spectral data. The stereochemistry of the newly generated stereocenter in both the separated shikimate derivatives was deduced using the NOE spectral analysis (Fig. 3). Thus, in an NOE experiment, irradiation of the signal for H-5 in the major isomer **15** led to the enhancement of H-4
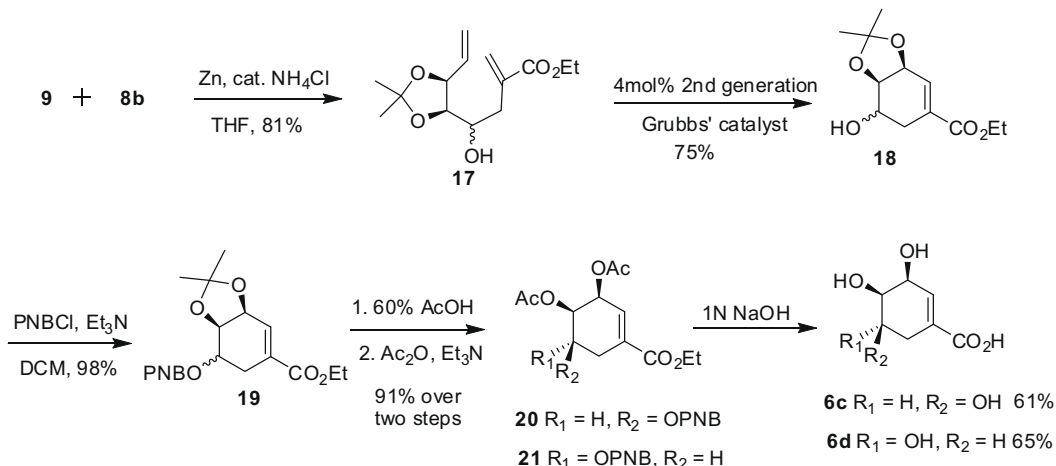
Scheme 2. Synthesis of (−)-5-*epi*-shikimic acid **6a** and (−)-shikimic acid **6b**.
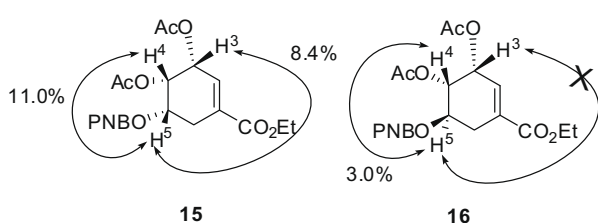
Figure 3. Diagnostic NOE correlations for the compounds **15** and **16**.

(11%) and H-3 signals (8.4%) indicating that H-5 is cis to H-3 and correspondingly revealing the cis relation between the OPNB group and both the acetoxy groups and thus concluding the major isomer to be the 5-*epi*-shikimate derivative. However, irradiation of the signal for H-5 in the minor isomer **16** also led to a small enhancement[23] (3%) of the signal for H-4 and no enhancement in the signal for H-3. It is clear that the conformations of molecules **15** and **16** are either half chair or slightly distorted[23b] which allows H-5 and H-4 to come closer and exhibit small NOE in compound **16**. How-

ever, the absolute configurations at C-5 in both **15** and **16** are as shown in Figure 3 which was further confirmed by converting them into known (−)-5-*epi*-shikimic acid **6a** and (−)-shikimic acid **6b** (vide infra), respectively. The global deprotection of both the shikimate derivatives was carried out in one pot, by treating with 1 N NaOH solution and the products were obtained in their pure forms[24–26] after passing through a short plug of silica gel. Thus, (−)-5-*epi*-shikimic acid was obtained in 19% overall yield whereas the naturally occurring (−)-shikimic acid was obtained with an overall yield of 9% starting from the aldehyde **8a**.

Similarly, (+)-5-*epi*-shikimic acid **6c** and (+)-shikimic acid **6d** were also synthesized (Scheme 3) following the same synthetic sequence starting from the D-ribose-derived aldehyde **8b**. All the spectral data[24,26] of the intermediates as well as the final compounds, except the rotation being opposite, were in absolute match with their enantiomers.

In summary, we have developed a concise route for the synthesis of (−)-5-*epi*-shikimic acid, (+)-5-*epi*-shikimic acid, and (+)-shikimic acid along with the naturally occurring (−)-shikimic acid via Barbier reaction followed by ring-closing metathesis as key steps. This approach toward the synthesis of functionalized cyclo-

Scheme 3. Synthesis of (+)-5-*epi*-shikimic acid **6c** and (+)-shikimic acid **6d**.

hexenes, especially to derive different stereoisomers of shikimic acid, is exemplary and might also be applicable to several other pseudosugars and biologically important molecules.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.111.

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25. Experimental data of selected compounds.*Ethyl 4-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-4-hydroxy-2-ethylenebutanoate* (**10**): To a cold (10 °C) and well stirred mixture of **8a** (500 g, 3.20 mmol), Zn dust (403 mg, 6.39 mmol) and bromoester **9** (611 mg, 3.19 mmol) in 10 mL of THF was added a saturated solution of NH$_4$Cl (1 mL). The mixture was stirred for 4 h at ambient temperature until the aldehyde was totally consumed (monitored by TLC).

The mixture was filtered and the precipitate was thoroughly washed with CHCl$_3$ (4 × 3 mL). The aqueous layer was separated and treated with 5% HCl to dissolve the suspended turbid material. The clear solution was extracted with CHCl$_3$ (3 × 25 mL). The combined organic layer was washed successively with 10% NaHCO$_3$, water, and finally with brine solution. After removal of the solvent under reduced pressure a residue was obtained, which was purified by column chromatography to give compound **10** (709 mg, 81%) as a mixture of two diastereomers (1:2). Yellow oil, $R_f = 0.65$ (4:1 hexanes:EtOAc); IR (thin film) 3470, 3084, 2985, 2934, 1714, 1629, 1431, 1214, 1057 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.28 (d, $J = 1.1$ Hz, 1H, major), 6.27 (d, $J = 1.1$ Hz, 1H, minor), 6.07–6.0 (m, 1H, both isomers), 5.73 (s, 1H, major), 5.69 (d, $J = 1.1$ Hz, 1H, minor), 5.43 (dd, $J = 5.1$ Hz, $J = 17.1$ Hz, 1H, major), 5.30–5.39 (m, 2H, both isomers), 5.27 (d, $J = 10.9$ Hz, 1H, major), 4.68 (t, $J = 6.8$ Hz, 1H, major), 4.61 (t, $J = 7.4$ Hz, 1H, minor), 4.19–4.25 (m, 2H, major), 4.05 (dd, $J = 4.6$ Hz, $J = 6.8$ Hz, 1H, minor), 4.05 (dd, $J = 6.3$ Hz, $J = 8.6$ Hz, 1H, major), 3.79–3.75 (m, 1H, both isomers), 2.92 (d, $J = 4.0$ Hz, 1H), 2.84 (dd, $J = 2.3$ Hz, $J = 14.3$ Hz, 1H), 2.55–2.44 (m, 2H, both isomers), 1.53 (s, 3H, minor), 1.50 (s, 3H, major), 1.39 (s, 3H, minor), 1.37 (s, 3H, major), 1.33–1.29 (3H, both isomers); ^{13}C NMR (125 MHz, CDCl$_3$) δ (major): 168.6, 137.1, 134.3, 128.4, 117.9, 108.7, 80.2, 78.8, 68.4, 61.3, 36.8, 27.8, 25.5, 14.2. (minor): 167.3, 136.9, 134.3, 127.8, 119.7, 79.2, 68.4, 60.9, 37.1, 27.3, 25.0, 14.2. Calculated for C$_{19}$H$_{25}$NO$_6$Na [M+Na]+: 293.1365, found 293.1361.

(3aR,7aS)-Ethyl 7-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxole-5-carboxylate (**13**): To a stirred solution of compound **10** (300 mg, 0.9 mmol) in dry CH$_2$Cl$_2$ (5 mL) at room temperature was added Grubbs' 2nd generation catalyst (4 mol %, 30.5 mg). The mixture was refluxed for 5 h and after completion of the reaction, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to give compound **13** (193 mg, 72% yield) as a viscous colorless liquid. $R_f = 0.22$ (4:1 hexanes:EtOAc); IR (thin film) 3426, 2985, 2933, 1714, 1651, 1446, 1373, 1296, 1238, 1095, 1058 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.93 (m, 1H, minor), 6.79 (m, 1H, major), 4.72–4.76 (m, 1H, both isomers), 4.41 (dd, $J = 2.8$ Hz, $J = 5.7$ Hz, major), 4.24–4.20 (m, 2H, both isomers), 4.08 (dd, $J = 6.2$ Hz, $J = 7.1$ Hz 1H, minor), 3.98–3.93 (m, 1H, major), 3.89–3.88 (m, 1H, minor), 2.81 (dd, $J = 4.5$ Hz, $J = 17.1$ Hz 1H, minor), 2.70 (dd, $J = 5.1$ Hz, $J = 16.6$ Hz 1H, major), 2.53–2.48 (m, 1H, minor), 4.19–4.25 (m, 2H, major), 4.05 (dd, $J = 6.8$ Hz, 1H minor), 4.05 (dd, $J = 6.3$ Hz, $J = 8.6$ Hz, 1H major), 3.79–3.75 (m, 1H, both isomers), 2.92 (d, $J = 4.0$ Hz, 1H), 2.84 (dd, $J = 2.3$ Hz, $J = 14.3$ Hz, 1H), 2.53–2.48 (m, 1H, major), 2.17–2.20 (m, 1H, minor), 1.46 (s, 3H minor), 1.42 (s, 3H, major), 1.41 (s, 3H, major), 1.40 (3H, minor), 1.32–1.30 (m, 3H, both isomers); ^{13}C NMR (125 MHz, CDCl3) δ (major): 166.3, 134.5, 129.5, 110.0, 75.4, 72.9, 66.9, 61.1, 27.8, 27.4, 26.0, 14.2. (minor): 166.1, 133.5, 131.2, 109.8, 78.2, 72.3, 69.1, 61.1, 29.5, 28.1, 25.8, 14.2. Calculated for C$_{19}$H$_{25}$NO$_6$Na [M+Na]$^+$: 265.1052, found 265.1056.
Procedure for the deprotection of acetonide **14**.
Compound **14** (250 mg, 0.63 mmol) was dissolved in 1.5 mL of 60% acetic acid and refluxed for 10 h at 60 °C. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate (4 × 25 mL). The organic layer was dried over Na$_2$SO$_4$ and the filtrate was concentrated under vacuum to obtain the corresponding diol, which was subjected to acetylation with excess of triethylamine, Ac$_2$O (1:1, 1 mL) and a catalytic amount of DMAP at room temperature for 6 h. Removal of solvent under reduced pressure gave a residue which was purified by column chromatography (hexane/EtOAc 9:1) to obtain the mixture of diastereomers as light yellow oil. (**15/16**; 68:32 ratio) (253 mg, 91%).
(1S,2R,6S)-4-(Ethoxycarbonyl)-6-(4-nitrobenzoyloxy)-cyclohex-3-ene-1,2-diyl diacetate (**15**): Yellow oil, $\alpha_D^{24} = -100.0$ (c 1.10, CH$_2$Cl$_2$). $R_f = 0.37$ (9:1 hexanes:EtOAc); IR (thin film) 3112, 3055, 2924, 2853, 1749, 1729, 1659, 1234, 1146, 1079 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.29 (d, $J = 8.4$ Hz, 2H, Ph), 8.16 (d, $J = 8.4$ Hz, 2H, Ph), 6.83–6.82 (m, 1H, H2), 5.80 (t, $J = 4.2$ Hz, 1H, H3), 5.57–5.53 (m, 1H, H5), 5.43 (dd, $J = 3.8$ Hz, $J = 8.0$ Hz 1H, H4), 4.22 (q, $J = 7.2$ Hz, 2H, H2'), 3.13 (dd, $J = 5.7$ Hz, $J = 8.3$ Hz, 1H, H6), 2.54 (dd, $J = 6.4$ Hz, $J = 8.7$ Hz, 1H, H6), 2.10 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.30 (t, $J = 7.2$ Hz, 3H, H3'); ^{13}C NMR (125 MHz, CDCl3) δ 169.9, 165.2, 163.6, 150.7, 134.7, 132.0, 131.7, 120.8, 123.6, 68.5, 68.1, 65.8, 61.4, 29.0, 20.7, 20.6, 14.1. Calculated for C$_{19}$H$_{25}$NO$_6$Na [M+Na]$^+$: 458.1063, found 458.1061.
(1S,2R,6R)-4-(Ethoxycarbonyl)-6-(4-nitrobenzoyloxy)- cyclohex-3-ene-1,2-diyl diacetate (**16**): Yellow oil, $\alpha_D^{24} = -26.6$ (c 0.45, CH$_2$Cl$_2$). $R_f = 0.36$ (9:1 hexanes:EtOAc); IR (thin film) 3112, 2924, 2853, 1749, 1727, 1657, 1233, 1120, 1044 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.30–8.27 (m, 2H, Ph), 8.17–8.14 (m, 2H, Ph), 6.70 (br s, 1H, H2), 5.77 (br s, 1H, H3), 5.66 (br s, 1H, H4), 5.44–5.41 (m, 1H, H5), 4.25 (q, $J = 7.2$ Hz, 2H, H2'), 2.96(dd, $J = 5.8$ Hz, $J = 17.8$ Hz, 1H, H6), 2.75–2.73 (m, 1H, H6), 2.12(s, 3H, OAc), 2.04 (s, 3H, OAc), 1.33 (t, $J = 7.2$ Hz, 3H, H3'); ^{13}C NMR (125 MHz, CDCl3) δ 170.2, 169.7, 165.1, 163.6, 150.7, 134.8, 133.5, 130.8, 130.5, 123.5, 69.2, 67.5, 67.2, 61.3, 26.8, 20.7, 20.6, 14.1. Calculated for C$_{19}$H$_{25}$NO$_6$Na [M+Na]$^+$: 458.1063, found 458.1068.
26. Spectral data for these compounds were similar to the ones reported for them in the literature. See Ref. [24] and Supplementary data for details.