Stereoselective Total Synthesis of (+)-Valienamine and (+)-4-*epi*-Valienamine via a Ring-Closing Enyne Metathesis Protocol

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Abstract: Stereoselective total synthesis of (+)-valienamine is reported utilizing Sharpless asymmetric dihydroxylation, diastereoselective Carreira alkynylation, and ring-closing enyne metathesis (RCEYM) as key steps from L-serine. A similar strategy is also reported for the first total synthesis of (+)-4-*epi*-valienamine.

Key words: Sharpless asymmetric dihydroxylation, Carreira alkynylation, Grubbs' catalyst, ring-closing enyne metathesis, valienamine, 4-*epi*-valienamine

Glycosidases are the enzymes that cleave the glycosidic bonds and are responsible for the glycoprotein processing and carbohydrate digestion in animals. Hence, inhibition of these enzymes has significant implications in both antiviral and diabetic chemotherapy.[1] Valienamine [(1*S*,2*S*,3*S*,4*R*)-1-amino-5-(hydroxymethyl)cyclohex-5-ene-2,3,4-triol] (Figure 1), a carbasugar, was first isolated from microbial degradation of validoxylamine A with *Pseudomonas denitrificans*[2] or *Flavabacterium saccharophilum*[3] or from the NBS cleavage of validoxylamine A and its derivatives.[4] Valienamine is a core unit of many pseudo-oligosaccharides and pseudo-amino sugars such as validamycins, acarbose, amylostatins, adiposins, acarviosin, and trestatins.[5a] Valienamine shows strong α-glycosidase inhibitory activity against various hydrolases[6] inhibiting 50% activity of maltase and sucrase at concentrations of 3.4×10^{-4} and 5.3×10^{-5} M and antibiotic activity against *Bacillus* species.[7] Due to its varied and important biological activities, several syntheses[5] were reported in an effort to arrive at more potent modified analogues.

Ever since the pioneering work of Paulsen[8] et al. and others,[9] elegant syntheses of valienamine were reported.[5] While, most of them used D-glucose or its derivatives[10,11a,c] as the chiral starting material and built the carbocyclic framework using various key reactions, the most interesting to us was the use of ring-closing alkene metathesis protocol.[11] Owing to our broad interest in applying metathesis-based synthetic routes to access bioactive natural products,[12] herein we report the stereoselective total synthesis of valienamine (**1**) and the first synthesis of 4-*epi*-valienamine (**2**) wherein ring-closing enyne metathesis (RCEYM) is employed as the key step

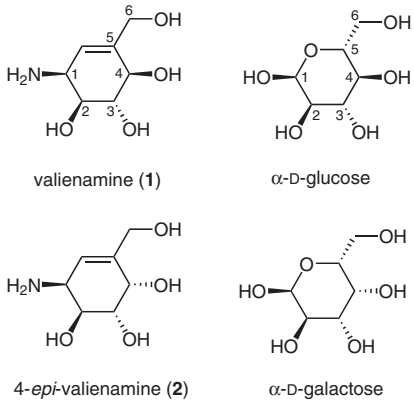

Figure 1

for constructing the carbocyclic ring system. We envisioned that the ensuing vinylic double bond would serve as a masked 'hydroxymethyl side chain' as well as a handle for designing New Chemical Entities (NCEs).[13]

Thus, the synthesis (Scheme 1) began following the literature procedure. The known[14] compound **3**, obtained from L-serine, on Sharpless asymmetric dihydroxylation (AD-mix-α, OsO_4, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0 °C) provided a separable mixture of diastereomers in 99:1 ratio. Diol **4** was protected as its MOM ether **5** (MOMCl, DIPEA, CH_2Cl_2, r.t., 93%). Next, reduction of **5** with $LiAlH_4$ in THF gave the primary alcohol **6** (75%). Alcohol **6** on Swern oxidation and quenching the ensuing aldehyde with TMS–acetylenic anion (TMS–acetylene, *n*-BuLi, THF, –78 °C) afforded propargylic alcohol which upon TMS deprotection (K_2CO_3, MeOH) furnished **7a** and **7b** (70% overall yield for three steps) as an inseparable diastereomeric mixture (8.0:2.0, *anti*/*syn*). The ratio of diastereomers was determined by the ^{1}H NMR analysis via the relative integration of the separable methoxy protons of the MOM groups. Herein, the predominant 1,2-*anti* selectivity maybe explained due to non-chelation addition protocol. In order to alter the stereoisomer in favor of the desired stereochemistry, various strategies were tried. Firstly, additives such as $ZnCl_2$, $ZnBr_2$ and $MgBr_2{\cdot}OEt_2$ were used in an attempt to augment the chelation-controlled addition as the means of enhancing the *syn* selectivity, but the observed de values were 5%, 16% and 32%, respectively. Later, the diastereomeric mixture of **7a** and **7b** was subjected to a Mitsunobu reaction (*p*-$NO_2C_6H_4COOH$, DIAD, TPP, THF, r.t.) followed by methanolysis (K_2CO_3, MeOH, r.t.) to provide the desired

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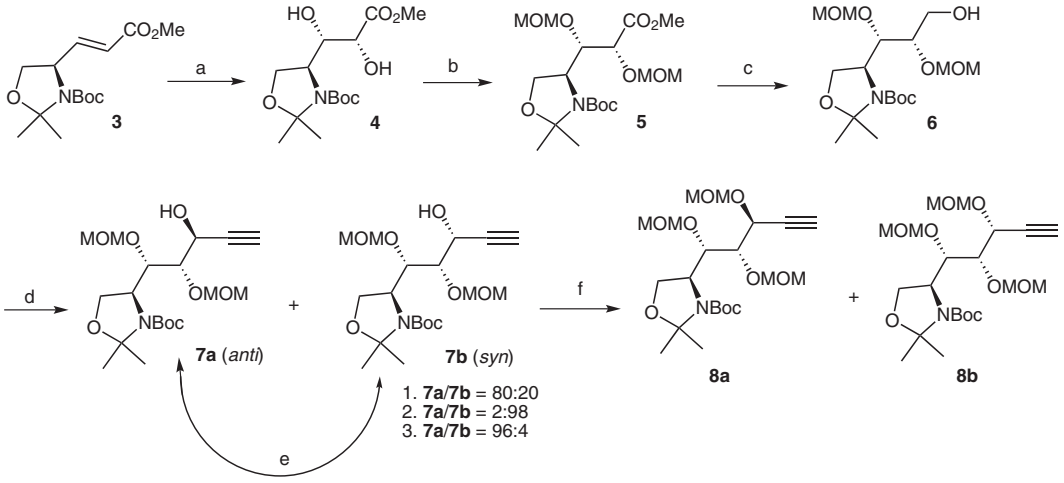
diastereomer as the major product (8.0:2.0 ratio). However, practical separation of **7a** and **7b** diastereomeric mixture into individual entities was possible after derivatization (MOMCl, DIPEA, CH_2Cl_2, 0 °C to r.t.) as MOM ethers **8a** and **8b**.

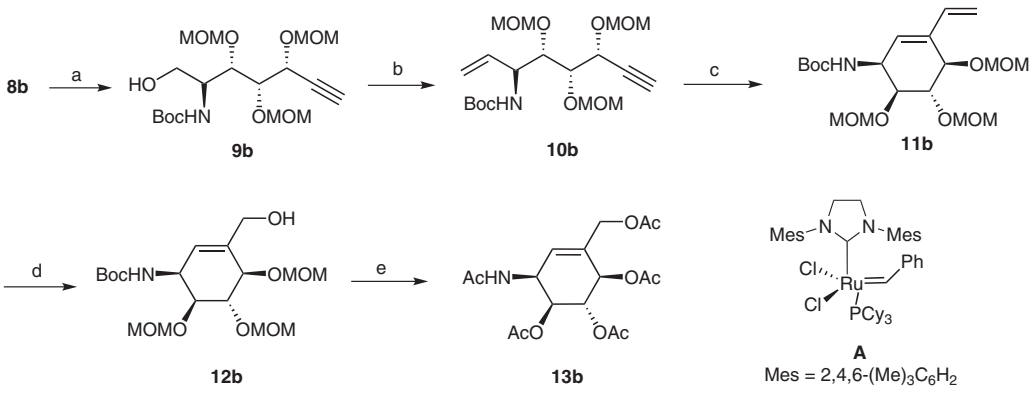
In order to enhance the diastereoselectivity in favor of the desired stereoisomer, Carreira asymmetric alkynylation reaction[15] [(–)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, TMS–acetylene, toluene, r.t.] was conducted on the corresponding aldehyde to furnish propargyl alcohol **7b** in higher yield (86%) and selectivity (96% de). Likewise, Carreira alkynylation reaction using (+)-*N*-methylephedrine as the chiral ligand under similar reaction conditions gave **7a** in equal optical and chemical yield. The absolute stereochemistry of the newly created stereogenic center of **7a** was assigned as *S* based on the literature precedence[15,16] and that of **7b** as *R*. Next, the secondary hydroxy group in **7b** was protected as its MOM ether (MOMCl, DIPEA, CH_2Cl_2, 0 °C, r.t.) to afford **8b** (90%). The thus-obtained diastereomer **8b** was taken up for further use.

Further, the independently accessed **8a** and **8b** were correlated with those obtained earlier and found to have identical spectral data.

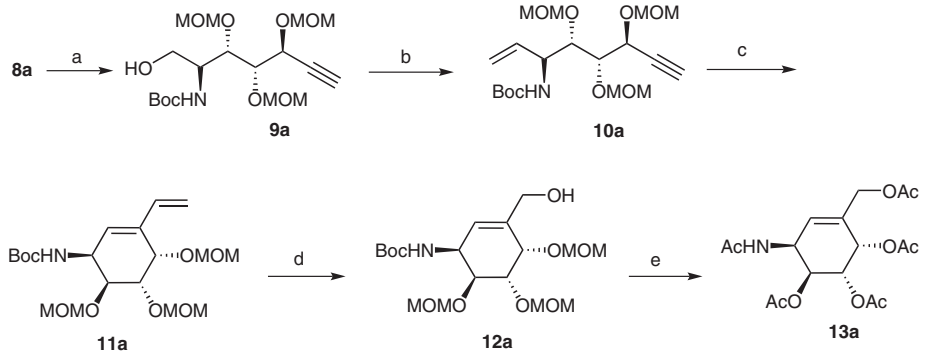
To continue the synthesis, **8b** on selective cleavage of acetonide group using $CuCl_2{\cdot}2H_2O$ in acetonitrile at 0 °C gave the free primary alcohol **9b** (92%; Scheme 2). Swern oxidation of **9b** followed by Wittig olefination ($Me^+PPh_3I^-$, *t*-BuOK, THF, 0 °C) furnished enyne **10b** (64%). Compound **10b** was characterized by its spectral data, wherein its ^1H NMR spectrum revealed the characteristic acetylenic proton at δ = 2.46 ppm as a doublet (*J* = 1.8 Hz) and the olefinic protons as multiplets at δ = 6.01 and at δ = 5.20–5.34 ppm. The IR spectrum displayed the characteristic C–H and C–C stretching frequencies at 3252 and 2154 cm^{-1} respectively. The critical ring-closing enyne metathesis reaction[17a] of **10b** was conducted with the Grubbs II catalyst [**A** (10 mol%), solvent, reflux, 12 h]



Scheme 1 *Reagents and conditions*: (a) AD-mix-α, OsO_4, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0 °C, 16 h, 84%; (b) DIPEA, MOMCl, CH_2Cl_2, 0 °C to r.t., 17 h, 93%; (c) $LiAlH_4$, THF, 0 °C to r.t., 1 h, 75%; (d) (i) $COCl_2$, DMSO, Et_3N, –78 °C; (ii) 1. TMS–acetylene, *n*-BuLi, –78 °C, 4 h; 2. $Zn(OTf)_2$, (–)-*N*-methylephedrine, Et_3N, toluene, 86%; 3. $Zn(OTf)_2$, (+)-*N*-methylephedrine, Et_3N, toluene, 80%; (iii) K_2CO_3, MeOH, 0 °C, 1 h; (e) (i) *p*-$NO_2C_6H_4COOH$, DIAD, TPP, THF, 0 °C to r.t., 1.5 h; (ii) K_2CO_3, MeOH, 0 °C (84% over two steps); (f) DIPEA, MOMCl, CH_2Cl_2, 0 °C to r.t., 8 h.



Scheme 2 *Reagents and conditions*: (a) $CuCl_2{\cdot}2H_2O$, MeCN, 0 °C, 0.5 h, 92%; (b) (i) $COCl_2$, DMSO, Et_3N, –78 °C; (ii) $Me^+PPh_3I^-$, *t*-BuOK, THF, 0 °C, 8 h, 64%; (c) Grubbs II (**A**, 10 mol%), ethylene atmosphere, toluene, 110 °C, 12 h, 92%; (d) (i) OsO_4, NMMO (0.05 equiv), acetone–H_2O (4:1), 5 h; (ii) $NaIO_4$, MeOH–H_2O (9:1), 0 °C, 1 h; (iii) $NaBH_4$, MeOH, 0 °C, 5 min (62% over three steps); (e) (i) TFA, CH_2Cl_2, 0 °C, 4 h; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t., 14 h (70% over two steps).



Scheme 3 *Reagents and conditions*; (a) $CuCl_2 \cdot 2H_2O$, MeCN, 0 °C, 0.5 h, 89%; (b) (i) $COCl_2$, DMSO, Et_3N, –78 °C; (ii) $Me^+PPh_3I^-$, *t*-BuOK, THF, 0 °C, 12 h, 61%; (c) Grubbs II (10 mol%), ethylene atmosphere, toluene, 110 °C, 8 h, 95%; (d) (i) OsO_4, NMMO (0.05 equiv), acetone–H_2O (4:1), 5 h; (ii) $NaIO_4$, MeOH–H_2O (9:1), 0 °C, 1 h; (iii) $NaBH_4$, MeOH, 0 °C, 5 min (70% over three steps); (e) (i) TFA, CH_2Cl_2, 0 °C, 4 h; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t., 14 h, (68% over two steps).

under two different solvents systems, in CH_2Cl_2 and in toluene independently. Both the reactions offered the desired product **11b**, albeit in low yields. Gratifyingly, the same reaction in toluene (110 °C) under an ethylene atmosphere[17b] furnished vinylcyclohexene derivative **11b** in high yield (92%). Compound **11b** was identified from its spectral data. The ^{1}H NMR spectrum of **11b** indicated the absence of the acetylenic and terminal olefinic protons whilst displaying the characteristic olefinic protons at δ = 6.24 ppm as a double doublet (*J* = 10.9, 17.3 Hz), at δ = 5.78 ppm as a double doublet (*J* = 3.0, 15.8 Hz), at δ = 5.44 as a doublet (*J* = 16.9 Hz) and at δ = 5.10 ppm as a doublet (*J* = 10.9 Hz). The mass spectrum had an [M + H] peak at *m*/*z* = 404 in support of the assigned structure.

With the vinylcyclohexene derivative **11b** in hand, the next task was the selective transformation of the vinylic double bond into a hydroxymethyl side chain. The conversion was planned via a sequential dihydroxylation–oxidative cleavage–reduction protocol. For example, selective dihydroxylation of the vinylic olefin **11b** (OsO_4, NMO, acetone–H_2O) and the oxidative cleavage of the ensuing diol ($NaIO_4$, MeOH–H_2O, r.t.) gave the corresponding aldehyde which was reduced ($NaBH_4$, MeOH, 0 ºC) to afford the carbocyclic methanol **12b** (62% overall yield for three steps) without any purification of the intermediates. Global deprotection of MOM and Boc protecting groups with TFA in CH_2Cl_2 at room temperature afforded valienamine (**1**) which on acetylation (Ac_2O, pyridine, DMAP, CH_2Cl_2, r.t., 14 h) furnished the pentaacetate derivative **13b** (70% overall yield for two steps) to facilitate its easy isolation and characterization. The physical and spectroscopic data of **13b** {mp 94 ºC, $[\alpha]^{25}_D$ +22.7 (*c* = 0.62, $CHCl_3$)} were identical to the reported values {lit.[11b] mp 91.5–93 ºC; $[\alpha]_D$ +21.1 (*c* = 0.9, $CHCl_3$) and lit.[9a] mp 92–94 ºC; $[\alpha]^{20}_D$ +20.1 (*c* = 0.8, $CHCl_3$)}.

In a related approach (Scheme 3), when **8a** was used as the starting material and subjected to the same set of transformations (Scheme 2), a non-natural 4-*epi*-valienamine (**2**; Figure 1) was obtained as the product. Compound **2** was thoroughly characterized[18] as its pentaacetate derivative **13a** (68% overall yield for two steps). Interestingly, aminocyclitol **2** (Figure 1) might be considered as a potential α-galactosidase inhibitor.

In conclusion, a stereoselective total synthesis of (+)-valienamine and (+)-4-*epi*-valienamine, a hitherto unreported diastereomer has been accomplished by the ring-closing enyne metathesis approach to access the carbocyclic framework possessing a vinylic olefin which was selectively transformed into a hydroxymethyl group. Interestingly a closer derivative *N*-octyl-4-*epi*-β-valienamine (NOEV)[19] was found useful in molecular therapy for certain patients with β-galactosidosis and other lysosomal storage associated diseases involving the central nervous system.

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(18) Spectral data for selected compounds: Compound **10b**: light yellow syrup; $[\alpha]_D^{25}$ +11.96 (*c* = 0.59, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.01 (m, 2 H), 5.20–5.34 (m, 2 H), 4.89 (q, 1 H, *J* = 8.8, 15.4 Hz), 4.80 (dd, 1 H, *J* = 4.0, 7.0 Hz), 4.66–4.76 (m, 2 H), 4.50–4.62 (m, 2 H), 4.38 (br s, 1 H), 4.02 (t, 1 H, *J* = 3.3 Hz), 3.76–3.83 (m, 2 H), 3.46 (s, 3 H), 3.43 (s, 3 H), 3.36 (s, 3 H), 2.46 (d, 1 H, *J* = 1.8 Hz), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 135.1, 116.6, 99.3, 97.2, 94.4, 79.5, 79.4, 77.9, 76.0, 67.1, 56.8, 56.1, 55.9, 53.8, 28.3. IR (neat): 3425, 3252, 2930, 2250, 2154, 1714, 1640, 1502, 1158, 1026 cm^{-1}. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{33}NO_8Na$: 426.2103; found: 426.2107. Compound **11b**: light yellow syrup; $[\alpha]_D^{25}$ –77.21 (*c* = 0.76, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.24 (dd, 1 H, *J* = 11.0, 17.4 Hz), 5.78 (dd, 1 H, *J* = 3.0, 15.9 Hz), 5.44 (d, 1 H, *J* = 16.9 Hz), 5.10 (d, 1 H, *J* = 10.9 Hz), 4.90 (dd, 1 H, *J* = 3.4, 7.1 Hz), 4.60–4.82 (m, 6 H), 4.50 (br d, 1 H, *J* = 2.2 Hz), 4.29 (br s, 1 H), 4.10 (dd, 1 H, *J* = 2.2, 5.2 Hz), 3.86 (t, 1 H, *J* = 4.9 Hz), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 136.6, 135.2, 129.5, 114.4, 96.4, 96.3, 95.9, 79.4, 73.5, 72.7, 72.4, 56.3, 55.8, 55.6, 29.0. IR (neat): 3416, 2925, 2854, 1717, 1609, 1510, 1156, 1024 cm^{-1}. HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{34}NO_8$: 404.2284; found: 404.2279. Compound **13b**: white solid; mp 94 °C; $[\alpha]_D^{25}$ +22.7 (*c* = 0.62, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.87 (d, 1 H, *J* = 4.4 Hz), 5.79 (br d, 1 H, *J* = 8.4 Hz), 5.43 (dd, 1 H, *J* = 6.4, 9.4 Hz), 5.34 (d, 1 H, *J* = 6.3 Hz), 4.98–5.10 (m, 2 H), 4.63 (d, 1 H, *J* = 13.2 Hz), 4.36 (d, 1 H, *J* = 13.2 Hz), 2.01–2.06 (m, 15 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.2, 170.1, 169.9, 169.8, 134.3, 126.1, 71.2, 69.0, 68.5, 62.9, 44.8, 23.3, 20.7. IR (neat): 3287, 2925, 1746, 1658, 1371, 1225, 1031 cm^{-1}. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{23}NO_9Na$: 408.1270; found: 408.1263. Compound **10a**: syrupy liquid; $[\alpha]_D^{25}$ –187.0 (*c* = 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.79–5.97 (m, 1 H), 5.15–5.32 (m, 2 H), 4.91 (q, 1 H, *J* = 8.3, 15.1 Hz), 4.75 (dd, 3 H, *J* = 6.0, 17.3 Hz), 4.60 (t, 2 H, *J* = 6.8, 15.1 Hz), 4.37–4.46 (m, 1 H), 3.91 (t, 1 H, *J* = 5.2 Hz), 3.78 (m, 2 H), 3.44 (s, 3 H), 3.37 (m, 6 H), 2.44 (d, 1 H, *J* = 2.2 Hz), 1.44 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 134.9, 112.3, 98.6, 96.9, 92.7, 79.8, 79.1, 78.4, 77.2, 66.8, 57.4, 56.7, 56.0, 52.9, 28.2. IR (neat): 3438, 3210, 2927, 2852, 2140, 1715, 1610, 1506, 1156, 1026 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{34}NO_8$: 404.2284; found: 404.2291. Compound **11a**: light yellow syrup; $[\alpha]_D^{25}$ +62.68 (*c* = 2.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.27 (dd, 1 H, *J* = 11.0, 17.5 Hz), 5.80 (br d, 1 H, *J* = 2.8 Hz), 5.44 (d, 1 H, *J* = 17.5 Hz), 5.06–5.12 (m, 2 H), 4.80 (d, 1 H, *J* = 7.0 Hz), 4.60–4.74 (m, 6 H), 4.28 (br s, 1 H), 4.10 (dd, 1 H, *J* = 2.1, 5.2 Hz), 3.86 (t, 1 H, *J* = 5.2 Hz), 3.42 (s, 3 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 136.8, 133.4, 129.0, 112.6, 97.5, 96.9, 96.3, 80.1, 74.7, 71.9, 71.0, 57.2, 56.0, 55.7, 28.3. IR (neat): 3366, 2925, 1714, 1158, 1020 cm^{-1}. HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{34}NO_8$: 404.2284; found: 404.2280. Compound **13a**: thick white syrup; $[\alpha]_D^{25}$ +69.6 (*c* = 0.58, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.99 (d, 1 H, *J* = 5.3 Hz), 5.82 (d, 1 H, *J* = 8.3 Hz), 5.44 (dd, 1 H, *J* = 6.8, 11.5 Hz), 5.27 (br dd, 1 H, *J* = 4.1, 6.2 Hz), 4.96–5.07 (m, 2 H), 4.66 (dd, 1 H, *J* = 1.5, 12.8 Hz), 4.33 (dd, 1 H, *J* = 1.5, 13.6 Hz), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.2, 170.1, 169.9, 169.8, 132.2, 127.0, 72.7, 70.9, 66.0, 62.2, 46.7, 23.1, 20.6. IR (neat): 3447, 2963, 1742, 1647, 1260, 1020 cm^{-1}. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{23}NO_9Na$: 408.1270; found: 408.1265.
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