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# Synthetic studies towards the novel neurotrophic diterpenoids neovibsanins A and B: construction of the ABC core

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ABSTRACT

A concise, general approach to the tricyclic furo-furan-based core structure present in the bioactive natural products neovibsanins A and B, from readily available Baylis–Hillman adducts, is delineated.



Vibsane-type diterpenoids constitute a rapidly expanding and structurally diverse family of natural products that occur exclusively in *Viburnum* species such as *V. awabuki*, *V. odoratissimum* and *V. suspensum*.[1,2] From a biogenetic perspective, the most important vibsane diterpenoid is the ten-membered vibsanin B **1**, which is structurally a higher isoprenologue of the sesquiterpene humulene, with potential to unfold a myriad cyclization patterns.[1–3] As many as ten sub-structural types are known among vibsane diterpenoids and this impressive collection, **1**–**10** is displayed in Figure 1. While many vibsanins exhibit some kind of bioactivity profile ranging from pesticidal and plant growth inhibition to cytotoxicity,[1] it is the neovibsanins A and B **10a,b** that exhibit the unique activity of promoting neurite outgrowth of NGF-mediated PC-12 cells.[4] This attribute makes **10a,b** important therapeutic leads for mitigating neurodegenerative disorders such as Alzheimer's.

The isolation of neovibsanins A and B (**10a** and **10b**) from *V. awabuki* was reported by Fukuyama in 1996 and their uncommon tricyclic formulation was arrived at through incisive NMR studies.[2] Architectural complexity combined with their unique bioactivity makes the neovibsanins challenging and attractive targets for total synthesis. A recent report[5] on studies aimed towards the synthesis of neovibsanins A and B prompts us to disclose our own efforts in the area. The present report, to our knowledge, constitutes the first acquisition of the core ABC framework of the neovibsanin natural products.

The initial focus of our synthetic efforts towards the natural products **10a,b** was to devise a rapid and diversity-oriented access to the cyclohexene-fused tricyclic furo-furan ABC core **11**. Retrosynthetically, it was planned to assemble this from a furo-furanone precursor **12** which in turn could be assembled through a tandem intramolecular lactonization-Michael addition protocol from **13**. The functionally embellished cyclohexene derivative **13** was to be prepared from the Baylis–Hillman product **14**[6] of the corresponding cyclohexenone, Scheme 1.

Initially, the TBS-protected Baylis–Hillman adduct[6b] of cyclohexenone **15** was reacted with the dianion derived from propargyl alcohol[7] to furnish **16**. The triple bond in **16** was regio- and stereoselectively reduced to the *cis*-alkene **17**. $MnO_2$-mediated oxidation of **17** led directly to the spiro-fused γ-lactone **18** via the intermediacy of the corresponding cyclic lactol. Fluoride-mediated deprotection in **18** triggered the intramolecular Michael addition to furnish the tricyclic furo-furanone **19** and further methylenation of the lactone carbonyl with the Tebbe reagent[8] led to **20** embodying the ABC core of the natural products, Scheme 2. To demonstrate the generality of this concise approach to the cyclohexene-fused furo-furan core, the above sequence was implemented on 5,5-dimethylcyclohex-2-en-1-one **21**, as the natural products **10a,b** harbour geminal dialkyl substitution in the same position. Thus **21** was readily transformed to the Baylis–Hillman adduct **22**[6b] and propargyl alcohol addition delivered **23**. Selective hydrogenation to **24**, oxidation to the γ-lactone **25** and TBS deprotection/Michael addition furnished the tricyclic furo-furanone **26**, Scheme 3.

Further evolution of our strategy towards neovibsanins required inclusion of the C-10 side arm. Towards this end, the protected Baylis–Hillman adduct **22** was allylated under kinetically controlled conditions to furnish **27**. Regioselective oxidative cleavage of the allyl group led to the aldehyde **28** with the requisite two-carbon C-10 side arm. Aldehyde protection in **28** as the acetal **29** set the stage for the acetal side arm-directed propargyl addition[9] and led to a 1:1.2 mixture of **30** and **31**, Scheme 4. The formation of two diastereomers **30** and **31** was considered a satisfactory outcome and they were individually elaborated to the tricyclic furo-furanones **36** and **37**, respectively, through stereoselective hydrogenation to **32** and **33**, $MnO_2$-oxidation to the γ-lactones **34** and **35** and fluoride-mediated Michael addition. In the context of the target natural products, it was important to delineate unambiguously the relative stereochemistry at C-4 and C-10 in **36** and **37** and this was achieved through single crystal X-ray structure

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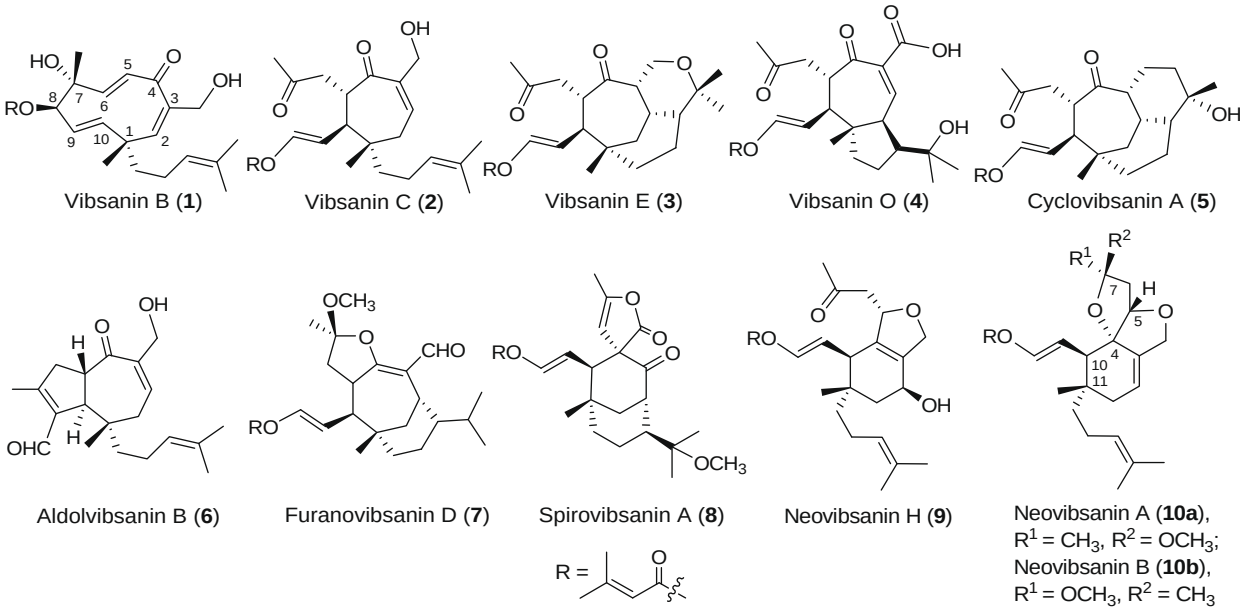
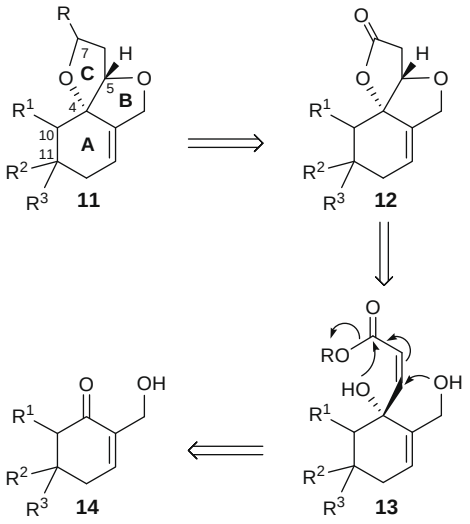
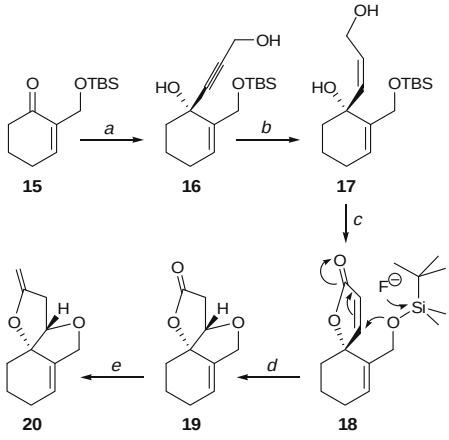


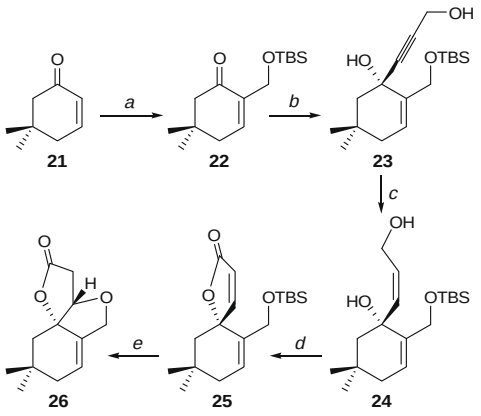

**Figure 1.** Structural diversity in vibsanin diterpenoids.




**Scheme 1.** Retrosynthetic analysis of the tricyclic core **11**.



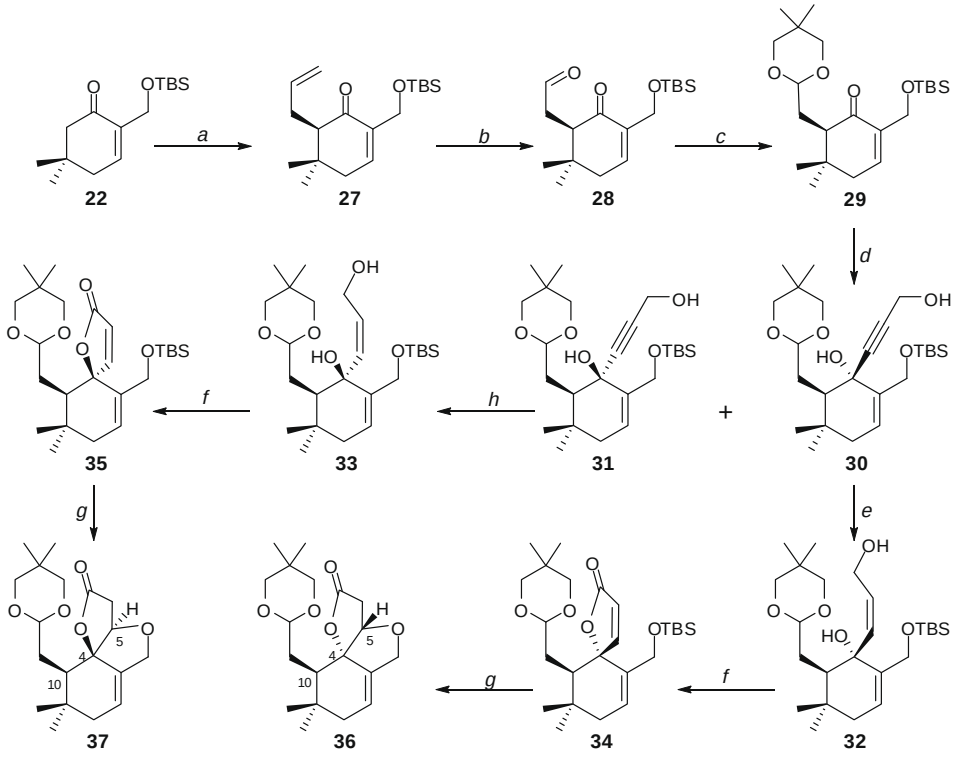

**Scheme 2.** Reagents and conditions. (a) propargyl alcohol, *n*-BuLi, THF, 0 °C, 4 h, 60%; (b) Lindlar catalyst, $H_2$ (1 atm), MeOH, rt, 2 h, 90%; (c) $MnO_2$, $CH_2Cl_2$, rt, 24 h, 88%; (d) TBAF, THF, rt, 20 min, 94%; (e) Tebbe reagent, THF:toluene (1:1), −40 °C to 0 °C, 2 h, 78%.




**Scheme 3.** Reagents and conditions. (a) (i) HCHO aq (37–41%, w/v), DMAP, THF:$H_2O$ (1:1), rt, 12 h, 65%; (ii) TBSCl, imidazole, DMAP, $CH_2Cl_2$, rt, 1 h, 98%; (b) propargyl alcohol, *n*-BuLi, THF, 0 °C, 6 h, 56%; (c) Lindlar catalyst, $H_2$ (1 atm), MeOH, rt, 10 h, 88%; (d) $MnO_2$, $CH_2Cl_2$, rt, 24 h, 92%; (e) TBAF, THF, rt, 20 min, 94%.

determination on **37**, Figure 2.[10] This established that in tricyclic diastereomer **36**, we had achieved the required relative stereochemistry at C-4, C-5 and C-10 as present in the neovibsanin natural products.

Our next major task was to establish the viability of our concise furo-furan strategy with a substrate having a preinstalled C-11 quaternary centre bearing the methyl and the homoprenyl moieties. With this objective in mind, the previously reported[11] dimedone derivative **38** was conveniently elaborated to the cyclohexenone **40** via the intermediacy of the enol ether **39**. Baylis–Hillman reaction of **40** led to **41** and the hydroxy group was protected as the TBS derivative **42**, Scheme 5. Addition of the dianion derived from propargyl alcohol to **42** furnished a mixture of diastereomers **43** (β–OH:α–OH, 1.2:1). The distal quaternary centre at C-11 only engendered marginal stereoselection in the addition reaction. Separation of the propargylated diastereomers **43** was difficult at this stage and it was considered prudent to con-




**Scheme 4.** Reagents and conditions. (a) LDA, allyl iodide, THF, −78 to 0 °C, 60%; (b) $OsO_4$, $NaIO_4$, 2,6-lutidine, dioxane:$H_2O$ (4:1), 0 °C, 2 h, 62%; (c) 2,2-dimethyl-1,3-propandiol, PPTS, benzene, reflux, 1 h, 94%; (d) propargyl alcohol, *n*-BuLi, THF, 0 °C, 12 h, 60% (based on recovered starting material); (e) 5% Pd/C, MeOH, $H_2$, rt, 85%; (f) $MnO_2$, $CH_2Cl_2$, rt, 24 h, **34** (90%), **35** (92%); (g) TBAF, THF, rt, 20 min, **36** (92%), **37** (88%); (h) Lindlar catalyst, $H_2$ (1 atm), MeOH, rt, 10 h, 80%.

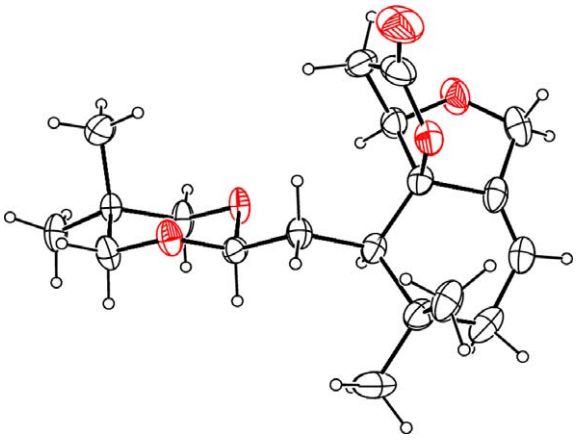
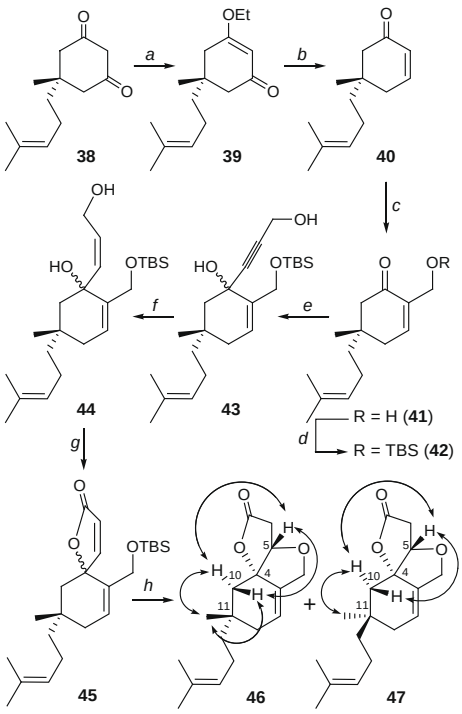


**Figure 2.** ORTEP diagram of compound **37** with 30% ellipsoidal probability.




**Scheme 5.** Reagents and conditions. (a) $TiCl_4$, EtOH, 0 °C–rt, 2 h, 90%; (b) (i) DIBAL-H, $CH_2Cl_2$, rt; (ii) HCl, acetone:$H_2O$ (20:1), 15 min, 65% (over 2 steps); (c) HCHO aq (37–41%, w/v), DMAP, sodium dodecyl sulfonate, THF:$H_2O$ (1:1), rt, 16 h, 56%; (d) TBSCl, imidazole, DMAP, $CH_2Cl_2$, rt, 1 h, 98%; (e) propargyl alcohol, *n*-BuLi, THF, 0 °C, 8 h, 52%; (f) Lindlar catalyst, $H_2$ (1 atm), MeOH, rt, 12 h, 84%; (g) $MnO_2$, $CH_2Cl_2$, rt, 24 h, 90%; (h) TBAF, THF, rt, 20 min, 90%.

tinue with the mixture. Partial hydrogenation of **43** led to *cis*-alkenes **44** and further oxidation with $MnO_2$ delivered the γ-spirolactones **45**, quite uneventfully. Fluoride-mediated deprotection of **45** resulted in concomitant Michael addition to furnish an easily separable mixture of **46** and **47**. The stereostructures **46** and **47** were assigned on the basis of 2D NMR studies, particularly through the key NOESY connectivities indicated. Once again, it was gratifying to note that **46** had the requisite stereochemistry at the C-4, C-5 and C-11 stereogenic centres of the tricyclic furo-furanone ABC core.[12]

In conclusion, we have outlined a very short approach of general utility to the tricyclic furo-furan-based core of neovibsanin diterpenoids **10a,b**. The structural and stereochemical challenges associated with the construction of the neovibsanin framework have been addressed and the stage is now set to translate the outcomes and experiences of this model study towards the total synthesis of the natural products.

## Acknowledgements

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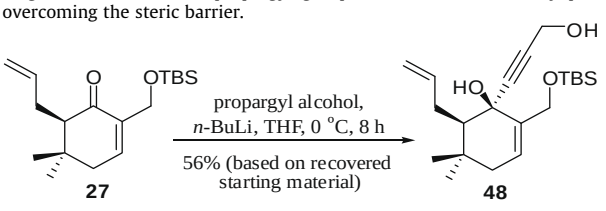
9. In this context, it is important to mention that propargyl addition to the allylated compound **27** was dominated by steric considerations with preferred addition from the less hindered opposite face to furnish exclusively **48** having the undesired stereochemical disposition at C-4 and C-10. Thus, we devised the tactic of using the acetal oxygen in **29** to coordinate with the organolithium reagent and deliver the propargyl group from the same face by partially overcoming the steric barrier.




27 48

10. X-ray data were collected at 291 K on a Bruker Kappa APEX II diffractometer with graphite monochromated $MoK_\alpha$ radiation ($\lambda = 0.7107$ Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on $F^2$ using SHELXL-97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-706720. *Compound* **37**: $C_{19}H_{28}O_5$, MW = 336.41, crystal system: monoclinic, space group: $P2_1/c$, cell parameters: $a = 9.0085(3)$ Å, $b = 13.3822(5)$ Å, $c = 17.5105(6)$ Å, $\beta = 118.891(2)^\circ$, $V = 1848.22(11)$ Å$^3$, $Z = 4$, $\rho_{calc} = 1.209$ g cm$^{-3}$, $F(000) = 728$, $\mu = 0.086$ mm$^{-1}$, number of l.s. parameters = 221, $R_1 = 0.0886$ for 2207 reflections with $I > 2\sigma(I)$ and 0.1290 for all 3672 data. $wR_2 = 0.2757$, GOF = 0.9550 for all data.
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12. All new compounds were fully characterized on the basis of IR, $^1$H NMR, $^{13}$C NMR and HRMS spectral data. Spectral data of selected compounds: **19** IR (neat) 2952, 2935, 1766, 1253, 1222, 837 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.93 (br s, 1H), 4.53–4.58 (m, 1H), 4.38 (dd, $J = 2.1$, 14.6 Hz, 1H), 4.31 (dd, $J = 1.8$, 3.6 Hz, 1H), 2.78 (d, $J = 3.6$ Hz, 2H), 2.23 (m, 1H), 1.99–2.15 (m, 2H), 1.84–1.91 (m, 2H), 1.53 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 134.9, 125.6, 88.4, 82.3, 70.2, 37.2, 29.5, 24.3, 17.5; HRMS (ES) *m/z* calcd for $C_{10}H_{12}O_3Na$ (M+Na$^+$): 203.0684; found: 203.0675; **20** IR (neat) 2925, 2854, 1600, 1447, 887 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.60 (br s, 1H) 4.86 (d, $J = 5.7$ Hz, 2H), 4.58 (dd, $J = 2.7$, 12.6 Hz, 1H), 4.25 (dd, $J = 2.4$, 12.9 Hz, 1H), 3.53 (m, 1H), 2.31–2.49 (m, 2H), 1.97–2.30 (m, 2H), 1.77–1.95 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 142.6, 140.6, 121.5, 112.4, 85.1, 73.9, 68.3, 36.8, 24.9, 22.7, 17.5; HRMS (ES) *m/z* calcd for $C_{11}H_{14}O_2K$ (M+K$^+$): 217.1183; found: 217.0631; **26** IR (neat) 2953, 2870, 1778, 1209, 1137, 914 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.88 (br s, 1H), 4.51–4.56 (m, 1H), 4.35 (d, $J = 11.3$ Hz, 1H), 4.23 (t, $J = 2.4$ Hz, 1H), 2.72 (br s, 2H), 2.09 (d, $J = 18.6$ Hz, 1H), 1.99 (d, $J = 18.6$ Hz, 1H), 1.79 (d, $J = 14.1$ Hz, 1H), 1.58 (d, $J = 14.1$ Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.4, 133.5, 125.6, 88.8, 83.3, 70.1, 42.1, 39.3, 36.9, 31.8, 29.3, 27.1; HRMS (ES) *m/z* calcd for $C_{12}H_{16}O_3Na$ (M+Na$^+$): 231.0997; found: 231.1005; **36** IR (neat) 2926, 1778, 1470, 1141, 1029, 834 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.82 (br s, 1H), 4.75 (d, $J = 4.5$ Hz, 1H), 4.52 (m, 1H), 4.39 (m, 1H), 4.32 (d, $J = 12.2$ Hz, 1H), 3.56 (d, $J = 11.0$ Hz, 2H), 3.39 (m, 2H), 2.85 (dd, $J = 4.3$, 18.8 Hz, 1H), 2.61 (d, $J = 17.9$ Hz, 1H), 1.67–2.06 (m, 3H), 1.33–1.42 (m, 2H), 1.18 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 0.72 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.2, 133.7, 124.8, 101.9, 93.2, 81.4, 77.2, 77.1, 69.9, 42.8, 36.4, 35.8, 33.3, 31.4, 30.0, 29.3, 28.1, 22.9, 21.7; HRMS (ES) *m/z* calcd for $C_{19}H_{28}O_5Na$ (M+Na$^+$): 359.1834; found: 359.1834; **37** IR (neat) 2957, 2854, 1779, 1470, 1141, 1029, 907 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.81 (br s, 1H), 4.56 (d, $J = 6.0$ Hz, 1H), 4.41 (m, 2H), 4.24 (d, $J = 10.8$ Hz, 1H), 3.57 (d, $J = 11.1$ Hz, 2H), 3.38 (m, 2H), 2.99 (dd, $J = 5.4$, 18.6 Hz, 1H), 2.62 (d, $J = 18.6$ Hz, 1H), 2.08 (br s, 2H), 1.78–1.86 (m, 2H), 1.37–1.46 (m, 1H), 1.15 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.71 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.9, 134.8, 124.2, 101.6, 90.5, 83.1, 77.1, 69.4, 43.1, 41.6, 38.2, 33.2, 29.9, 29.6, 23.0, 22.3, 21.7; HRMS (ES) *m/z* calcd for $C_{19}H_{28}O_5Na$ (M+Na$^+$): 359.1834; found: 359.1834; **46** IR (neat) 2955, 2855, 1781, 1458, 1203, 1036, 912 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.86 (br s, 1H), 5.09–5.12 (m, 1H), 4.50–4.55 (m, 1H), 4.34 (dd, $J = 1.2$, 11.3 Hz, 1H), 4.23 (m, 1H), 2.73 (d, $J = 2.4$ Hz, 2H), 2.05–2.21 (m, 1H), 1.95 (d, $J = 14.3$ Hz, 1H), 1.87–2.05 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.49 (d, $J = 14.3$ Hz, 1H), 1.23–1.35 (m, 4H), 1.03 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.2, 133.6, 131.1, 125.4, 124.7, 88.5, 83.3, 70.2, 39.8, 38.5, 38.3, 36.9, 32.2, 28.1, 25.7, 22.9, 17.1; HRMS (ES) *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na$^+$): 299.1623; found: 299.1611; **47** IR (neat) 2955, 2856, 1782, 1458, 1145, 1037, 907 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.88 (br s, 1H), 5.06–5.10 (m, 1H), 4.52–4.56 (m, 1H), 4.36 (dd, $J = 1.3$, 11.3 Hz, 1H), 4.24 (t, $J = 2.5$ Hz, 1H), 2.73 (d, $J = 6.1$ Hz, 2H), 1.93–2.04 (m, 4H), 1.83 (d, $J = 13.9$ Hz, 1H), 1.71 (s, 3H), 1.61 (s, 3H), 1.54 (d, $J = 14.0$ Hz, 1H), 1.23–1.35 (m, 2H), 1.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.4, 133.7, 131.7, 125.4, 124.3, 88.5, 83.5, 70.2, 44.8, 40.4, 37.9, 36.9, 32.0, 25.6, 24.4, 22.2, 17.6; HRMS (ES) *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na$^+$): 299.1623; found: 299.1611.