Synthetic studies toward the PPAP natural products, prolifenones A and B and hyperforin: an Effenberger cyclization approach

Goverdhan Mehta *, Thangavel Dhanbal, Mrinal K. Bera

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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ABSTRACT

A synthetic approach toward the geranylated PPAP natural products, prolifenones A and B, employing Effenberger cyclization as the key step, is delineated. The efficacy of this approach is further expanded through access to an advanced precursor of hyperforin.

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Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a growing family of functionally complex natural products, all based on a bicyclo[3.3.1]nonane-2,4,9-trione core, and occurring in the plants and shrubs of the family Clusiaceae (Guttiferae), which in turn is composed of many genera and species.[1,2] PPAPs are notable for their dense and varied functionalization pattern, mixed biosynthesis based on the polyketide and mevalonate pathways, and wide ranging bioactivity profile.[1,2] Clusianone (1), nemorosone (2), and hyperforin (3), embodying a bicyclo[3.3.1]nonane framework, generously substituted with prenyl groups and exhibiting impressive biological activity are typical examples of PPAPs (Fig. 1).[1a] Considering these attributes, it is hardly surprising that considerable synthetic efforts,[3] including our own,[4] have been directed toward this group of natural products and there have been some noteworthy successes.

More recently, new structural variants among PPAPs, bearing one or more geranyl substituents at different positions, have been
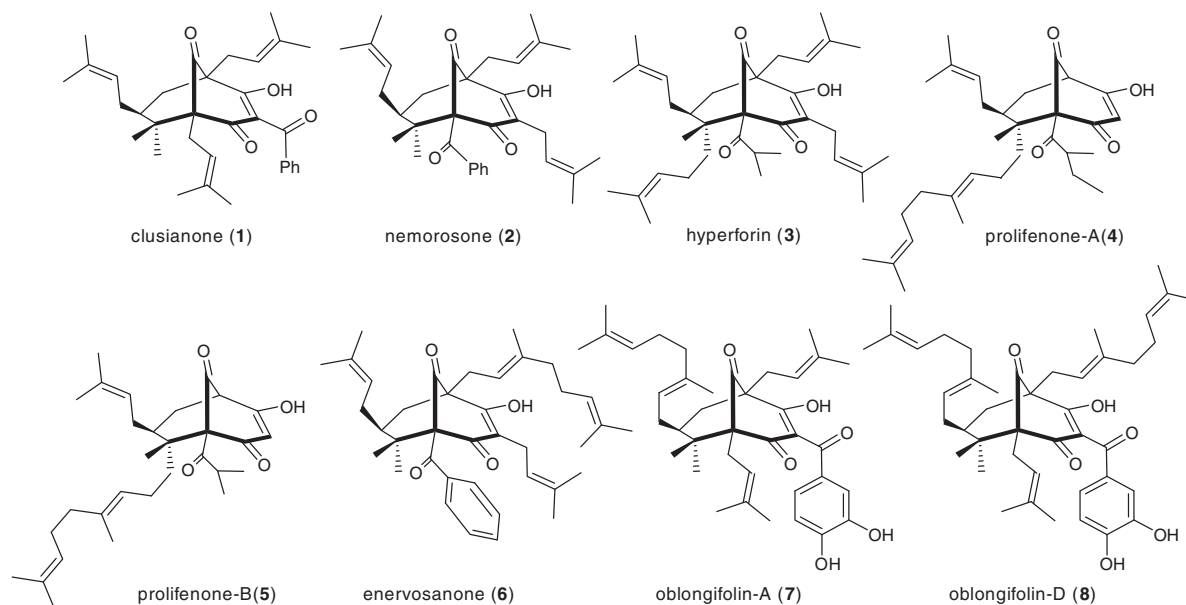

clusianone (1) nemorosone (2) hyperforin (3) prolifenone-A(4)

prolifenone-B(5) enervosanone (6) oblongifolin-A (7) oblongifolin-D (8)

Figure 1.

* Corresponding author. Tel.: +91 4023134848; fax: +91 4023012460.
 E-mail address: gmsc@uohyd.ernet.in (G. Mehta).

unraveled. These include prolifenone A (**4**), prolifenone B (**5**),[2n] enervosanone (**6**), oblongifolin A (7),[2o] and a di-geranylated oblongifolin D (**8**) as significant examples (Fig. 1). These geranylated PPAPs **4**–**8** are attractive targets for total synthesis endeavors, particularly as they display interesting bioactivities.[2] However, no synthetic report directed toward any member of this family has appeared in the literature so far. As part of our ongoing interest in the synthesis of PPAP natural products,[4] we became interested in the synthesis of these geranylated PPAPs and wanted to harness the efficacy of the Effenberger[5] cyclization (annulation) as the pivotal reaction.[3aa] This choice was dictated by the presence of an enolic 1,3-dicarbonyl moiety in one of the C_3 bridges of the bicyclo[3.3.1]nonane framework of the PPAPs **4**–**8**, and the demonstrated utility of the Effenberger cyclization protocol in the synthesis of the important PPAP natural product clusianone (**1**).[3c,g,i,m]

Among the prototypical geranylated PPAPs, prolifenones A (**4**) and B (**5**) interested us as the setting-up of their C8 quaternary center bearing a homogeranyl chain, in a stereoselective manner, was considered a challenge worth pursuing. In this Letter, we report our initial studies toward accessing the core structure of prolifenones **4** and **5**, employing the Effenberger cyclization, and further extension of this protocol in the context of the closely related PPAP, hyperforin (**3**).

Our proposed approach in the context of the prolifenones **4** and **5** is displayed retrosynthetically (for **5**) in Scheme 1 and hinged on the key Effenberger cyclization[5] on stereodefined **10** to furnish **9**, the penultimate precursor of the natural product, embodying the requisite bicyclo[3.3.1]nonanone framework. The precursor **10** was to be accessed from farnesyl-derived methyl ketone **11** through the intermediacy of the dimedone derivative **12** and cyclohexadione enol ether **13**, Scheme 1.

The first task was to devise a convenient access to the dimedone derivative **12** harboring the key C8 quaternary center. For this purpose, commercial farnesol (**14**) was oxidized to farnesol in a routine manner and addition of methyl lithium led to the homofarnesol **15**, which on further oxidation delivered the farnesyl-derived methyl ketone **11**. Tandem Michael addition–Claisen condensation in **11** with dimethyl malonate led to **16** which delivered, on further decarboxylation, the required dimedone derivative **12**[6] embodying the C8 quaternary center and a homogeranyl chain, Scheme 2.

The dimedone derivative **12** was readily transformed into the ethyl enol ether **17** and kinetically controlled alkylation with
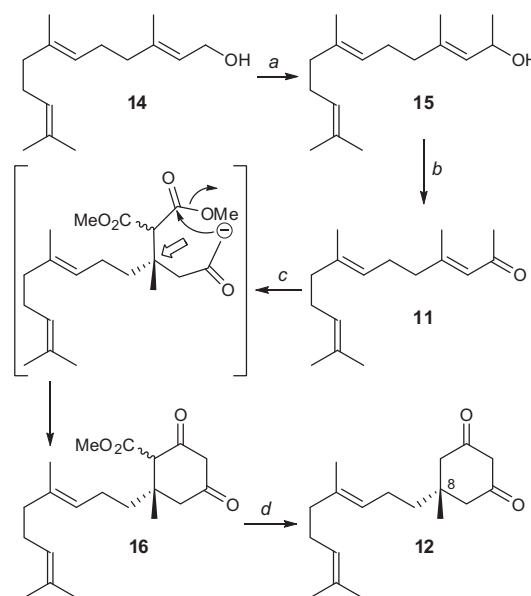
Scheme 2. Reagents and conditions. (a) (i) MnO_2, hexane, 0 °C to rt, 24 h, 82%; (ii) MeLi, Et_2O, −78 °C to 0 °C, 3 h, 89%; (b) MnO_2, hexane, 0 °C to rt, 48 h, 68%; (c) $CH_2(COOMe)_2$, NaOEt, EtOH, 60 °C, 12 h; (d) KOH, EtOH, 60 °C, 72 h, 64% (over two steps).

prenyl bromide furnished a readily separable diastereomeric mixture of **18** and **19**[6] (1:1.1), among which the latter had the required relative stereochemistry of the prenyl and the homogeranyl substituents, Scheme 3. The stereochemistry of **18** and **19** was settled unambiguously through extensive 2D NMR analyses and the key nOes are displayed on their respective structures. Enone transposition of the desired diastereomer **19** via DIBAL-H reduction and acid-mediated elimination of ethanol furnished the transposed enone **20**. Chemoselective reduction of the enone double bond in **20** was accomplished with $NiCl_2$–$NaBH_4$ to furnish **10**,[6] Scheme 3. Cyclohexanone **10** was regioselectively transformed into its TBS–enol ether **21** to set the stage for the contemplated Effenberger annulation.

Exposure of **21** to malonyl chloride, essentially following Stoltz's conditions,[3aa] and subsequent base hydrolysis furnished stereoselectively the bicyclo[3.3.1]nonanone scaffold **9**, bearing the enolic 1,3-dicarbonyl moiety, as a mixture of regioisomers, Scheme
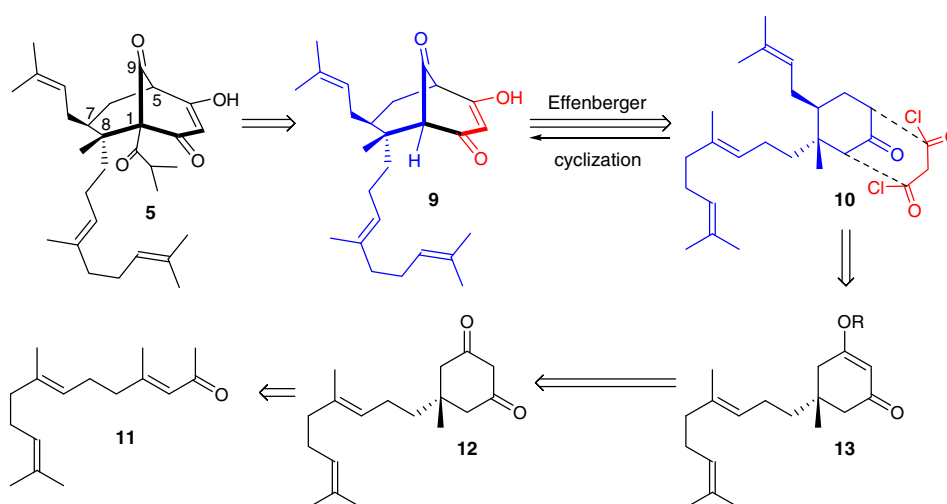
Scheme 1. Retrosynthetic analysis of prolifenone B (**5**) from farnesyl-derived methyl ketone **11**.
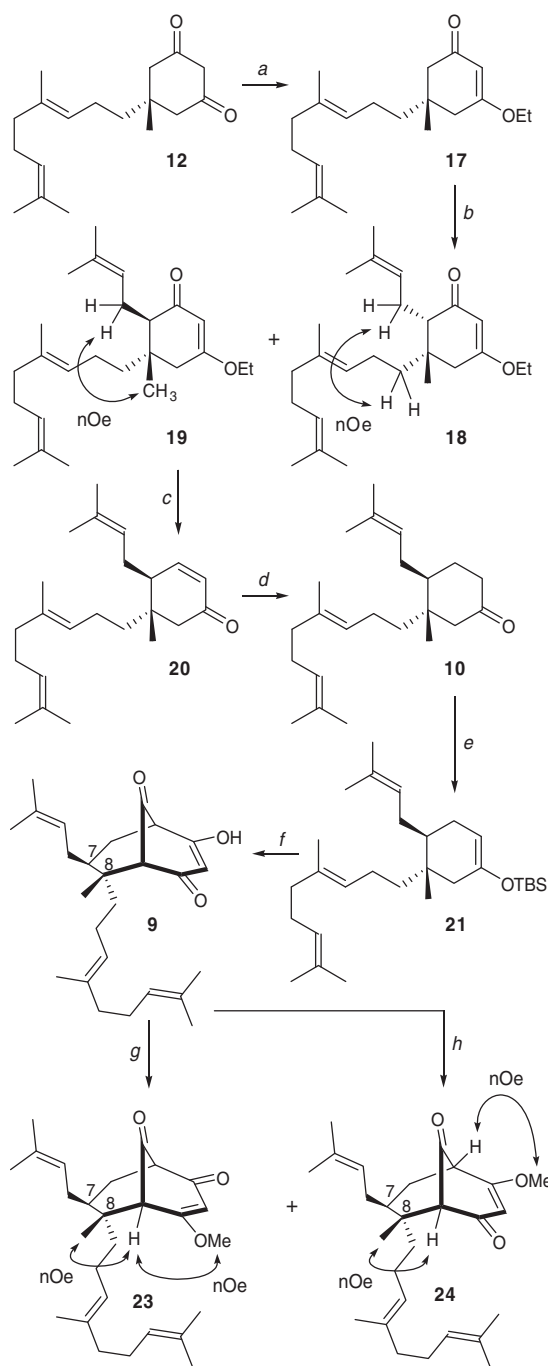
Scheme 3. Reagents and conditions: (a) TiCl$_4$, EtOH, 0 °C to rt, 1 h, 86%; (b) LDA, prenyl bromide, −78 °C to 0 °C, 10 h, 92% (**18**:**19** = 1:1.1); (c) (i) DIBAL-H, CH$_2$Cl$_2$, 0 °C, 30 min; (ii) concd HCl, acetone/H$_2$O (20:1), 0 °C, 15 min, 63% (over 2 steps); (d) NiCl$_2$, NaBH$_4$, MeOH, 0 °C to rt, 1 h, 97%; (e) TBSOTf, Et$_3$N, DMAP, 0 °C to rt, 3 h, 93%; (f) CH$_2$(COCl)$_2$, CH$_2$Cl$_2$, KOH, PTC, −20 °C, 24 h, 38%; (g) TMS-CHN$_2$, Et$_2$O, 0 °C, 1 h, 66% (**23**:**24** = 1:1); (h) CH(OMe)$_3$, PTSA, MeOH, reflux, 48 h, 45%.

Figure 2.

annulation of TBS–enol ether **21**, could be converted directly into the desired regioisomer **24** on exposure to trimethyl orthoformate and *p*-toluenesulfonic acid in refluxing methanol. With the acquisition of **24** with requisite C7 and C8 relative stereochemistry, we had reached the penultimate stage in our synthesis of the prolifenones **4** and **5**, and the task that remained was the introduction of the requisite C1 substituent. However, our initial efforts in this direction through direct bridge-head substitution at C1, following appropriate precedence,[3m,p] were consistently unsuccessful, however, some tactical modifications are being explored currently.

Having successfully demonstrated the preparation of the prolifenone framework lacking the C1 substituent, we next explored the efficacy of the Effenberger cyclization in the related context of hyperforin (**3**). Toward this objective, cyclohexanone **25**, recently reported by us,[4e] and having a preinstalled quaternary center with a homoprenyl substituent, appeared to be a suitable precursor. The TBS- protected enol ether **26** of **25**, on exposure to malonyl chloride underwent smooth and stereoselective Effenberger cyclization to furnish the bicyclo[3.3.1]nonanone scaffold **27** bearing an enolic 1,3-dicarbonyl moiety, as a mixture of regioisomers. The stereochemical outcome and malonyl group addition from the α-face once again mirror the observation made in the case of the prolifenones (vide supra). Brief exposure of **27** to TMS-diazo-

Scheme 4. Reagents and conditions: (a) TBSOTf, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 3 h, 95%; (b) CH$_2$(COCl)$_2$, KOH, CH$_2$Cl$_2$, H$_2$O, −10 °C, 24 h; (c) TMS-CHN$_2$, Et$_2$O, 0 °C, 1 h, 25% (over two steps) (**28**:**29** = 1:1); (d) CH(OMe)$_3$, PTSA, MeOH, 50 °C, 48 h, 66%; (e) LDA, prenyl bromide, THF, −78 °C, 1 h, 61%.

3. The origin of the stereoselectivity during the Effenberger annulation on **21** leading to **9** may be attributed to the stereoinductive effect of the axial methyl group which hinders the β-face as shown in structure **22** (Fig. 2). Exposure of **9** to TMS-diazomethane led to two readily separable regioisomeric methyl enol ethers **23** and **24**,[6] Scheme 3. The two regioisomeric methyl enol ethers were differentiated on the basis of 2D NMR studies, more notably through the key nOes depicted on structures **23** and **24**. It was further observed that the regioisomeric mixture **9**, obtained from the Effenberger
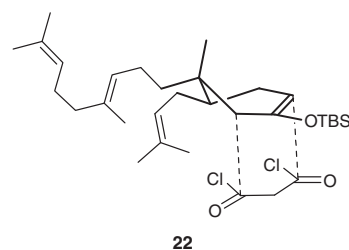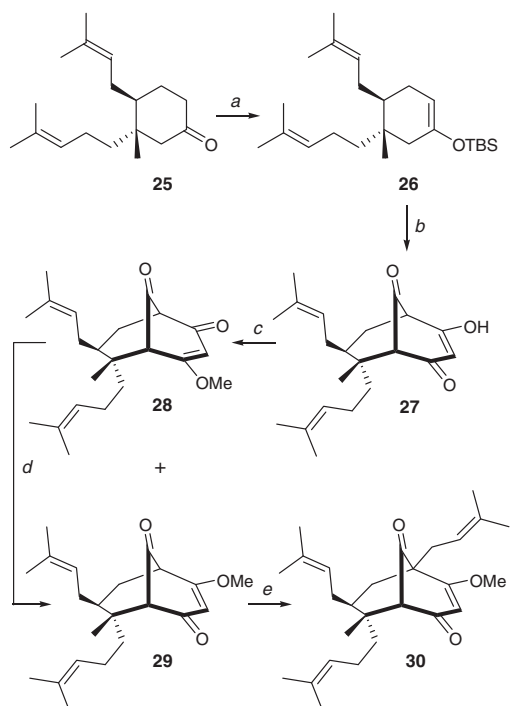
methane led to a separable mixture (1:1) of the enol ethers **28** and **29**,[6] Scheme 4. When equilibrated with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid in refluxing methanol, the mixture of **28** and **29**, or **28** alone was converted into the thermo-dynamically more stable **29**, Scheme 4. Finally, the more stable 1,3-dicarbonyl-derived enol methyl ether **29** was subjected to prenyl-ation in the presence of LDA to furnish **30**,[6] an advanced interme-diate in quest for the natural product hyperforin, Scheme 4. The present approach to **30**, only requiring further introduction of the C1 and C3 substituents, should pave the way for developing a short synthesis of hyperforin.

In conclusion, we have demonstrated the utility of an Effenber-ger cyclization-based approach in the stereoselective synthesis of the penultimate precursor of the geranylated PPAPs, prolifenones A and B. The efficacy of this tactic has been further demonstrated through a short access to an advanced intermediate of hyperforin.

Acknowledgments

References and notes

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6. All new compounds reported here are racemic and characterized on the basis of spectroscopic data (IR, ^{1}H, ^{13}C NMR and HRMS). Compound **12**: IR (neat): ν_{max} 1588, 1576 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.06–5.02 (m, 2H), 3.34 (s, 2H), 2.60 (1/2ABq, *J* = 14 Hz, 2H), 2.48 (1/2ABq, *J* = 14 Hz, 2H), 2.05–1.93 (m, 6H), 1.67 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.42–1.22 (m, 2H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.76 (2C), 135.99, 131.45, 124.11, 123.01, 57.51, 52.46, 44.64, 41.17, 39.58, 33.59, 26.57, 25.66, 25.05, 22.19, 17.65, 15.92. HRMS (ES): *m/z* calcd for C$_{18}$H$_{28}$O$_2$Na (M+Na): 299.1987, found: 299.1985. Compound **19**: IR (neat): ν_{max} 1660, 1614 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.25 (s, 1H), 5.20–5.16 (m, 1H), 5.07–5.03 (m, 2H), 3.76 (q, *J* = 6.9 Hz, 2H), 2.37–1.93 (m, 12H), 1.68 (s, 6H), 1.60 (s, 6H), 1.57 (s, 3H), 1.43–1.41 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 202.05, 174.00, 135.31, 131.65, 131.37, 124.24, 123.91, 123.22, 100.80, 64.04, 55.32, 40.32, 39.64, 39.59, 37.83, 26.63, 25.78, 25.68, 24.56, 22.26, 22.16, 17.80, 17.67, 15.92, 14.15. HRMS (ES): *m/z* calcd for C$_{25}$H$_{40}$O$_2$ (M+H): 373.3106, found: 373.3114. Compound **10**: IR (neat): ν_{max} 1716, 1450 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.12–5.06 (m, 3H), 2.38–2.18 (m, 5H), 2.12–1.96 (m, 8H), 1.71 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 6H), 1.23–1.54 (m, 2H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 212.73, 135.27, 132.62, 131.37, 124.23, 124.01, 123.36, 52.52, 42.70, 41.35, 40.93, 40.84, 39.66, 27.45, 27.27, 26.65, 25.84, 25.68, 21.75, 20.05, 17.88, 17.67, 15.94. HRMS (ES): *m/z* calcd for C$_{23}$H$_{38}$ONa (M+Na): 353.2820, found: 353.2814. Compound **23**: IR (neat): ν_{max} 1737, 1659, 1599 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.73 (s, 1H), 5.10–5.02 (m, 2H), 4.97–4.95 (m, 1H), 3.76 (s, 3H), 3.15 (br s, 1H), 3.10 (s, 1H), 2.26–1.86 (m, 8H), 1.72–1.53 (m, 4H), 1.68 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H), 1.17–1.09 (m, 1H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.38, 195.64, 175.57, 135.28, 133.37, 131.40, 124.19, 123.88, 122.15, 105.96, 61.44, 61.06, 56.61, 44.57, 39.68, 38.92, 38.56, 33.55, 28.09, 26.66, 25.78, 25.68, 21.51, 17.88, 17.68, 17.49, 15.89. HRMS (ES): *m/z* calcd for C$_{27}$H$_{40}$O$_3$Na (M+Na): 435.2875, found: 435.2864. Compound **24**: IR (neat): ν_{max} 1739, 1657, 1606 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.68 (s, 1H), 5.12–5.07 (m, 2H), 4.96 (m, 1H), 3.77 (s, 3H), 3.13 (d, *J* = 4 Hz, 1H), 3.10 (s, 1H), 2.46–2.38 (m, 1H), 2.19–2.15 (m, 1H), 2.09–2.04 (m, 3H), 1.98–1.95 (m, 2H), 1.88–1.85 (m, 1H), 1.73–1.70 (m, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.51–1.52 (m, 1H), 1.35–1.31 (m, 1H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.58, 194.09, 175.53, 135.33, 133.21, 131.22, 124.41, 124.02, 122.33, 105.43, 69.41, 56.85, 53.04, 45.71, 39.73, 39.58, 38.47, 32.05, 27.50, 26.72, 25.80, 25.67, 21.49, 17.90, 17.66, 17.51, 15.95. HRMS (ES): *m/z* calcd for C$_{27}$H$_{40}$O$_3$Na (M+Na): 435.2875, found: 435.2878. Compound **28**: IR (Neat): ν_{max} 1737, 1660, 1599 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.74 (s, 1H), 5.05–4.95 (m, 2H), 3.77 (s, 3H), 3.15 (s, 1H), 3.10 (s, 1H), 2.21–2.15 (m, 4H), 1.89–1.84 (m, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.54 (s, 3H), 1.23–1.06 (m, 3H), 0.91 (s, 3H), 0.89–0.84 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.43, 195.68, 175.60, 133.39, 131.70, 124.00, 122.12, 105.95, 61.39, 61.04, 56.65, 44.54, 38.92, 38.54, 33.52, 28.06, 25.79, 25.73, 21.61, 17.90, 17.58, 17.47. HRMS (ES): *m/z* calcd for C$_{22}$H$_{33}$O$_3$ (M+H): 345.2429, found: 345.2427. Compound **29**: IR (Neat): ν_{max} 1737, 1654, 1604 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.68 (s, 1H), 5.11–4.96 (m, 2H), 3.77 (s, 3H), 3.13 (br s, 1H), 3.09 (s, 1H), 2.44–2.40 (m, 1H), 2.16–2.06 (m, 3H), 1.88–1.78 (m, 1H), 1.68 (s, 9H), 1.56 (s, 3H), 1.35–1.25 (m, 2H), 0.88 (s, 3H), 0.89–0.85 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.66, 194.14, 175.57, 133.24, 131.78, 124.18, 122.30, 105.43, 69.37, 56.87, 53.03, 45.71, 39.56, 38.47, 32.03, 27.49, 25.81, 25.73, 21.60, 17.93, 17.65, 17.48. HRMS (ES): *m/z* calcd for C$_{22}$H$_{33}$O$_3$ (M+H): 345.2429, found: 345.2427. Coumpound **30**: IR (Neat): ν_{max} 1732, 1656, 1598 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.71 (s, 1H), 5.09–5.06 (m, 1H), 4.98–4.95 (m, 2H), 3.74 (s, 3H), 3.14 (s, 1H), 2.48–2.34 (m, 3H), 2.17–2.11 (m, 1H), 1.95–1.84 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.54–1.38 (m, 2H), 1.29–1.18 (m, 2H), 0.85 (s, 3H), 0.89–0.81 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 207.05, 193.84, 177.39, 133.66, 133.12, 131.67, 124.28, 122.49, 119.36, 106.23, 70.39, 56.83, 56.74, 45.88, 40.71, 39.20, 38.49, 29.63, 27.59, 25.87, 25.82, 25.72, 21.71, 17.95, 17.89, 17.67, 17.60. HRMS (ES): *m/z* calcd for C$_{27}$H$_{40}$O$_3$Na (M+Na): 435.2875, found: 435.2871.