

A stereodefined approach towards the bicyclo[3.3.1]nonan-9-one core of the phloroglucin natural products guttiferone A and hypersampsonse F

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Abstract

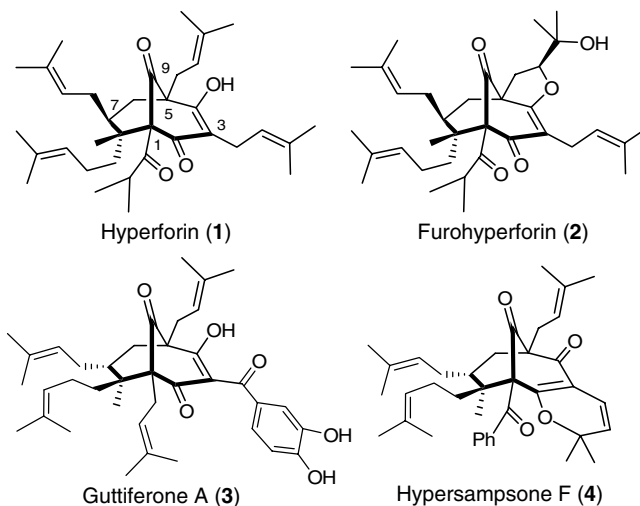
An approach towards the highly functionalized bicyclo[3.3.1]nonan-9-one core present in the phloroglucin natural products guttiferone A and hypersampsonse F is disclosed in which the key C7 and C8 stereogenic centres have been successfully installed.

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Polycyclic polyprenylated acyl phloroglucinols (PPAPs) are a growing class of complex natural products that embody a basic bicyclo[3.3.1]nonan-9-one framework with varied substitution and stereochemical patterns.^{1,2} A notable feature of the PPAPs is the generous distribution of isoprenoid fragments on the polyketide derived core structure and the wide ranging bioactivity profile exhibited by many members of this family. An important sub-group among PPAPs is represented by hyperforin **1**,^{2a} believed to be responsible for much of the antidepressant activity of *Hypericum perforatum* (St. John's wort). In structural terms, hyperforin **1** has a prenyl group at C7 and a quaternary centre at C8 bearing a homoprenyl moiety in a well defined stereochemical disposition. Indeed setting-up this stereochemistry is a challenge from total synthesis perspectives.

Several other phloroglucins such as furohyperforin **2**^b share the C7, C8 stereodisposition with hyperforin **1**, but, there are other siblings including guttiferone A **3** (from *Symphonia globulifera*, Guttiferae)^{2c,1} and hypersampsonse F **4** (from *Hypericum sampsonii*, Guttiferae),^{2f} which display diversified stereochemical orientation at these two stereocentres. Thus, the C7 prenyl (*exo*) and C8 homoprenyl (*endo*) are *trans* in **1** and **2**, but quite interestingly, in gutti-

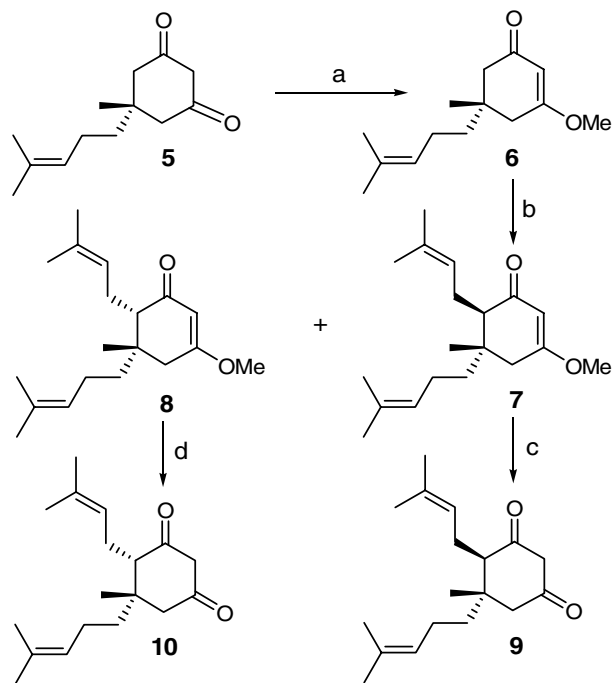
ferone A **3** and hypersampsonse F **4**, the C7 prenyl is *endo* and the C8 homoprenyl is *exo*, although their *trans* relationship is retained. Such subtle variation in stereochemistry at remote C7 and C8 stereogenic centres is quite challenging to negotiate from a synthetic point of view. Herein, we report a synthetic approach that addresses the issue of the C7, C8 stereochemistry and enables access to the core structures present in guttiferone A **3** and hypersampsonse F **4**. This constitutes the first endeavor towards this sub-group of complex, bioactive phloroglucin natural products.^{3,4}



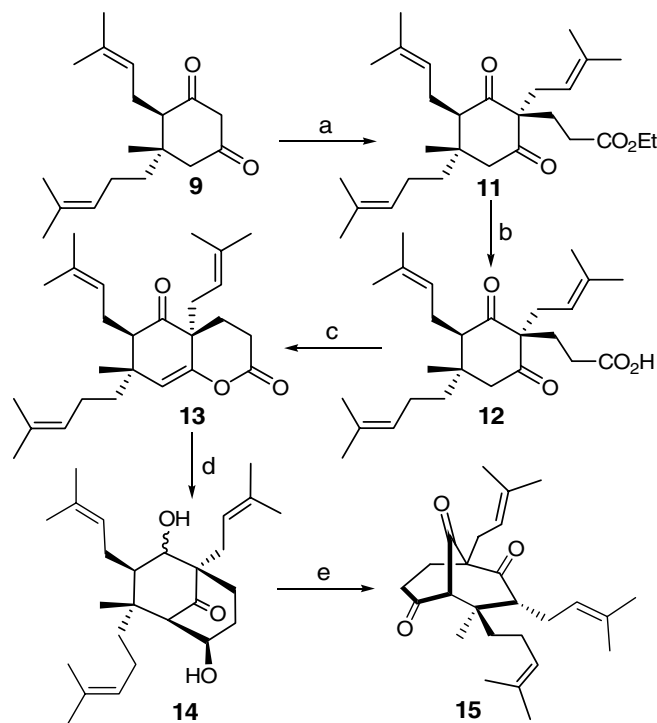
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Our synthetic approach towards guttiferone A **3** and hypersampsonone F **4** emanated from the readily available racemic dimedone analogue **5**, in which the key homo-prenyl group bearing C8 quaternary centre is pre-installed and whose facile synthesis from commercially available citral has been outlined in the accompanying paper. The 1,3-dicarbonyl moiety in **5** was readily elaborated to methyl enol ether **6**⁵ and further prenylation under kinetically controlled conditions led to a diastereomeric mixture of enol ethers **7**⁵ and **8**⁵ (1:1.2), Scheme 1. As anticipated, there was only marginal diastereoselection during this alkylation but the two stereogenic centres corresponding to C7 and C8 of the target structures were now duly installed. Acid mediated hydrolysis of **7** and **8** led to the readily separable 1,3-diketones **9** and **10**, respectively.⁵

Diastereomer **9** was subjected to one-pot, DBU promoted tandem alkylations with 3-bromoethyl propionate and prenyl bromide to furnish penta-alkylated 1,3-cyclohexanedione **11**⁵ as a single diastereomer, Scheme 2. This was a very pleasing outcome as we had envisaged stereo-selection through 1,3-stereoinduction by the bystander prenyl group. The prenyl group in **9** directs the sequential alkylations from the opposite β -face and the order in which the tandem protocol is implemented determines the stereochemical outcome. In this case, realizing the requisite C7, C8 stereochemistry of the target guttiferone A **3** mandated that **9** was first subjected to propionate alkylation followed by prenylation, Scheme 2. Ester hydrolysis of **11** to **12** and enol-lactonization delivered enol lactone **13**⁵ to set the stage for executing the retro-aldol–aldol protocol to deliver



Scheme 1. Reagents and conditions: (a) TiCl_4 , MeOH, $0^\circ\text{C} \rightarrow \text{rt}$, 1 h, 90%; (b) LDA, $\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$, THF, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 12 h, 90% (**7**:**8** = 1:1.2); (c) concd HCl, acetone, H_2O , rt, 12 h, 83%; (d) concd HCl, acetone, H_2O , rt, 12 h, 85%.



Scheme 2. Reagents and conditions: (a) (i) 3-bromoethyl propionate, DBU, THF, rt, 3 h; (ii) $\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$, DBU, THF, rt, 3 h, 45% (over two steps); (b) concd HCl, acetone, H_2O , 50°C , 12 h, 87%; (c) NaOAc, Ac_2O , 140°C , 1 h, 70%; (d) DIBAL-H, DCM, 0°C , 2 h, 41%; (e) PCC, DCM, $0^\circ\text{C} \rightarrow \text{rt}$, 1 h, 70%.

the bicyclo[3.3.1]nonanone framework. Towards this end, enol lactone **13** was reduced with DIBAL-H to trigger the desired structural rearrangement and furnish **14** with concurrent reduction of the ketone carbonyl. PCC oxidation of the diol readily furnished tricyclic compound **15**⁵ endowed with the core bicyclic framework of guttiferone A **3** and hypersampsonone F **4** with requisite C7, C8 stereochemistry, Scheme 2. To fully secure the stereochemical assignment in **15**, its precursor enol lactone **13** was subjected to controlled DIBAL-H reduction to furnish a crystalline hydroxyl-dione **16** whose crystal structure was determined,⁶ Figure 1.

Attention was now turned to diastereomer **10** and this was subjected to the same protocol as **9** to generate the bicyclo[3.3.1]nonan-9-one framework with predictable and potentially useful outcome as displayed in Scheme 3. Thus, tandem alkylations of **10** with 3-bromoethyl propionate and prenyl bromide in the presence of DBU proceeded with the expected 1,3-stereoinduction to furnish a single diastereomer **17**, Scheme 3. The pre-existing α -prenyl group in the present case ensured the delivery of the second prenyl group from the β -face to afford **17**.⁵ Ester hydrolysis of **17** to carboxylic acid **18** was routine but further enol-lactonization in this case proved problematic. After some trials, enol-lactone **19** could be obtained but this step needs to be refined and improved further. Enol-lactone **19**⁵ was subjected to DIBAL-H reduction to trigger the retro-aldol/aldol cyclization process. In the event, the anticipated

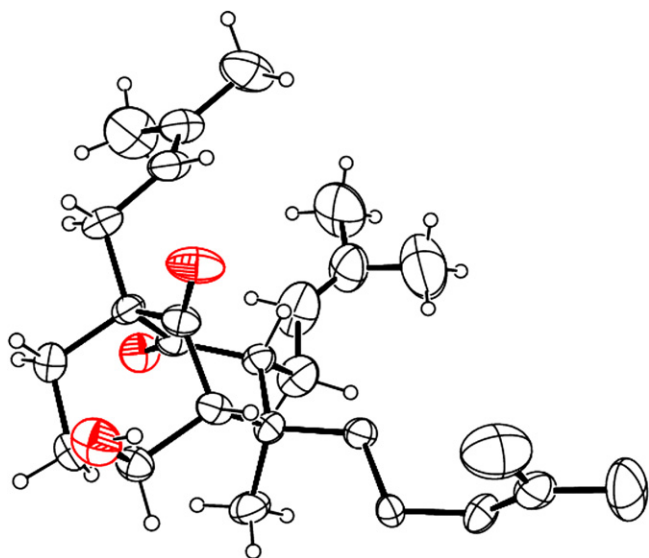
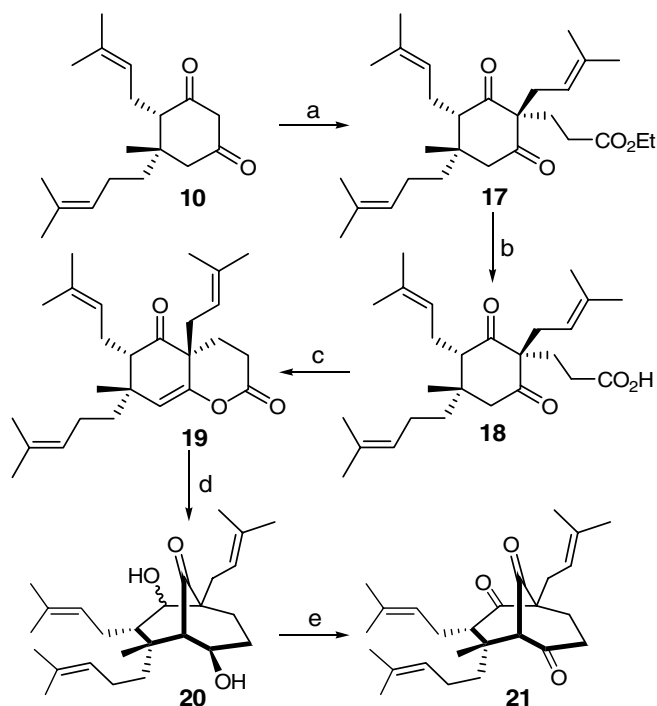


Fig. 1. The ORTEP diagram of hydroxyl-dione **16**, obtained upon controlled DIBAL-H reduction of **13**. Displacement ellipsoids of all non-hydrogen atoms have been drawn at 30% probability level. Hydrogen atoms bonded to the disordered C8 homoprenyl group have not been shown.



Scheme 3. Reagents and conditions: (a) (i) 3-bromoethyl propionate, DBU, THF, rt, 3 h; (ii) Me₂C=CHCH₂Br, DBU, THF, rt, 3 h, 40% (over two steps); (b) concd HCl, acetone, H₂O, 50 °C, 12 h, 87%; (c) NaOAc, Ac₂O, 140 °C, 1 h, 55%; (d) DIBAL-H, DCM, 0 °C, 2 h, 40%, (e) PCC, DCM, 0 °C→rt, 1 h, 65%.

bicyclo[3.3.1]nonane diol mixture **20** was realized, Scheme 3. PCC oxidation of **20** delivered the bicyclic triketone **21**⁵ in which the C7 prenyl and C8 homoprenyl groups were both *endo*- and *cis*-disposed. This unusual stereo-

chemical arrangement is quite interesting and has yet to be encountered among the phloroglucin natural products.

In summary, we have delineated a concise strategy towards the polyprenylated bicyclo[3.3.1]nonan-9-one core present in guttiferone A **3** and hypersampsonse F **4** in which the installation of the key C7, C8 substituents with requisite stereochemistry has been realized. These results, in conjunction with those described in the preceding communication in the context of hyperforin, set the stage for total synthesis endeavors towards this class of exotic natural products.

Acknowledgements

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5. All new compounds reported here are racemic and were fully characterized on the basis of their IR, ^1H NMR, ^{13}C NMR and mass spectral data. Selected spectral data for key compounds: **6**: IR (neat): ν_{max} 1658, 1612 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.36 (1H, s), 5.09–5.04 (1H, m), 3.69 (3H, s), 2.43–2.17 (4H, m), 1.97–1.92 (2H, m), 1.67 (3H, s), 1.59 (3H, s), 1.41–1.36 (2H, m), 1.05 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 199.4, 176.8, 131.8, 123.9, 100.5, 55.7, 49.2, 41.5, 41.0, 35.2, 25.7, 24.7, 22.4, 17.6; HRMS (ES): m/z calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Na}$: 245.1517 ($\text{M}+\text{Na}$) $^+$, found: 245.1515. Compound **7**: IR (neat): ν_{max} 1660, 1619 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.28 (1H, s), 5.20–5.16 (1H, m), 5.06–5.01 (1H, m), 3.67 (3H, s), 2.37–2.11 (5H, m), 2.04–1.82 (2H, m), 1.68 (3H, s), 1.66 (3H, s), 1.59 (3H, s), 1.58 (3H, s), 1.43–1.37 (2H, m), 0.99 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 201.9, 174.8, 131.7, 124.0, 123.1, 100.4, 55.5, 55.3, 40.3, 39.3, 37.9, 25.7, 25.6, 24.5, 22.3, 22.2, 22.1, 17.8, 17.6; HRMS (ES): m/z calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{Na}$: 313.2144 ($\text{M}+\text{Na}$) $^+$, found: 313.2149. Compound **8**: IR (neat): ν_{max} 1658, 1616 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.25 (1H, s), 5.15–5.05 (2H, m), 3.67 (3H, s), 2.44 (1H, 1/2 ABq, $J = 18.0$ Hz), 2.29–2.20 (1H, m), 2.17–2.05 (3H, m), 1.97–1.89 (2H, m), 1.68 (6H, s), 1.59 (3H, s), 1.57 (3H, s), 1.46–1.28 (2H, m), 1.05 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 202.2, 174.6, 132.1, 131.7, 124.1, 122.2, 100.1, 56.1, 55.5, 39.4, 38.1, 37.2, 25.7, 25.6, 25.3, 24.8, 21.7, 17.7, 17.5; HRMS (ES): m/z calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{Na}$: 313.2144 ($\text{M}+\text{Na}$) $^+$, found: 313.2168. Compound **9**: IR (neat): ν_{max} 1590, 1577 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.12–5.02 (2H, m), 3.38 (2H, br s), 2.69–2.35 (4H, m), 2.45–2.18 (1H, m), 2.05–1.89 (2H, m), 1.68 (6H, s), 1.66 (3H, s), 1.59 (3H, s), 1.49–1.30 (2H, m), 0.84 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 204.6, 203.6, 133.1, 132.4, 123.1, 121.9, 58.0 (2C), 51.5, 40.4, 39.2, 25.8, 25.6, 22.9, 22.2, 21.7, 17.9, 17.6. Compound **10**: IR (neat): ν_{max} 1590, 1577 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.10–4.99 (2H, m), 3.36 (2H, d, $J = 8.4$ Hz), 2.71 (1H, 1/2 ABq, $J = 15.0$ Hz), 2.48–2.27 (4H, m), 1.94–1.88 (2H, m), 1.68 (3H, s), 1.67 (3H, s), 1.65 (3H, s), 1.58 (3H, s), 1.43–1.33 (2H, m), 1.04 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 204.9, 203.4, 133.5, 132.3, 123.3, 121.4, 60.4, 57.2, 51.0, 36.4, 35.9, 25.7, 25.6, 25.2, 23.5, 21.9, 17.8, 17.6; HRMS (ES): m/z calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{Na}$: 299.1987 ($\text{M}+\text{Na}$) $^+$, found: 299.1987. Compound **11**: IR (neat): ν_{max} 1737, 1694 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.06–5.04 (2H, m), 4.88–4.83 (1H, m), 4.09 (2H, q, $J = 7.5$ Hz), 2.97 (1H, 1/2 ABq, $J = 15.3$ Hz), 2.72–2.66 (1H, m), 2.57–2.49 (1H, m), 2.42–1.93 (10H, m), 1.67 (6H, s), 1.65 (6H, s), 1.59 (3H, s), 1.57 (3H, s), 1.49–1.41 (2H, m), 1.21 (3H, t, $J = 7.2$ Hz), 0.65 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 209.3, 208.9, 173.2, 136.5, 132.2, 131.9, 123.2, 123.0, 116.4, 68.7, 60.1, 54.4, 50.0, 40.5, 38.4, 36.3, 29.6, 25.9, 25.8, 25.7, 25.6, 25.4, 22.3, 21.8, 17.9, 17.7, 17.6, 14.1; HRMS (ES): m/z calcd for $\text{C}_{28}\text{H}_{44}\text{O}_4\text{Na}$: 467.3137 ($\text{M}+\text{Na}$) $^+$, found: 467.3136. Compound **13**: IR (neat): ν_{max} 1768, 1716, 1681 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.35 (1H, s), 5.09–5.07 (1H, m), 5.00–4.90 (2H, m), 2.87–2.84 (1H, m), 2.64–2.33 (4H, m), 2.03–1.92 (6H, m), 1.69 (6H, s), 1.66 (6H, s), 1.61 (3H, s), 1.56 (3H, s), 1.40–1.21 (2H, m), 0.79 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 209.2, 168.1, 148.8, 136.1, 132.2, 132.1, 123.5, 122.5, 117.9, 117.3, 51.9, 48.9, 40.3 (2C), 34.2, 27.3, 25.9, 25.8, 25.7, 24.6, 23.9, 23.5, 21.2, 17.9, 17.7, 17.6; HRMS (ES): m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{Na}$: 421.2719 ($\text{M}+\text{Na}$) $^+$, found: 421.2717. Compound **15**: IR (neat): ν_{max} 1715, 1700 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.16–5.12 (1H, m), 5.07–5.04 (1H, m), 4.88–4.85 (1H, m), 3.59 (1H, s), 2.50–2.34 (5H, m), 2.25–2.16 (2H, m), 2.05–1.94 (4H, m), 1.69 (3H, s), 1.66 (3H, s), 1.63 (3H, s), 1.57 (3H, s), 1.56 (6H, s), 1.51–1.38 (2H, m), 0.77 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 209.8, 206.2, 204.9, 135.7, 132.9, 132.7, 122.9, 121.6, 117.4, 75.6, 63.6, 59.9, 43.0, 38.6, 37.7, 31.5, 27.6, 25.9, 25.8, 25.7, 22.3, 22.1, 18.5, 17.8, 17.7, 17.6; HRMS (ES): m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{Na}$: 421.2719 ($\text{M}+\text{Na}$) $^+$, found: 421.2733. Compound **17**: IR (neat): ν_{max} 1736, 1693 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.09–5.07 (1H, m), 4.99–4.95 (1H, m), 4.88–4.86 (1H, m), 4.10 (2H, q, $J = 7.5$ Hz), 2.67–2.34 (7H, m), 2.24–2.02 (5H, m), 1.95–1.75 (1H, m), 1.68 (6H, s), 1.66 (3H, s), 1.62 (3H, s), 1.57 (3H, s), 1.55 (3H, s), 1.23 (3H, t, $J = 7.2$ Hz), 1.17 (3H, s), 1.17–1.10 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): δ 208.6, 208.3, 173.1, 136.3, 132.1, 131.8, 123.4, 123.2, 116.3, 68.7, 59.9, 59.1, 49.7, 38.4, 36.7, 34.5, 29.5, 25.8, 25.6, 25.5, 25.4, 25.2, 21.9, 17.8, 17.7, 17.6, 17.3, 14.1; HRMS (ES): m/z calcd for $\text{C}_{28}\text{H}_{44}\text{O}_4\text{Na}$: 467.3137 ($\text{M}+\text{Na}$) $^+$, found: 467.3129. Compound **19**: IR (neat): ν_{max} 1767, 1715 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.38 (1H, s), 5.03–4.89 (3H, m), 2.65–2.58 (4H, m), 2.50–2.36 (2H, m), 2.08–1.96 (5H, m), 1.68 (3H, s), 1.65 (6H, s), 1.64 (3H, s), 1.55 (6H, s), 1.26 (3H, s), 1.22–1.16 (2H, m); ^{13}C NMR (75 MHz, CDCl_3): δ 208.9, 168.2, 148.6, 136.2, 132.2, 131.9, 123.8, 122.9, 117.2, 117.1, 56.5, 48.9, 40.1, 38.4, 34.4, 28.1, 27.4, 25.9, 25.8, 25.6, 24.1, 23.2, 21.6, 18.1, 17.9, 17.6; HRMS (ES): m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{Na}$: 421.2719 ($\text{M}+\text{Na}$) $^+$, found: 421.2715. Compound **21**: IR (neat): ν_{max} 1715, 1699 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.14–5.13 (1H, m), 4.90–4.86 (2H, m), 3.58 (1H, s), 2.47–2.42 (4H, m), 2.37–2.33 (3H, m), 2.08–1.98 (4H, m), 1.65 (3H, s), 1.63 (3H, s), 1.56 (12H, s), 1.42–1.34 (2H, m), 1.31 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 209.5, 205.4, 203.9, 135.4, 133.1, 132.2, 123.5, 121.7, 117.3, 78.8, 63.8, 63.3, 40.2, 38.3, 33.4, 31.3, 29.7, 28.2, 27.3, 25.9, 25.8, 25.7, 23.1, 22.9, 17.7, 17.6; HRMS (ES): m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{Na}$: 421.2719 ($\text{M}+\text{Na}$) $^+$, found: 421.2730.
6. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K. The X-ray generator was operated at 50 kV and 35 mA using $\text{MoK}\alpha$ radiation. The data were collected with an ω scan width of 0.3° . A total of 606 frames per set were collected using SMART in three different settings of φ (0° , 90° and 180°) keeping the sample to detector distance of 6.062 cm and the 2θ value fixed at -25° . The data were reduced by SAINTPLUS; an empirical absorption correction was applied using the package SADABS, and XPREP was used to determine the space group. The structures were solved using SIR92 and refined using SHELXL 97. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, CCDC 664807. Crystal data for compound **16**: $\text{C}_{26}\text{H}_{35}\text{O}_3$, $M = 395.54$, triclinic, space group $P\bar{1}$, $a = 8.996(2)$ Å, $b = 12.056(3)$ Å, $c = 12.660(3)$ Å, $\alpha = 71.812(4)^\circ$, $\beta = 84.176(4)^\circ$, $\gamma = 69.777(4)^\circ$, $V = 1223.9(5)$ Å 3 , $Z = 2$, $\rho_{\text{calcd}} = 1.073$ g cm^{-3} , $F(000) = 430$, $\mu = 0.068$ mm $^{-1}$, $T = 291$ K, number of l.s. parameters = 300, $R = 0.0923$, $R_w = 0.2494$, GOF = 1.021 for 2721 reflections with $I > 2\sigma(I)$.