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Synthetic studies towards the phloroglucin natural product hyperforin: construction of the fully prenylated bicyclic core

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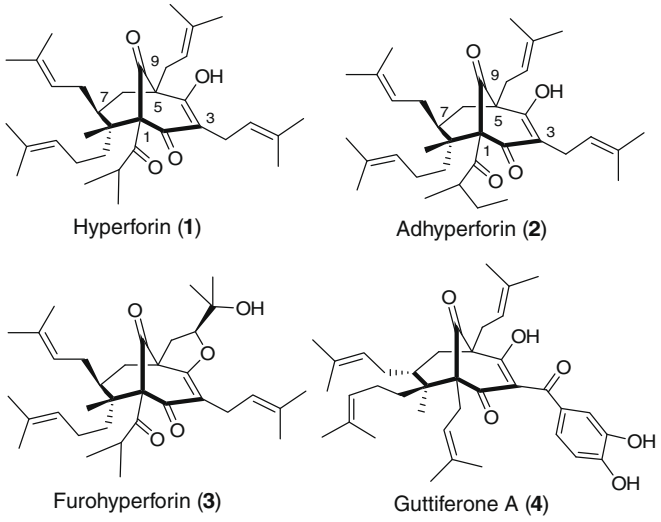
ABSTRACT

An approach towards the highly functionalized bicyclo[3.3.1]nonan-9-one core of the complex PPAP-based natural product hyperforin, with the full complement of prenyl substituents in required stereo-disposition, is delineated.

Hyperforin **1**, the major bioactive constituent of *Hypericum perforatum* (St. John's wort), belongs to a small, but rapidly growing class of complex natural products commonly referred to as polycyclic polyprenylated acyl phloroglucinols (PPAPs).[1,2c] In structural terms, PPAP natural products embody a highly oxygenated and densely substituted bicyclo[3.3.1]nonan-9-one framework with subtle stereochemical variations.[1,2] A distinctive feature of the PPAPs is the copious distribution of isoprenoid fragments on its polyketide-derived core bicyclic structure and the wide-ranging bioactivity profile exhibited by many members of this family. Hyperforin **1** is a representative of an important sub-group (see structures **1–4**, Scheme 1) among PPAPs.

A remarkable feature of hyperforin **1** is its broad bioactivity profile.[3,4] While the ability of **1** as a reuptake inhibitor of various neurotransmitters, and therefore as an antidepressant, is well recognized,[4a,d] its activity against MRSA is also quite impressive.[4e] The activity of **1** as an antiviral agent against HIV/AIDS and hepatitis C is also under investigation. Very recently, hyperforin and its derivatives have been shown to exhibit antimalarial activity[4f] against *Plasmodium falciparum* and inhibit human sirtuins SIRT1 and SIRT2.[4g] These exceptional and diverse bioactivity attributes[3,4] make hyperforin **1** an interesting compound for generating therapeutic leads, probing biomolecular mechanisms and analogue design.

For reasons of structural complexity and biological activity, hyperforin has emerged as a challenging and alluring target for total synthesis. Several synthetic approaches[5] directed towards this natural product, including our own,[5a] have appeared in the recent literature. However, only limited progress[5] towards this target has been made so far, and to our knowledge, no total synthesis has been achieved. In this Letter, we disclose further progress towards hyperforin which has led to the first acquisition of its core structure with the full complement of prenyl substituents with requisite stereochemistry.



Scheme 1. Hyperforin and representative PPAPs.

The major challenge in the synthesis of **1** resides in the installation of a prenyl group at C-7 and a quaternary centre at C-8 bearing a homoprenyl moiety on the bicyclo[3.3.1]nonane framework in a well-defined stereochemical disposition. The retrosynthesis of **1** is depicted in Scheme 2. Accordingly, bicyclic enone **5** was envisaged as an advanced intermediate which could be accessed from the pentaalkylated bicyclic dione **6**. Bridged bicyclic system **6** was to be realized following our previously tested, reconstructive aldol strategy[5a,6] from enol lactone **7**. The enol lactone **7** can be readily obtained from pentaalkylated cyclohexanone derivative **8** through ester hydrolysis followed by enol lactonization. The cyclohexanone

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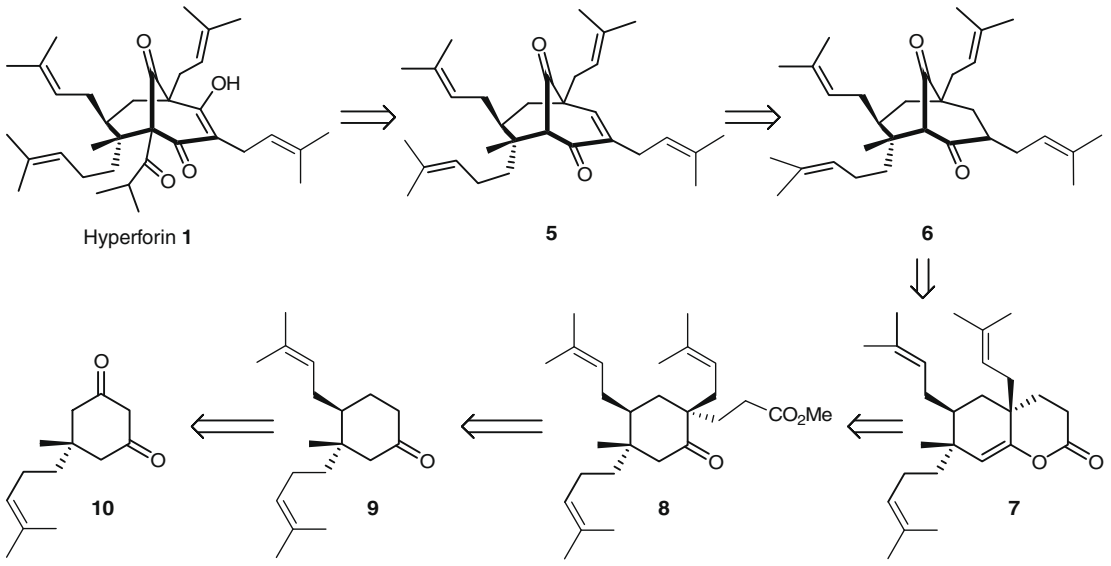
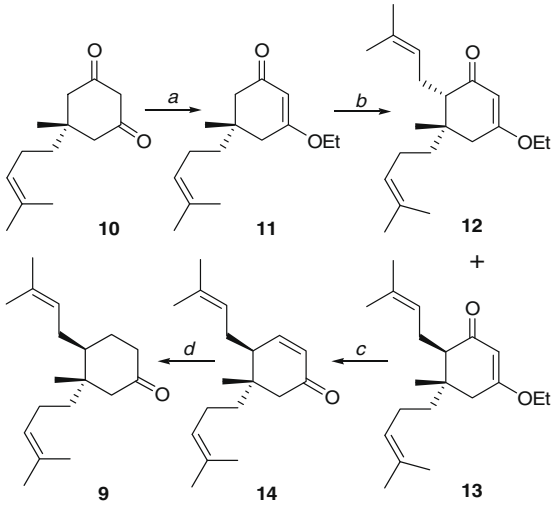


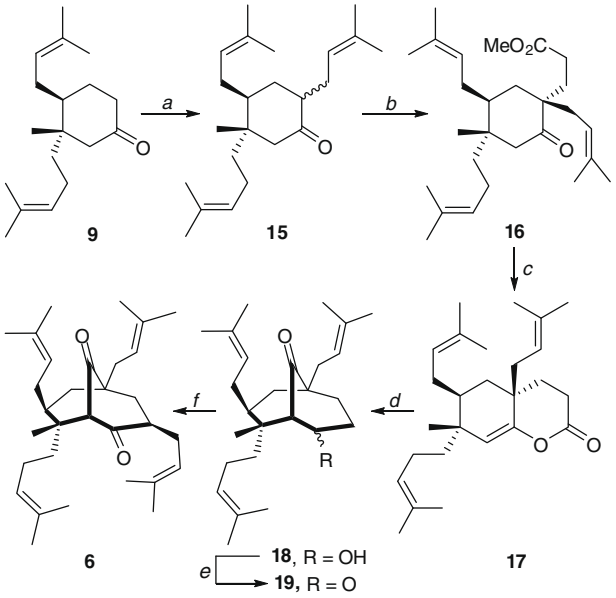
Scheme 2. Retrosynthetic strategy towards hyperforin **1**.

derivative **8** in which the C-7 and C-8 stereogenic centres are duly installed was to be accessed from cyclohexanone derivative **9**. Lastly, **9** was to be elaborated from the versatile building block **10**, Scheme 2.

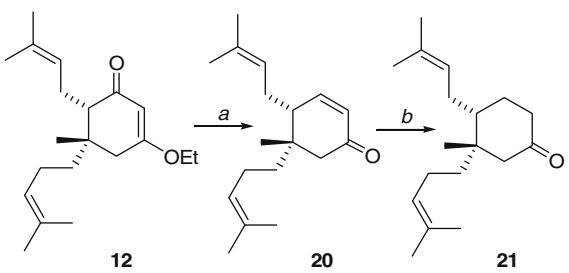
Thus, the recently reported cyclohexa-1,3-dione derivative **10**[5] was elaborated to the ethyl enol ether **11** and further LDA-promoted prenylation under kinetically controlled conditions led to a readily separable mixture of diastereomers **12** and **13** (1.2:1), Scheme 3.[7] Among these two diastereomers, **13** had the requisite C-7 and C-8 relative stereochemistry in the context of the target structure **1**. The prenylated enol ether derivative **13** was reduced with DIBAL-H and the resulting mixture of epimeric allylic alcohols, on exposure to aqueous acid, led to the desired eliminative unmasking of the carbonyl group to deliver the enone **14**, Scheme 3. Chemoselective reduction of the conjugated double bond in **14** with nickel boride[8] was successfully implemented to afford the key precursor **9**.



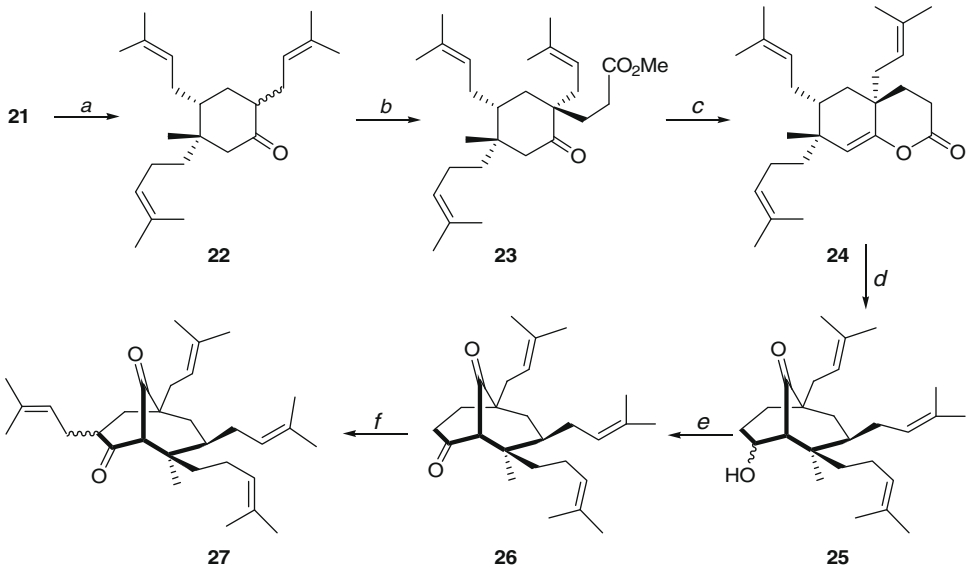
Scheme 3. Reagents and conditions: (a) $TiCl_4$, EtOH, 0 °C–rt, 1 h, 83%; (b) LDA, prenyl bromide, −78 °C to 0 °C, 10 h, 92% (**12**:**13** = 1.2:1); (c) (i) DIBAL-H, CH_2Cl_2, 0 °C, 30 min; (ii) concd HCl, acetone–H_2O (20:1), 0 °C, 15 min, 68% (over 2 steps); (d) $NiCl_2$, $NaBH_4$, MeOH, 0 °C–rt, 1 h, 97%.



Scheme 4. Reagents and conditions: (a) LDA, prenyl bromide, THF, −78 °C, 4 h, 73%; (b) ^tBuOK, $CH_2{=}CHCO_2Me$, C_6H_6, rt, 15 min, 65%; (c) (i) KOH, MeOH, H_2O, 60 °C, 89%; (ii) NaOAc, Ac_2O, 140 °C, 1 h, 69%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 64%; (e) PCC, CH_2Cl_2, rt, 1 h, 87%; (f) LDA, prenyl bromide, THF, −78 °C, 1 h, 73%.



Scheme 5. Reagents and conditions: (a) (i) DIBAL-H, CH_2Cl_2, 0 °C, 30 min; (ii) concd HCl, acetone–H_2O (20:1), 0 °C, 15 min, 71% (over 2 steps); (b) $NiCl_2$, $NaBH_4$, MeOH, 0 °C–rt, 1 h, 92%.



Scheme 6. Reagents and conditions: (a) LDA, prenyl bromide, THF, −78 °C, 4 h, 69%; (b) ^{t}BuOK, CH_2=$CHCO_2Me$, C_6H_6, rt, 15 min, 74%; (c) (i) KOH, MeOH, H_2O, 60 °C, 2 h, 83%; (ii) NaOAc, Ac_2O, 140 °C, 1 h, 68%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 62%; (e) PCC, CH_2Cl_2, rt, 1 h, 91%; (f) LDA, prenyl bromide, THF, −78 °C, 1 h, 70%.

With the acquisition of the cyclohexanone derivative **9**, the crucial issue of setting up the C-5 quaternary centre with appropriate stereochemistry was addressed. LDA-promoted prenylation of **9** was regioselective and furnished the tetraalkylated cyclohexanone **15**, Scheme 4 without any perceptible formation of diprenylated product. Michael addition of the anion derived from **15** to methyl acrylate was stereoselective, directed through the 1,3-stereoinduction effect of the pre-existing C-7 prenyl group, and installed the key quaternary centre to furnish pentaalkylated cyclohexanone derivative **16**[7] as a single diastereomer. Such 1,3-stereoinductions have been observed by us in related systems and the stereochemical outcome has been firmly established on the basis of X-ray and NMR studies.[5a,6a,b] Setting up of this C-5 quaternary centre was crucial and it ensured that the stereochemistry of the C-7 prenyl and the C-8 methyl group would be cis to each other and that they would be exo disposed on the bicyclic framework as was required for the synthesis of hyperforin.

Base-promoted hydrolysis of the ester group in **16** proceeded smoothly and the resulting carboxylic acid was readily elaborated to the bicyclic enol lactone **17** in a routine manner. Access to enol lactone **17** set the stage for executing the key retro-aldol/re-aldol reaction cascade.[6] Thus, reduction of enol lactone **17** with DIBAL-H triggered the structural reconstitution and delivered the bicyclo[3.3.1]nonan-9-one derivative **18** as a mixture of C-2 hydroxy epimers. The epimeric mixture **18** was routinely oxidized with PCC to afford the bicyclic diketone **19**[7] having the key substitution of the hyperforin core. In the bicyclo[3.3.1]nonan-9-one derivative **19**, the stereogenic centres at C-5, C-7 and C-8 were appropriately positioned and the placement of the carbonyl functionalities at C-2 and C-9 as handles for further transformation towards the target was important. The next task was to install the C-3 prenyl side chain by exploiting the C-2 carbonyl functionality in **19**. Thus, LDA-promoted prenylation of bicyclic dione **19** was executed under kinetically controlled conditions to furnish bicyclic dione derivative **6**[7] embodying the full complement of prenyl substituents on the bicyclic core as required in the target structure.

It was considered appropriate to implement the synthetic protocol outlined above on the diastereomer **12** to create stereochemical diversity on the PPAP framework. Towards this end, prenylated ethyl enol ether **12** was reduced with DIBAL-H to a mixture of epimeric allylic alcohols which on acid hydrolysis furnished cyclohexenone derivative **20**. The enone double bond was reduced chemoselectively with nickel boride[8] to the ring saturated cyclohexanone **21**,[7] Scheme 5.

Access to cyclohexanone derivative **21** enabled the tandem prenylation and Michael addition with full stereo- and regiocontrol. Thus, LDA-mediated prenylation of **21** delivered epimeric monoprenylated **22** regioselectively. Michael addition of the anion derived from **22** to methyl acrylate proceeded as contemplated, to set up the C-5 quaternary centre in **23**[7] in a stereoselective fashion, Scheme 6.

Hydrolysis of **23** to the carboxylic acid and conversion to enol lactone **24** set the stage for executing the retro-aldol/re-aldol cascade.[6] Thus, enol lactone **24** was exposed to DIBAL-H to initiate the desired structural rearrangement leading to bicyclo[3.3.1]nonan-9-one derivative **25** as a mixture of C-2 epimeric hydroxy compounds. PCC oxidation of **25** readily furnished bicyclic dicarbonyl compound **26**.[7] LDA-promoted prenylation of **26** under kinetically controlled conditions led to the prenylated products **27**, Scheme 6. Once again it was possible to arrive at the basic PPAP core with full complement of prenyl groups. Interestingly, the stereochemical architecture in **27** with the C-7 and C-8 prenyl arms disposed cis and exo has not been encountered in Nature and is a useful demonstration of how total synthesis can facilitate creation of un-natural diversity around complex natural products.

In summary, the preparation of bicyclic dione **6** with appropriate positioning of all four prenyl/homoprenyl side arms, with correct stereochemistry at C-5, C-7 and C-8, and placement of the C-2 and C-9 carbonyl functionalities for further elaboration, reflects the furthest advance so far towards the target natural product and sets the stage for completion of the synthesis of hyperforin.

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7. All new compounds were fully characterized on the basis of their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Selected spectral data for key compounds: **9**: IR (neat): ν_{max} 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13–5.06 (m, 2H), 2.38–2.19 (m, 5H), 2.07–1.87 (m, 4H), 1.72 (s, 3H), 1.69 (s, 3H), 1.61 (s, 6H), 1.56–1.41 (m, 2H), 1.34–1.22 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.73, 132.62, 131.65, 124.19, 123.34, 52.51, 42.72, 41.37, 40.91, 40.84, 27.45, 27.27, 25.82, 25.66, 21.86, 20.02, 17.88, 17.58; HRMS (ES): *m/z* calcd for $C_{18}H_{30}O$ (M+Na): 285.2194, found: 285.2189. **16**: IR (neat): ν_{max} 1741, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11–5.02 (m, 3H), 3.65 (s, 3H), 2.54 (1/2ABq, J = 10.5 Hz, 1H), 2.27–2.12 (m, 6H), 1.98–1.89 (m, 6H), 1.72 (s, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 6H), 1.44–1.38 (m, 4H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.36, 173.82, 134.31, 132.57, 131.61, 124.22, 123.20, 119.32, 51.68, 50.96, 49.97, 41.22, 41.05, 38.93, 38.29, 32.14, 31.03, 28.69, 27.81, 26.04, 25.86, 25.67, 22.01, 19.33, 17.97, 17.91, 17.62; HRMS (ES): *m/z* calcd for $C_{27}H_{44}O_3$ (M+Na): 439.3188, found: 439.3185. **19:** IR (neat): ν_{max} 1723, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22–5.18 (m, 1H), 5.07–5.03 (m, 2H), 3.19 (s, 1H), 2.75–2.68 (m, 1H), 2.57–2.55 (m, 1H), 2.26–2.08 (m, 6H), 1.95–1.81 (m, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.31–1.16 (m, 2H), 0.91–0.80 (m, 2H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.87, 208.12, 134.50, 133.08, 131.91, 123.97, 122.71, 119.35, 75.10, 49.18, 48.47, 42.71, 42.62, 39.75, 38.86, 35.37, 29.76, 29.46, 26.04, 25.85, 25.69, 22.67, 21.48, 18.19, 17.93, 17.59; HRMS (ES): *m/z* calcd for $C_{26}H_{40}O_2$ (M+Na): 407.2926, found: 407.2922. **6**: IR (neat): ν_{max} 1724, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22–5.18 (m, 1H), 5.08–5.01 (m, 3H), 3.22 (s, 1H), 2.73–2.69 (m, 1H), 2.51–2.49 (m, 1H), 2.24–2.02 (m, 7H), 1.88–1.84 (m, 2H), 1.73 (s, 6H), 1.69 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H), 1.58 (s, 6H), 1.57 (s, 3H), 1.31–1.12 (m, 3H), 0.89–0.79 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.62, 208.11, 134.38, 133.90, 133.00, 131.95, 123.98, 122.79, 120.94, 119.53, 75.64, 50.25, 48.84, 48.26, 42.52, 42.46, 38.93, 37.09, 35.47, 29.81, 29.25, 27.83, 26.06, 25.89, 25.85, 25.69, 21.42, 18.45, 17.97, 17.91, 17.61; HRMS (ES): *m/z* calcd for $C_{31}H_{48}O_2$ (M+Na): 475.3552, found: 475.3549. **21**: IR (neat): ν_{max} 1717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15–5.05 (m, 2H), 2.52–2.19 (m, 4H), 2.07–1.79 (m, 7H), 1.72 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.30–1.11 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.27, 132.60, 131.63, 124.38, 123.60, 51.80, 46.07, 40.99, 40.09, 34.35, 26.98, 26.57, 26.20, 25.81, 25.66, 21.79, 17.85, 17.52; HRMS (ES): *m/z* calcd for $C_{18}H_{30}O$ (M+Na): 285.2194, found: 285.2191. **23**: IR (neat): ν_{max} 1741, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09–5.02 (m, 3H), 3.65 (s, 3H), 2.28–2.11 (m, 7H), 1.97–1.90 (m, 2H), 1.81–1.61 (m, 4H), 1.72 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.59 (s, 9H), 1.51–1.44 (m, 2H), 1.10–1.06 (m, 2H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.80, 173.88, 134.27, 132.53, 131.68, 124.44, 123.62, 119.43, 51.68, 50.92, 49.48, 44.15, 41.20, 38.27, 32.22, 32.06, 31.35, 28.73, 27.86, 26.31, 26.00, 25.85, 25.68, 21.72, 17.99, 17.88, 17.49; HRMS (ES): *m/z* calcd for $C_{27}H_{44}O_3$ (M+Na): 439.3188, found: 439.3189. **26**: IR (neat): ν_{max} 1724, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.21–5.18 (m, 1H), 5.08–5.04 (m, 2H), 3.22 (s, 1H), 2.73–2.66 (m, 1H), 2.57–2.53 (m, 1H), 2.22–2.03 (m, 7H), 1.99–1.92 (m, 1H), 1.85–1.79 (m, 3H), 1.72 (s, 6H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.20–1.12 (m, 2H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.84, 209.25, 134.46, 133.07, 132.22, 123.79, 122.95, 119.34, 73.92, 48.96, 48.09, 44.21, 42.17, 39.58, 35.26, 32.81, 29.89, 28.92, 26.06, 25.86, 25.69, 23.62, 21.23, 17.93, 17.89, 17.53; HRMS (ES): *m/z* calcd for $C_{26}H_{40}O_2$ (M+Na): 407.2926, found: 407.2926.
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