Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1417–1420
Tetrahedron Letters

A concise approach towards the bicyclo[3.3.1]nonan-9-one core present in the phloroglucin natural product hyperforin

Goverdhan Mehta *, Mrinal K. Bera

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

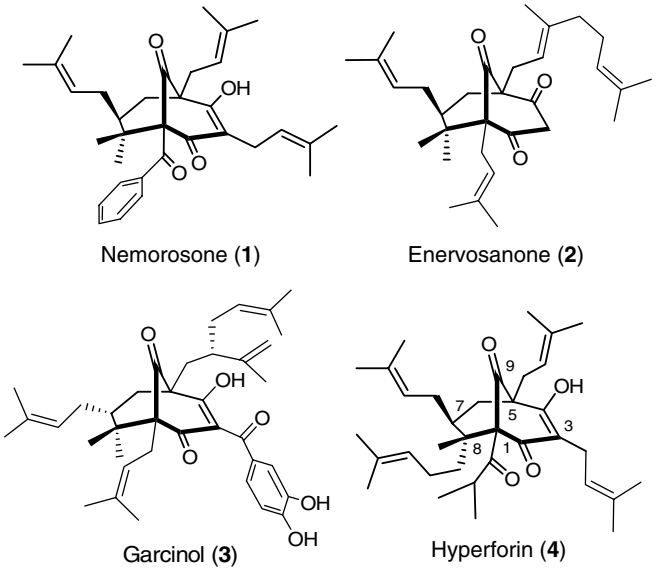
Received 25 October 2007; revised 2 December 2007; accepted 12 December 2007
Available online 14 January 2008

Abstract

An approach towards the bicyclo[3.3.1]nonan-9-one core present in the bioactive phloroglucin natural product hyperforin is delineated in which the key C8 stereogenic quaternary centre is appropriately installed.

A large number of polycyclic polyprenylated acyl phloroglucinol derivatives (PPAPs) with varying levels of structural and stereochemical complexity, from diverse plant sources, have surfaced in the recent chemical literature.[1,2] Among the more prominent examples of this growing family of natural products, based on the bicyclo[3.3.1]nonane framework and generously substituted with prenyl appendages and a dense oxygenation pattern, are nemorosone **1**,[2d,h] enervosanone **2**,[2v] garcinol **3**[2b] and hyperforin **4**[2c] to name a few. Besides their complex architecture and varied functionalization, these pholoroglucinol based natural products display wide range of biological activity including enhanced in vitro choline acetyltransferase (ChAT) activity in P10 rat septal neurons and cytotoxicity against several human cancer cell lines and even antibacterial activity.[1] Thus, it is hardly surprising that PPAPs have emerged as challenging and much sought after targets for total synthesis in recent years.[3–6]

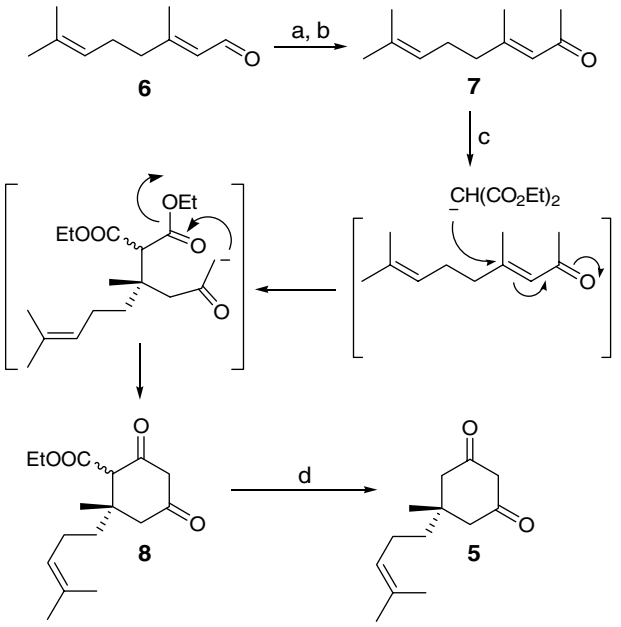
From a structural perspective, the majority of natural PPAPs (such as **1**–**3**) embody a *gem*-dimethyl group at C8 on the bicyclo[3.3.1]nonan-9-one framework and it is mainly this type that has received attention from synthetic chemists.[3–5] However, there are other PPAPs including hyperforin, which bear a stereogenic centre at C8 with a methyl and a homoprenyl substitution at the quaternary centre. This type of natural products poses greater synthetic challenge compared to the C8 *gem*-dimethyl bearing PPAPs. It is hardly surprising therefore that there has been only one synthetic approach reported[6] so far towards hyperforin **4** but which does not address the crucial issue of setting the C8 quaternary centre. Besides its architectural novelty, hyperforin **4** is also exceptional for its bioactivity responses, being a constituent of St. John's wort



* Corresponding author. Tel.: +91 8023600367; fax: +91 8023600283.
E-mail address: gm@orgchem.iisc.ernet.in (G. Mehta).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.065

(*Hypericum perforatum*), a widely used over the counter to fight mild depression, anxiety and schizophrenia.[7] Such remarkable attributes associated with hyperforin **4** make it a very tempting target for total synthesis. As part of our ongoing interest in the synthesis of PPAPs,[4] we were attracted to hyperforin **4** and report here our preliminary results that have resulted not only in the framework construction but also provide a solution to the more vexatious issue of setting-up the C8 quaternary centre.

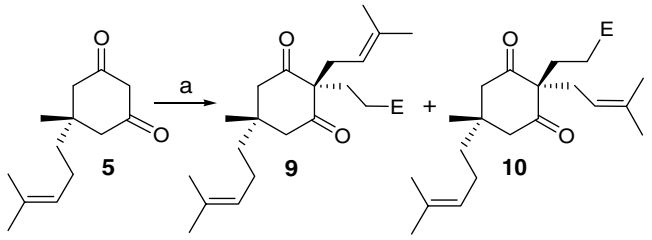


Scheme 1. Reagents and conditions: (a) MeLi, Et_2O, 0 °C, 3 h, 82%; (b) MnO_2, hexane, rt, 12 h, 72%; (c) $CH_2(COOEt)_2$, NaOEt, EtOH, 60 °C, 12 h; (d) KOH, EtOH, 60 °C, 72 h, 58% (over two steps).

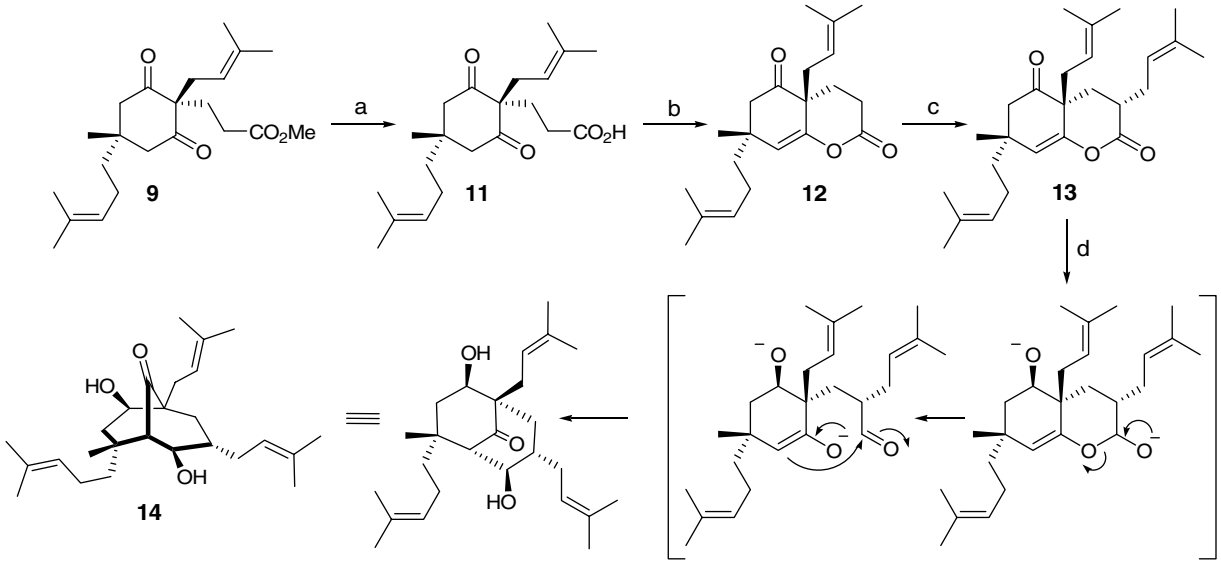
For our synthetic approach towards hyperforin **4**, it was considered prudent to identify a starting material in which the key C8 quaternary centre was pre-installed. Towards this end, the racemic cyclohexane-1,3-dione derivative **5** was identified as the synthon but as it was not reported in the literature, a straightforward multi-gram access from commercially available citral **6** via the homogeranyl ketone **7** was devised, Scheme 1. This involved a tandem Michael reaction–Claisen condensation of **7** with diethyl malonate to deliver **8** and further decarboxylation delivered the requisite **5**.[8]

One-pot tandem Michael addition to methyl acrylate and prenylation of 1,3-diketone **5** in the presence of DBU led to a readily separable mixture of diastereomers **9**[8] and **10** (1:1.2),[8] Scheme 2. Each of the two diastereomers **9** and **10** was further processed to deliver the desired bicyclo[3.3.1]nonan-9-one framework through an enol-lactonization and retro-aldol/aldol cyclization protocol.

Diasteromer **9** was hydrolyzed to carboxylic acid **11** and further elaborated to enol-lactone **12**.[8] At this stage, it was felt useful to introduce an additional prenyl unit that would eventuate at the C3 position in hyperforin **4**. This was



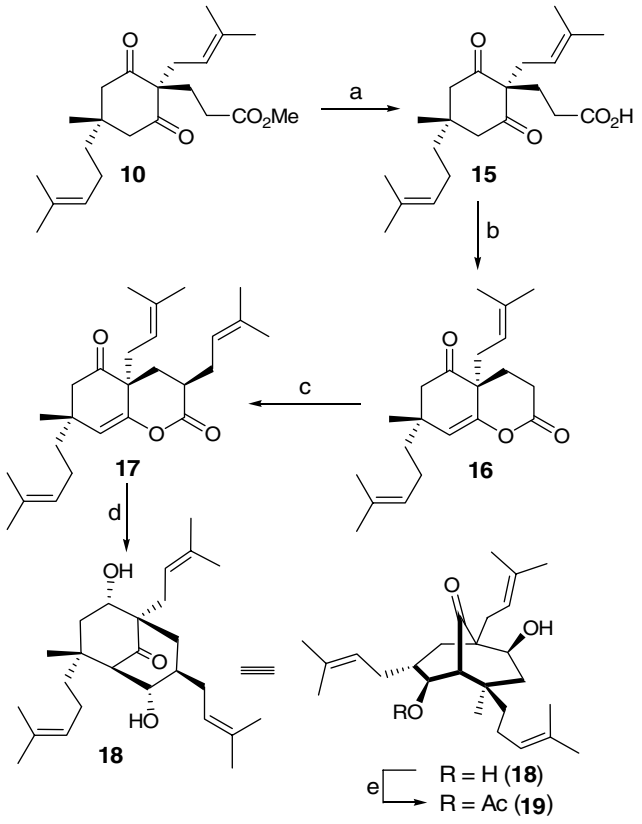
Scheme 2. Reagents and conditions: (a) (i) Methyl acrylate, DBU, THF, rt, 3 h; (ii) $Me_2C{=}CHCH_2Br$, DBU, THF, rt, 3 h, 48% (over two steps) [**9**:**10** = 1:1.2; E ≡ CO_2Me].



Scheme 3. Reagents and conditions: (a) concd HCl, acetone, H_2O, 50 °C, 12 h, 88%; (b) NaOAc, Ac_2O, 140 °C, 1 h, 75%; (c) LDA, $Me_2C{=}CHCH_2Br$, −78 °C, 1 h, 51%; (d) DIBAL-H, DCM, 0 °C, 2 h, 54%.

readily realized through kinetic deprotonation of **12** and a prenyl bromide quench to furnish **13** through 1,3-stereoinduction attributable to the pre-existing bridgehead prenyl group, Scheme 3. Chemoselective DIBAL-H reduction of the lactone moiety in **13** initiated the thermodynamically controlled retro-aldol and re-aldolization cascade to furnish the desired bicyclo[3.3.1]nonan-9-one scaffold **14**[8] as shown in Scheme 3. This was a very satisfying outcome as in **14** we not only had the correctly installed C8 stereogenic centre but also adequate functionality in the two bridges for further elaboration to the target structure **4**.

Next, attention was turned to diastereomer **10** and this was subjected to the same protocol as **9** as depicted in Scheme 4 to generate the bicyclo[3.3.1]nonan-9-one framework. Thus, ester hydrolysis in **10** delivered acid **15**, which was transformed to enol-lactone **16**.[8] Regio- and stereoselective kinetic prenylation in **16** led to **17**. DIBAL-H reduction of **17** triggered the retro-aldol/re-aldolization cascade and led to the anticipated bicyclo[3.3.1]nonan-9-one derivative **18**[8] quite smoothly in which the homoprenyl chain at C8 was in the *exo*-position. Acetylation in **18** was regioselective and furnished the crystalline monoacetate **19**, Scheme 4. A single crystal X-ray structure determination[9] secured its formulation, and by extrapolation, the diastereomeric bicyclo[3.3.1]nonan-9-one derivative **14**. The



Scheme 4. Reagents and conditions: (a) concd HCl, acetone, H_2O, 50 °C, 12 h, 80%; (b) NaOAc, Ac_2O, 140 °C, 1 h, 69%; (c) LDA, $Me_2C{=}CHCH_2Br$, −78 °C, 1 h, 53%; (d) DIBAL-H, DCM, 0 °C, 2 h, 50%; (e) Ac_2O, Et_3N, DMAP, DCM, rt, 1 h, 89%.

exo-orientation of the homoprenyl group in **18** was not an entirely unwelcome outcome as this stereochemical arrangement is also found in Nature and lends flexibility to our overall synthetic approach, which can be exploited in other contexts.[10]

In summary, we have delineated a concise and promising synthetic strategy towards the acquisition of the polyprenylated bicyclo[3.3.1]nonan-9-one core present in the phloroglucin natural product hyperforin in which the key C8 quaternary centre bearing a methyl and homoprenyl group could be installed.

Acknowledgements

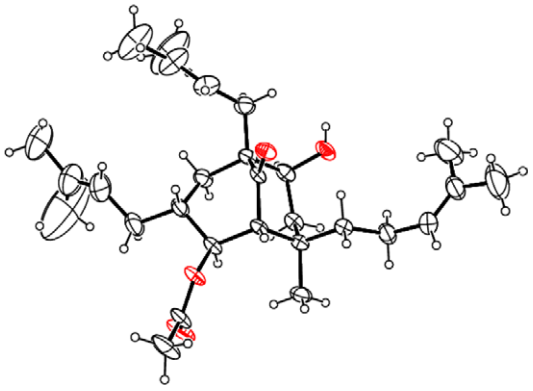
One of us, M.K.B., thanks UGC for the award of a research fellowship. We thank the CCD facility at IISc for the single crystal X-ray diffraction data.

References and notes

1. Review Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963–3986.
2. Selected references: (a) Karanjgoakar, C. G.; Rama Rao, A. V.; Venkataraman, K.; Palmer, K. J. *Tetrahedron Lett.* **1973**, *14*, 4977–4980; (b) Krishnamurthy, N.; Lewis, Y. S.; Ravindranath, B. *Tetrahedron Lett.* **1981**, *22*, 793–796; (c) Baystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, *16*, 2791–2794; (d) de Oliveira, C. M. A.; Porto, M. A.; Brittich, V.; Venkato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427–6430; (e) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947–949; (f) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochemistry* **1998**, *49*, 853–857; (g) de Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochemistry* **1999**, *50*, 1073–1079; (h) Cuesta-Rubio, O.; Velez-Castro, H.; Frontana-Uribe, B. A.; Cárdenas, J. *Phytochemistry* **2001**, *57*, 279–283; (i) Shan, M. D.; Hu, L. H.; Chen, Z. L. *J. Nat. Prod.* **2001**, *64*, 127–130; (j) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701–706; (k) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramírez-Apan, T.; Cárdenas, J. *Z. Naturforsch.* **2002**, *57c*, 372; (l) Šavikin-Fodulović, K.; Aljančić, I.; Vajs, V.; Menković, N.; Macura, S.; Gojgić, G.; Milosavljević, S. *J. Nat. Prod.* **2003**, *66*, 1236–1238; (m) Wu, J.; Cheng, X.-F.; Harrison, L. J.; Goh, S.-H.; Sim, K.-Y. *Tetrahedron Lett.* **2004**, *45*, 9657–9659; (n) Verotta, L.; Lovaglio, E.; Sterner, O.; Appendino, G.; Bombardelli, E. *J. Org. Chem.* **2004**, *69*, 7869–7874; (o) Weng, J.-R.; Tsao, L.-T.; Wang, J.-P.; Wu, R.-R.; Lin, C.-N. *J. Nat. Prod.* **2004**, *67*, 1796–1799; (p) Wu, C.-C.; Weng, J.-R.; Won, S.-J.; Lin, C.-N. *J. Nat. Prod.* **2005**, *68*, 1125–1127; (q) Gartner, M.; Müller, T.; Simon, J. C.; Giannis, A.; Sleeman, J. P. *ChemBioChem* **2005**, *6*, 171–177; (r) Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Guan, Z.; Borris, R. P.; Stijfhoorn, E.; Stevenson, D.; Wang, J.; Sharma, N.; Macnaul, K.; Menke, J. G.; Ali, A.; Schulman, M. J.; Singh, S. B. *J. Nat. Prod.* **2005**, *68*, 617–619; (s) Baggett, S.; Protiva, P.; Mazzola, E. P.; Yang, H.; Ressler, E. T.; Basile, M. J.; Weinstein, I. B.; Kennelly, E. J. *J. Nat. Prod.* **2005**, *68*, 354–360; (t) Massoit, G.; Long, C.; David, B.; Serrano, M. J.; Daubie, F.; Alby, F.; Ausseil, F.; Knibiehler, M.; Moretti, C.; Hoffmann, J. S.; Cazaux, C.; Lavaud, C. *J. Nat. Prod.* **2005**, *68*, 979–984; (u) Hernandez, I. M.; Fernandez, M. C.; Cuesta-Rubio, O.; Piccinelli, A. N.; Rastrelli, L. *J. Nat. Prod.* **2005**, *68*, 931–934; (v) Taher, M.; Idris, M. S.; Ahmad, F.; Arbain, D. *Phytochemistry* **2005**, *66*, 723–726; (w) Cao, S.; Brodie, P. J.; Miller, J. S.; Ratovoson, F.; Birkinshaw, C.; Randrianasolo, S.; Rakotobe, E.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2007**, *70*, 686–688.
3. For synthetic studies toward garsubellin A and related natural products see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H.

X. *J. Am. Chem. Soc.* **1999**, *121*, 4724–4725; (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859–862; (c) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621–3624; (d) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943–1946; (e) Young, D. G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134–3137; (f) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659–661; (g) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401–7405; (h) Shimizu, Y.; Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4173–4177.

4. (a) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113–1116; (b) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2006**, *47*, 689–692.
5. For total syntheses of garsubellin A and related natural products, see: (a) Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201; (b) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048–1049; (c) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283–5285; (d) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287–289; (e) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803–4815.
6. Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895–3899.
7. Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786–4793.
8. All new compounds reported here are racemic and 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: **5**: IR (neat): ν_{max} 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06–5.02 (1H, m), 3.34 (2H, s), 2.63–2.46 (4H, m), 2.04–1.93 (2H, m), 1.67 (3H, s), 1.59 (3H, s), 1.33–1.26 (2H, m), 0.99 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7 (2C), 132.4, 123.2, 57.5, 52.5 (2C), 41.2, 33.6, 25.6, 25.0, 22.3, 17.6. HRMS (ES): *m*/*z* calculated for $C_{13}H_{20}O_2Na$: 231.1361 $(M+Na)^+$, found: 231.1356. **9**: IR (neat): ν_{max} 1741, 1693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.03–4.98 (1H, m), 4.91–4.86 (1H, m), 3.65 (3H, s), 2.59 (4H, s), 2.45 (2H, d, $J = 7.2$ Hz), 2.21–2.15 (2H, m), 2.09–2.03 (2H, m), 1.96–1.88 (2H, m), 1.66 (6H, s), 1.61 (3H, s), 1.57 (3H, s), 1.16–1.10 (2H, m), 1.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9 (2C), 173.4, 136.2, 132.3, 123.1, 117.2, 67.9, 51.6, 50.1 (2C), 40.5, 35.1, 33.2, 29.1, 27.4, 25.9, 25.8, 25.6, 22.2, 17.5 (2C). HRMS (ES): *m*/*z* calculated for $C_{22}H_{34}O_4Na$: 385.2355 $(M+Na)^+$, found: 385.2354. **10**: IR (neat): ν_{max} 1741, 1693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06–5.02 (1H, m), 4.89–4.85 (1H, m), 3.65 (3H, s), 2.70 (2H, 1/2ABq, $J = 14.4$ Hz), 2.47–2.42 (4H, m), 2.23–2.16 (2H, m), 2.11–2.04 (2H, m), 1.99–1.88 (2H, m), 1.67 (6H, s), 1.59 (6H, s), 1.35–1.29 (2H, m), 0.87 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0 (2C), 173.4, 136.5, 132.2, 123.4, 116.9, 68.2, 51.6, 49.9 (2C), 42.4, 36.1, 33.2, 29.3, 26.6, 25.9, 25.6, 24.9, 22.2, 18.0, 17.6; HRMS (ES): *m*/*z* calculated for $C_{22}H_{34}O_4Na$: 385.2355 $(M+Na)^+$, found: 385.2366; **12**: IR (neat): ν_{max} 1768, 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45(1H, s), 5.04–4.96 (2H, m), 2.66–2.31 (6H, m), 2.01–1.81 (4H, m), 1.69 (3H, s), 1.66 (3H, s), 1.58 (3H, s), 1.56 (3H, s), 1.35–1.27 (2H, m), 1.14 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.1, 168.2, 148.6, 136.5, 132.1, 123.5, 117.6, 117.1, 49.1, 48.8, 43.3, 36.1, 33.7, 28.5, 27.5, 25.8, 25.5, 25.2, 23.1, 17.9, 17.6. HRMS (ES): *m*/*z* calculated for $C_{21}H_{30}O_3Na$: 353.2093 $(M+Na)^+$, found: 353.2094. **14**: IR (neat): ν_{max} 3442, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17–5.06 (3H, m), 3.96 (1H, br s), 3.80–3.72 (1H, m), 2.45–2.36 (2H, m), 2.19–1.76 (12H, m), 1.73 (3H, s), 1.70 (3H, s), 1.69 (3H, s), 1.66 (3H, s), 1.62 (6H, s), 1.51–1.43 (2H, m), 1.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.5, 135.1, 133.9, 131.9, 131.8, 124.5, 121.5, 118.7, 78.4, 74.4, 66.3, 52.1, 41.9, 41.1, 40.7, 37.2, 34.9, 30.9, 26.1, 25.9, 25.7, 25.5, 21.6, 17.9 (2C), 17.6. HRMS (ES): *m*/*z* calculated for $C_{26}H_{42}O_3H$: 403.3212 $(M+H)^+$, found: 403.3218. **16**: IR (neat): ν_{max} 1768, 1716, 1679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.44 (1H, s), 5.09–5.04 (1H, m), 4.99–4.94 (1H, m), 2.84–2.15 (6H, m), 2.00–1.93 (4H, m), 1.68 (6H, s), 1.59 (3H, s), 1.57 (3H, s), 1.43–1.37 (2H, m), 0.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9, 168.1, 148.6, 136.5, 132.1, 123.6, 117.5, 117.2, 48.8, 48.2, 42.6, 36.5, 33.8, 28.6, 27.4, 25.9, 25.6, 24.9, 23.1, 17.9, 17.6; HRMS (ES): *m*/*z* calculated for $C_{21}H_{30}O_3Na$: 353.2093 $(M+Na)^+$, found: 353.2095; **18**: IR (thin film): ν_{max} 3451, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13–5.06 (3H, m), 3.92 (1H, br s), 3.79–3.75 (1H, m), 2.42–2.35 (3H, m), 2.17–2.13 (3H, m), 2.02–1.85 (6H, m), 1.72 (3H, s), 1.70 (3H, s), 1.65 (6H, s), 1.62 (3H, s), 1.58 (3H, s), 1.54–1.15 (3H, m), 1.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 135.1, 133.9, 131.2, 124.6, 121.4, 118.7, 78.7, 74.9, 66.9, 52.1, 42.1, 41.0, 40.4, 35.2, 35.0, 30.9, 30.2, 26.1, 25.9, 25.7, 23.9, 22.7, 17.9 (2C), 17.6; HRMS (ES): *m*/*z* calculated for $C_{26}H_{42}O_3Na$: 425.3032 $(M+Na)^+$, found: 425.3048.
9. Single crystal X-ray diffraction data on **19** were collected on a Bruker AXS SMART APEX CCD diffractometer at 292 K. The X-ray generator was operated at 50 KV and 35 mA using MoK_α 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 at a 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 SHELXL97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-664808. Crystal data for compound **19**: $C_{28}H_{44}O_4$, $M = 444.63$, monoclinic, space group $P2_1/c$, $a = 24.474(6)$ Å, $b = 6.2143(17)$ Å, $c = 18.784(5)$, $\beta = 90.957(5)°$, $V = 2856.3(13)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.034$ g cm^{-3}, $F(000) = 976$, $\mu = 0.067$ mm^{-1}, $T = 291$ K, number of l.s. parameters = 298, $R = 0.0852$, $R_w = 0.2466$, GOF = 1.041 for 2862 reflections with $I > 2\sigma(I)$. An ORTEP diagram of **19**, drawn at 30% ellipsoidal probability, is shown below:



10. Mehta, G.; Bera, M. K.; Chatterjee, S. *Tetrahedron Lett.* **2008**, *49*, 1121–1124.