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A general, concise, 'collective' approach to eudesmanolide sesquiterpenoids: total synthesis of bioactive atractylenolides I–IV and related natural products

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ABSTRACT

Total synthesis of seven bioactive atractylenolide-type eudesmanolides from Hagemann's ester, following, a short, scalable, adaptable, and diversity oriented protocol, has been accomplished. This effort opens a gateway to access through synthesis an exceptionally potent and promising group of natural products and their congeners of contemporary interest.

Dried root and stem of *Atractylis ovata* and *Atractylodes japonica* (known in Chinese as *cangzhu*) and from a related plant species *Atractylodes macrocephala koidz* (known in Chinese as *baizhu*) are part of the traditional Chinese medicine (TCM) and used in diverse disorders like chronic asthenia, spleen qi deficiency, anorexia, dyspepsia, and excessive perspiration among others.[1,2] Following the first isolation of a eudesmane sesquiterpene atractylon **1**,[1] from these plant species over half a century ago, a steady stream of bioactive eudesmanolides like atractylenolides (ATL) I **2**, II **3**, and III **4** have been unraveled from the same sources. Emergent world-wide interest in TCM with the intent to scientifically explore new therapeutic possibilities, while validating their efficacy in previously observed indications, through modern biology probes has rekindled interest in atractylenolides I–IV **2**–**5** (Fig. 1) which are regarded as the main bioactive constituents of *Atractylodes macrocephala* responsible for anti-tumor, anti-inflammatory, anti-bacterial, and anti-aging properties.

More recently, bioactivity assay guided fractionation of the extracts of *Atractylodes macrocephala* and other plants like *Sarcandra glabra*, *Lindera strychnifolia*, and some *Chloranthus* species have led to the isolation of several eudesmanolides **6**–**9** closely related to atractylenolides and are presented in Figure 1.[2]

Indeed, atractylenolides in general and ATL I–IV **2**–**5** in particular pack a remarkably impressive range of bioactivity attributes which have witnessed a massive resurgence of interest in recent years evidenced through a spate of observations and publications.[3] A few notable examples: in vivo study on lung carcinoma cell line (A549), ATL-I **2**, and ATL-III **4** effectively suppressed tumor growth with up-regulation of caspase-3, caspase-9, and Bax and down-regulation of Bcl-2 and Bcl-XL and activated the mitochondria-mediated death pathway, respectively.[3g,c] Similarly, ATL-I **2** induces apoptosis by inactivating Notch1, Jagged1, and its downstream Hes1/Hey1 and attenuating gastric cancer stem cell traits.[3j] Powerful neuroprotection activity of ATL-III **4** manifests through inhibition of glutamate-induced neuronal apoptosis[3h] and preventing learning and memory loss induced by high homocysteine levels in experimental animals.[3n] Thus, it is quite evident that atractylenolides I–IV or their close structural siblings are poised to evolve into therapeutic candidates for a variety of disorders of contemporary concern like cancer and neurodegeneration.

These developments underscore the need for accessing ATLs I–IV through enabling total syntheses which will concurrently facilitate full exploration of chemical space around their scaffold. However, it was quite surprisingly to find that synthesis efforts toward atractylenolides have been sporadic although the first synthesis was accomplished nearly five decades ago. Minato and Nagasaki were the first to achieve a total synthesis of atractylon **1** and atractylenolide II **3** from α-tetralone precursor **10**,

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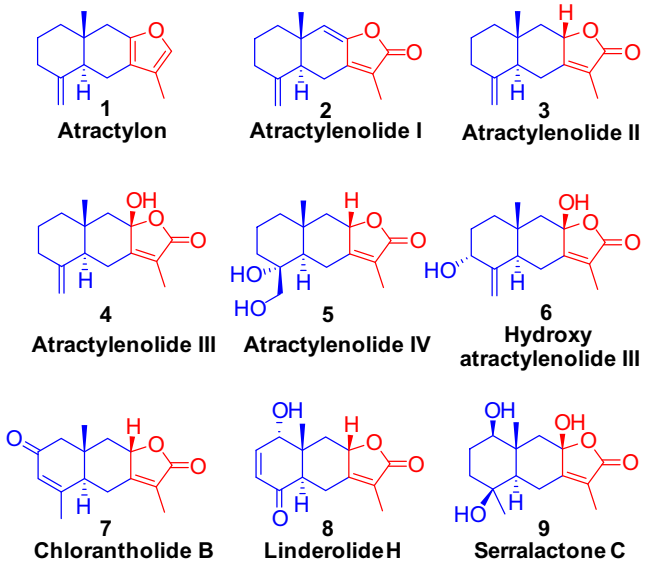
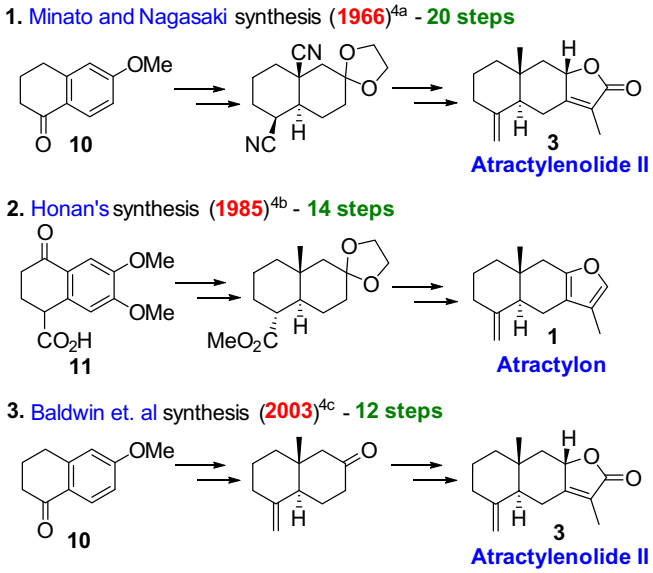


Figure 1. Representative examples of eudesmanolide sesquiterpenoids.

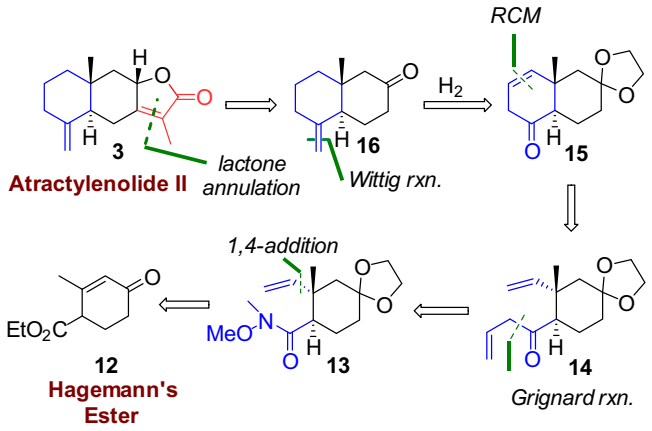
Scheme 1.[4a] Honan achieved a synthesis of **1** from α-tetralone **11**[4b] and most recently Baldwin group reported a synthesis of atractylenolides I–III also from α-tetralone **10** following a modified/shortened version[4c] of the Minato protocol, Scheme 1.

In the light of the prevailing scenario of limited options for gaining synthetic access to eudesmanolides **1–9**, we ventured to devise a *de novo* approach to this family of natural products which embraces the elements of brevity, flexibility, and is intrinsically diversity oriented. In this Letter, we divulge our strategy which enables amplification of chemical space around this bioactive scaffold and has culminated in the total syntheses of as many as seven atractylenolides and related natural products.

Contours of our proposed synthetic strategy were unveiled through the retrosynthetic analysis directed toward atractylenolides II **3** depicted in Scheme 2 and could be traced to versatile, commercially available Hageman's ester **12**. Evolution of **12** toward the projected objective envisaged setting-up of the quaternary carbon center and installation of two terminal olefin bearing



Scheme 1. Earlier synthetic approaches to atractylenolides.

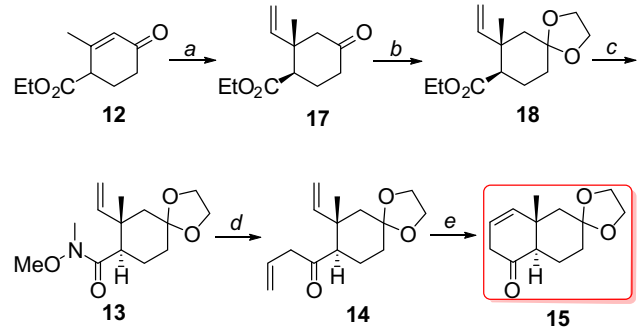


Scheme 2. Retrosynthetic analysis for atractylenolide II.

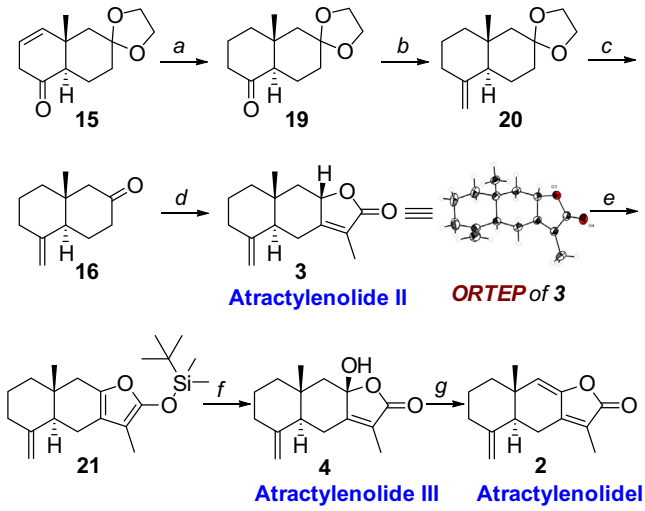
side arms with requisite stereodisposition through 1,4-vinyl addition, carbonyl protection, conversion of the ester moiety into Weinreb amide (**12** → **13**) and allylation (**13** → **14**), respectively. Further advance toward the target required implementation of RCM protocol (**14** → **15**), a few routine interventions including a Wittig olefination would lead to **16**, Scheme 2. Finally, a direct regioselective Tanabe[5] γ-lactone annulation was to be implemented on **16** to furnish atractylenolide II **3**, Scheme 2.

To operationalize the theme delineated in Schemes 2, 1,4-vinyl-cuprate addition on Hagemann's ester **12** was carried out to install the quaternary center in a stereoselective manner as described previously[6a] to deliver **17**, Scheme 3. The carbonyl group in **17** was protected as ketal **18** and the ester moiety in it was activated as Weinreb amide **13**.[6b] Addition of allylmagnesium bromide to **13** led to the allylketone **14** and set the stage to execute the RCM protocol. Exposure of **14** to UMICORE M2 catalyst[7] smoothly and efficiently delivered the *trans*-decalone **15**, Scheme 3 which was to serve as the key common intermediate in the diverse syntheses reported here.[8]

In the initial foray toward the synthesis of atractylenolides I–III, unsaturated decalone **15** was catalytically hydrogenated to **19** and further Wittig olefination with the ylide derived from methyltriphenylphosphonium bromide led quite smoothly to **20**.[8] Ketal deprotection in **20** gave **16** and was subjected to Ti^{+4} mediated regioselective one pot Tanabe γ-lactone annulation[5] to furnish natural product atractylenolide II **3**[9] quite uneventfully, Scheme 4.[8] To fully reaffirm the structure of **3** we also carried out a routine X-ray crystal structure determination on it.[10] Atractylenolides I **2** and III **4** were prepared from synthetic natural product **3**. For this



Scheme 3. (a) VMB, CuBr·Me_2S, THF, −78 °C, 92%; (b) ethylene glycol, pTSA, benzene, reflux, 8 h, 95%; (c) MeNHOMe·HCl, BuLi, HMDS, THF, −10 °C to rt, 94%; (d) allylmagnesium bromide, −78 °C, THF, 1 h, 86%; (e) UMICORE M2 (3 mol %), rt, 7 h, 92%.



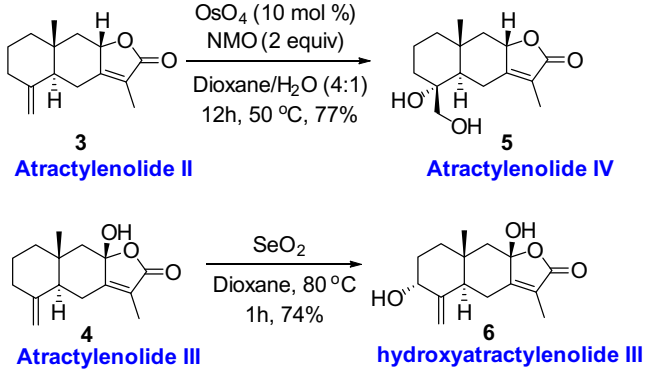
Scheme 4. Reagents and conditions: (a) H_2/Pd on C (10 mol %), EtOAc, rt, 5 h, 93%; (b) PPh_3CH_3Br, ^tBuOK, toluene, reflux, 2 h, 87%; (c) pTSA, acetone, rt, 9 h, 97%; (d) $TiCl_4$, Bu_3N, DCM, α,α-dimethoxyacetone, −78 °C to rt, 17 h, 63%; (e) TBDMSOTf, Et_3N, DCM, 0 °C–rt, 48 h; (f) mCPBA, DCM, rt, 2 h, 63% (overall 2 steps); (g) MsCl, Et_3N, 0 °C–rt, 1 h, 82%.

transformation, **3** was converted[4c] to TBDMS protected tricyclic hydroxyfuran **21** and further peracid oxidation readily delivered natural product **4**[9] which was dehydrated in methanesulfonyl chloride–TEA milieu to install the double bond and deliver atractylenolide I **2**,[9] Scheme 4.[8]

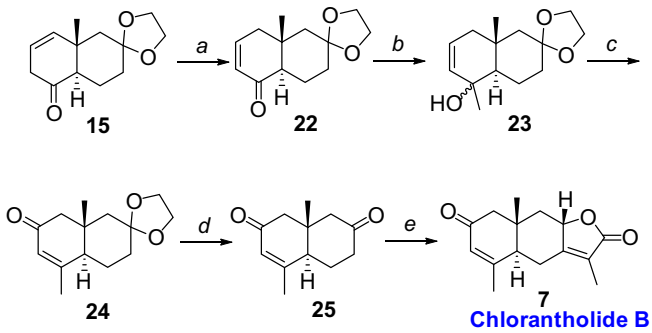
For the amplification of our atractylenolides synthesis theme, natural products atractylenolide IV **5** and hydroxyatractylenolide **6**, which are very scarce in Nature, were chosen as next targets for synthesis. Our one step preparation of **5** and **6** from readily available synthetic precursors **3** and **4**, respectively, confirms their formulation and makes them available for further biological evaluation. Thus, catalytic OsO_4-mediated dihydroxylation of **3** delivered **5**[9] quite efficiently.[8] Similarly, SeO_2 allylic oxidation in **4** was regio- and stereoselective and led to **6**,[9] Scheme 5.[8]

We now turned attention to more functionally embellished atractylenolide-type natural product chlorantholide B **7**, recently isolated from *Chloranthus elatior*.[2d] Toward this end, multipurpose intermediate **15** came quite handy. DBU mediated double bond isomerization in **15** to conjugated enone **22** and chemoselective 1,2-addition of methyllithium led to the tertiary alcohol **23**. An oxidative transposition in **23** employing PCC delivered the enone **24**, Scheme 6.[8]

Carbonyl deprotection in **24** to **25** and regio- and chemoselective Tanabe γ-lactone annulations[5] delivered the natural product chlorantholide B **7**[9] quite uneventfully.[8]



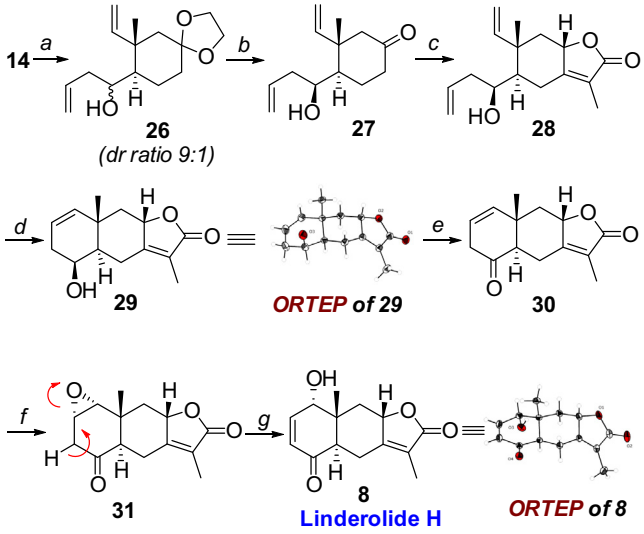
Scheme 5. Synthesis of atractylenolide IV and hydroxyatractylenolide III.



Scheme 6. Reagents and conditions: (a) DBU (0.5 equiv), DCM, 0 °C–rt, 12 h, 93%; (b) MeLi, THF, −78 °C, 1 h, 89% (dr ratio = 8:2); (c) PCC, DCM, rt, 12 h, 74%; (d) pTSA/acetone, rt, 5 h, 90%; (e) $TiCl_4$, Bu_3N, DCM, α,α-dimethoxyacetone, −78 °C to rt, 17 h, 46%.

As the last example of the present total synthesis campaign, we selected linderolide H **8** as an important objective to test our platform for targeted functionalization and functional group compatibility, necessary for chemical space exploration. In the event, we reverted to the precursor **14** and stereoselective carbonyl reduction led to the diastereomer **26** (dr = 9:1). Carbonyl deprotection to **27** and Tanabe γ-lactone annulation gave **28**, Scheme 7.[8] RCM in **28** proceeded well with low loading of UMICORE M2 catalyst[7] and **29** was readily obtained and its stereostructure was secured through single crystal X-ray structure determination.[10] Oxidation of the secondary hydroxyl group in **29** to enone **30** and chemoselective mCPBA oxidation furnished epoxide stereoselectively. Silica-gel promoted epoxide opening in **31** delivered natural product linderolide H **8**.[8,9] It was considered appropriate at this stage to reconfirm the structure of **8** through X-ray crystal structure determination.[10]

In summary, we have outlined the total synthesis of seven atractylenolide-type natural products through an approach which is short, sleek, and efficacious and provides access to a precious group of bioactive natural products by circumventing tedious isolation procedures. Our strategy is eminently geared to scale-up and analoging for exploring the full biological potential of these exceptional chemical entities. Lastly, as Hagemann's ester is available in both its enantiomeric forms, the approach delineated here is well poised to deliver the chiral variants of the natural products.



Scheme 7. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 5 h, 0 °C–rt, 87%; (b) pTSA (10 mol %), acetone, rt, 6 h, 93% (c) $TiCl_4$, Bu_3N, DCM, −78 °C to rt, 62%; (d) UMICORE M2 (1.5 mol %), DCM, rt, 7 h, 89%; (e) PCC, MS, DCM, rt, 91%; (f) mCPBA (2.5 equiv), DCM, 0 °C–rt; (g) SiO_2, EtOAc, 50 °C, 10 h, 72%, (overall 2 steps).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.045.

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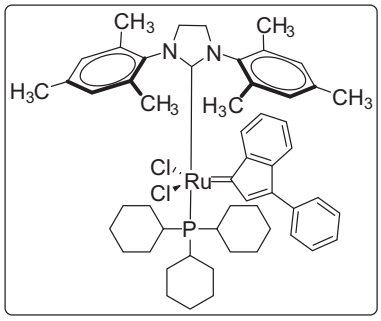
7. UMICORE M2 catalyst



8. All compounds reported here are racemic and were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of final compounds are given here while the rest are included in the Supplementary material.
Compound **2**. IR (KBr): 2945, 1739, 1287, 1025, 1260, 1106, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.63 (s, 1H), 4.94 (s, 1H), 4.65 (s, 1H), 2.69–2.74 (m, 1H), 2.51–2.59 (m, 1H), 2.35–2.42 (m, 2H), 2.04–2.09 (m, 1H), 1.93 (s, 3H), 1.67–1.75 (m, 4H), 0.96 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) 171.2, 148.2, 148.0, 147.9, 120.3, 119.0, 107.3, 48.3, 39.0, 38.0, 36.1, 22.9, 22.5, 18.4, 8.3; HRMS (ESI-MS) calcd for $C_{15}H_{18}O_2$; 231.1385 (M+H), found 231.1381. Compound **3**. IR (KBr): 2926, 2854, 1753, 1682, 1435, 1331, 1227, 1084, 882 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.86 (s, 1H), 4.80–4.85 (m, 1H), 4.59 (s, 1H), 2.71 (dd, J = 13.8 & 3.4 Hz, 1H), 2.35–2.38 (m, 1H), 2.26–2.33 (m, 2H), 1.93–2.00 (m, 1H), 1.84–1.88 (m, 1H), 1.81 (s, 3H), 1.56–1.63 (m, 3H), 1.26–1.34 (m, 1H), 1.12 (t, J = 11.9 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.9, 162.6, 148.6, 120.3, 107.0, 78.1, 50.1, 47.7, 41.0, 37.1, 36.4, 25.8, 22.5, 16.5, 8.3; HRMS (ESI-MS) calcd for $C_{15}H_{20}O_2$; 255.1361 (M+Na), found 255.1363. Compound **4**. IR (KBr): 3347, 2947, 2926, 1742, 1693, 1435, 1232, 1117, 893 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.89 (s, 1H), 4.62 (s, 1H), 3.45 (s, 1H), 2.62–2.66 (m, 1H), 2.38–2.49 (m, 2H), 2.29 (d, J = 13.8 Hz, 1H), 1.95–2.03 (m, 1H), 1.86–1.90 (m, 1H), 1.84 (s, 3H), 1.66–1.72 (m, 2H), 1.62–1.64 (m, 1H), 1.54–1.58 (m, 1H), 1.21–1.30 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5, 161.1, 148.5, 122.0, 106.7, 103.7, 51.6, 51.1, 41.2, 36.6, 36.0, 24.5, 22.2, 16.5, 8.1; HRMS (ESI-MS) calcd for $C_{15}H_{20}O_3$; 271.1310 (M+Na), found 271.1309. Compound **5**. IR (KBr): 2958, 2920, 2854, 1742, 1682, 1254, 1106, 1030, 794 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) 4.91–4.94 (m, 1H), 3.70 (d, J = 11.5 Hz, 1H), 3.58 (d, J = 11.4 Hz, 1H), 3.20 (dd, J = 13.9 & 3.3 Hz, 1H), 2.33 (t, J = 13.8 Hz, 1H), 2.17–2.33 (m, 2H), 1.81 (s, 3H), 1.57–1.63 (m, 3H), 1.42 (dd, J = 13.6 & 3.3 Hz, 1H), 1.19–1.27 (m, 1H), 1.14–1.18 (m, 1H), 1.10 (s, 3H), 1.02 (t, J = 11.7 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) 177.4, 166.3, 120.0, 79.9, 74.6, 63.7, 55.4, 52.1, 41.5, 37.3, 36.7, 23.5, 20.2, 19.4, 8.0; HRMS (ESI-MS) calcd for $C_{15}H_{22}O_4$; 289.1416 (M+Na), found 289.1418. Compound **6**. IR (KBr): 2953, 2920, 1742, 1457, 1375, 1260, 1106, 794 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) 5.06 (s, 1H), 4.76 (s, 1H), 4.24–4.25 (m, 1H), 2.60–2.64 (m, 1H), 2.37–2.40 (m, 2H), 2.22 (d, J = 13.2 Hz, 1H), 1.78–1.84 (m, 4H), 1.63–1.72 (m, 2H), 1.48 (d, J = 12.8 Hz, 1H), 1.30 (d, J = 12.1 Hz, 1H), 1.0 (s, 3H); ^{13}C NMR (400 MHz, CD_3OD) 174.4, 163.0, 151.6, 122.5, 109.8, 105.4, 73.4, 52.0, 47.1, 37.6, 36.5, 30.1, 25.1, 16.3, 8.0; HRMS (ESI-MS) calcd for $C_{15}H_{20}O_4$; 287.1260 (M+Na), found 287.1255. Compound **7**. IR (KBr): 2958, 2920, 1747, 1556, 1260, 1106, 1035, 800 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) 5.88 (s, 1H), 5.04–5.08 (m, 1H), 3.15–3.20 (m, 1H), 2.57–2.60 (m, 1H), 2.35–2.41 (m, 2H), 2.17–2.27 (m, 2H), 2.04 (s, 3H), 1.83 (s, 3H), 1.29–1.32 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 197.3, 174.0, 162.4, 161.4, 126.0, 119.8, 77.2, 52.5, 46.9, 45.2, 38.2, 24.5, 21.6, 16.7, 8.2; HRMS (ESI-MS) calcd for $C_{15}H_{18}O_3$; 269.1154 (M+Na), found 269.1147. Compound **8**. IR (KBr): 3052, 2849, 1731, 1682, 1452, 1260, 734, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.89–6.92 (m, 1H), 6.09 (d, J = 10.0 Hz, 1H), 4.87–4.91 (m, 1H), 4.04 (t, J = 5.5 Hz, 1H), 3.36–3.37 (m, 1H), 3.19 (dd, J = 15.0 & 4.6 Hz, 1H), 2.86 (dd, J = 12.3 & 4.6, 1H), 2.38 (t, J = 13.7 Hz, 1H), 2.15–2.19 (m, 1H), 1.88–1.93 (m, 1H), 1.86 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) 198.5, 175.3, 161.4, 144.6, 129.3, 121.3, 78.3, 70.8, 47.4, 41.4, 41.3, 22.1, 18.0, 8.4; HRMS (ESI-MS) calcd for $C_{14}H_{16}O_4$; 271.0947 (M+Na), found 271.0943.
9. All the natural products obtained here by synthesis were spectroscopically (^{1}H and ^{13}C NMR) compared with the data for natural products and their identities were unambiguously matched.
10. Single crystal X-ray data for **3**, **29**, **8** was collected on Oxford CCD X-ray diffractometer (Yarnton, Oxford, UK) equipped with Cu-K$_\alpha$ radiation (k = 1.54 Å) source. 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 crystal structure was solved by direct methods using *SIR92* and refined by the full-matrix least-squares method on F^2 using *SHELXL97*. Crystal data for **3**: (CCDC 1414561), $C_{15}H_{20}O_2$, M = 232.31, triclinic, *P-1*, a = 10.3618(10) Å, b = 11.1340(10) Å, c = 12.2599(11) Å, V = 1290.9(2) Å^3, Z = 4, ρ_{calcd} = 1.195 g/cm^3, 7089 reflections measured, 3522 unique (R(int) = 0.0273), R_1 = 0.0599 and wR_2 = 0.1872; Crystal data for **29**: (CCDC 1414562), $C_{14}H_{18}O_3$, M = 234.28, monoclinic, C2/c, a = 19.4230(9) Å, b = 9.7292(5) Å, c = 13.1532(5) Å, V = 2481.9(2) Å^3, Z = 8, ρ_{calcd} = 1.254 g/cm^3, 4608 reflections measured, 2365 unique (R(int) = 0.0267), R_1 = 0.0718 and wR_2 = 0.2280; Crystal data for **8**: (CCDC 1414563), $C_{14}H_{16}O_4$, M = 248.27, orthorhombic, Pbcn, a = 15.1100(8) Å, b = 12.1055(7) Å, c = 13.3644(11) Å, V = 2444.5(3) Å^3, Z = 8, ρ_{calcd} = 1.349 g/cm^3, 5249 reflections measured, 2326 unique (R(int) = 0.0316), R_1 = 0.0604 and wR_2 = 0.1881.