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Synthetic studies towards bioactive frondosins: rapid framework access and diversity creation

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ABSTRACT

A very concise and diversity-oriented approach to rapidly access frondosin-related frameworks from commercially available building blocks is outlined.

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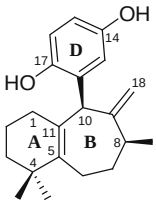
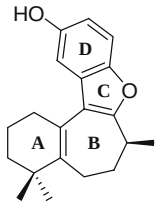
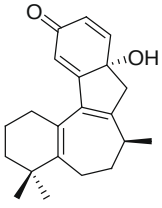
Freyer and co-workers reported the isolation and structure determination of five novel meroterpenoids from the marine sponge *Dysidea frondosa* collected from the Pacific island, Pohnpei in the Federated States of Micronesia.[1] A bioassay-guided effort yielded frondosins A-E **1–5**, possessing novel carbon skeleta that emanated through a mixed biosynthetic pathway. The structures of **1–5** were derived through extensive two-dimensional NMR studies.[1] Besides their unusual molecular architecture, frondosins **1–5** exhibited promising bioactivity profiles. In particular, frondosins inhibited binding of interleukin-8 (IL-8) to its receptor and also protein kinase C in low micromolar range. Among the frondosins, the simplest member frondosin **1** was found to be the most active with IC_{50} values against IL-8Rα and IL-8Rβ of 3.4 and 3.2 μM, respectively.[1] The IC_{50} value of **1** against PKC-α was even more promising at 1.8 μM. Subsequently, researchers at the National Cancer Institute (NCI) reported the isolation of antipodal frondosins A and D from another sponge, *Euryspongia* sp.,[2] and observed that these natural products exhibited HIV-inhibitory activity in anti-HIV assays.[2]



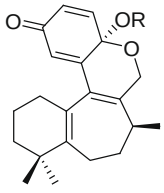
1: Frondosin A



2: Frondosin B



3: Frondosin C



4: Frondosin D (R = H)
5: Frondosin E (R = Me)

Since IL-8, a chemoattractant peptide for neutrophils, is implicated in acute and chronic inflammatory disorders, tumour progression and metastasis,[3] the promising bioactivity of frondosins **1–5** against this target has stimulated a great deal of interest and activity towards their synthesis.

Several research groups have developed and successfully implemented impressive synthetic strategies towards bioactive frondosins.[4–9] We have also accomplished the total synthesis of frondosins A and B.[10] However, recognizing the importance and promise of frondosins in general, and of frondosin A in particular, we decided to embark on a second-generation approach for the rapid acquisition of the oxyarylated bicyclo[5.4.0]undecane-based AB-ring core. The mandate of the present study was to enable creation of diversity around the frondosin scaffold, particularly with regard to the arene and the seven-membered B-ring, rather than achieve a particular target. In this Letter, we disclose a very concise and practical synthesis of the frondosin core that enables ready access to interesting functional variants and diversified structures.

Claisen–Schmidt condensation between cyclohexanone and the dimethyl ether of gentisic aldehyde **6a** led to the arylidene **7a** and further exhaustive methylation furnished the *gem*-dimethylated product **8a**,[10] Scheme 1. Hosomi–Sakurai addition of allyltrimethylsilane to **8a** in the presence of $TiCl_4$ was stereoselective to furnish **9a** as a single $10S^*,11R^*$-diastereomer (frondosin numbering).[11] The origin of stereoselectivity in this addition could possibly be attributed to the intermediacy of a tight arene π-stabilized titanium enolate (see Scheme 1), which facilitates protonation from the more open arene-bearing face. In a similar fashion, aldehydes **6b,c** furnished **7b,c** and were further *gem*-dimethylated to **8b,c**, respectively. Hosomi–Sakurai allylation of **8b,c** led to **9b,c** with

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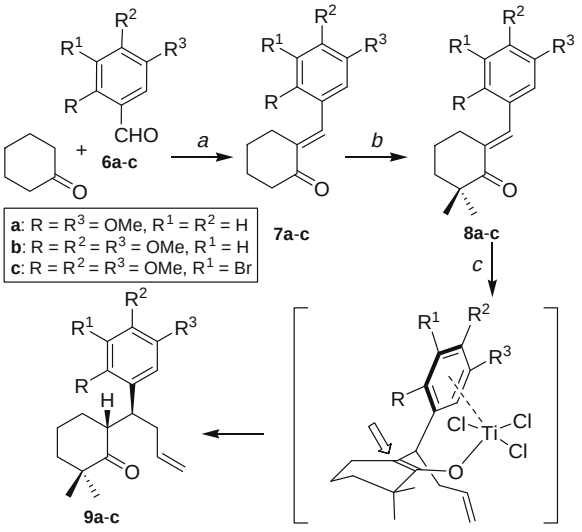
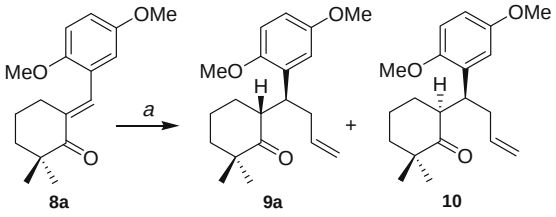


Scheme 1. Reagents and conditions: (a) 1.0 M aq NaOH, 12 h, 70% (**7a**, **7c**), 80% (**7b**); (b) ^{t}BuOK, MeI, toluene, 0 °C to rt, 3–4 h, 85% (**8a**), 80% (**8b**), 50% (**8c**); (c) (i) $TiCl_4$, −78 °C, CH_2Cl_2, 30 min, (ii) allyltrimethylsilane, −30 °C, 3–4 h, 98% (**9a**, **9b**), 65% (**9c**).

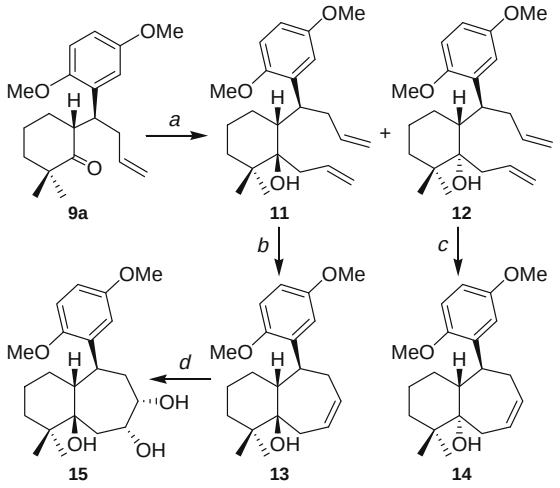
excellent diastereocontrol, Scheme 1. The involvement of an electron-rich arene-stabilized titanium enolate species in the diastereoselection was further supported by the fact that when the Hosomi–Sakurai reaction was performed in the presence of iodine instead of $TiCl_4$, according to a recently reported protocol,[12] a 1:1 diastereomeric mixture of 10*S**, 11*R**-**9a** and 10*S**,11*S**-**10**[11] was obtained, Scheme 2. Thus, the observed diastereoselection leading to **9a–c** appears to be a consequence of a subtle, but interesting long-range interaction between the electron-rich arene ring and the Ti-enolate.

Barbier-type addition of allyl bromide to **9a** in the presence of zinc led to a readily separable diastereomeric mixture (1:1) of **11** and **12** to set-up the contemplated RCM protocol. Indeed, exposure of tertiary alcohols **11** and **12** to Grubbs' I catalyst smoothly led to oxyarylated bicyclo[5.4.0]undecanes **13** and **14**, respectively.[11] OsO_4-Mediated dihydroxylation of **13** led to a crystalline triol **15** whose X-ray crystal structure secured the stereochemical assignment of its precursors **13**, **11** and **9a** and by extrapolation of **12** and **14**, Scheme 3.[13] Access to the frondosin core could also be achieved from the 10*S**,11*S**-isomer **10** through Barbier addition to give diastereomeric tertiary alcohols **16** and **17** and RCM mediated by Grubbs' I catalyst furnished bicyclic compounds **18** and **19**, respectively, Scheme 4.[11] The stereostructures of these were secured through single crystal X-ray structure determination of **18**.[13]

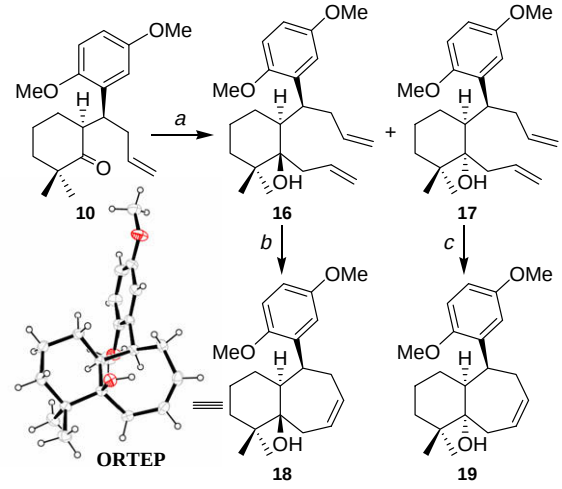
In a similar manner, **9b** and **9c** were subjected to Barbier reaction with allyl bromide in the presence of zinc; quite unexpectedly, the additions were stereoselective furnishing **20** and **21**, respectively, Scheme 5. A single crystal X-ray structure determination[13] of **21** settled the stereochemical issues. Both dienes **20** and **21**



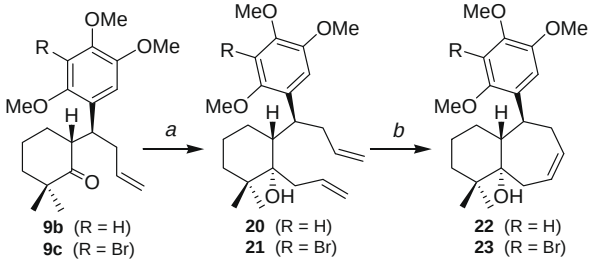
Scheme 2. Reagents and conditions: (a) allyltrimethylsilane, cat. I_2, CH_2Cl_2, 0 °C to rt, 5 h, 88%.



Scheme 3. Reagents and conditions: (a) zinc dust, allyl bromide, THF, sonication, 10–15 °C, 15 min, 96%; (b) Grubbs' 1st generation catalyst, C_6H_6, rt, 8 h, 98%; (c) Grubbs' 1st generation catalyst, C_6H_6, reflux, 2 h, 85%; (d) OsO_4, 50% aq 4-methylmorpholine N-oxide, acetone–water (4:1), rt, 12 h, 95%.

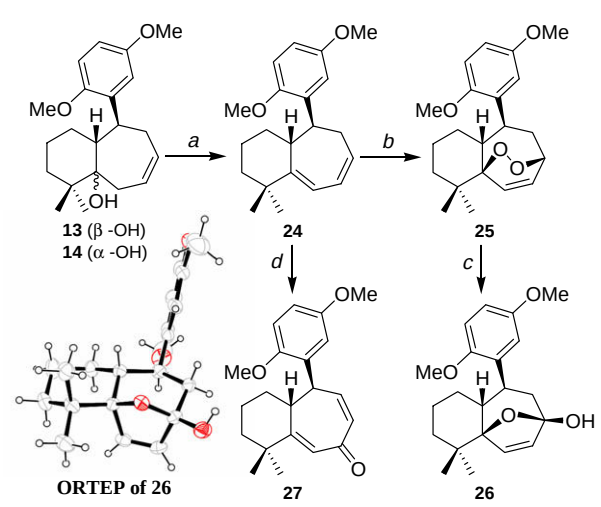


Scheme 4. Reagents and conditions: (a) zinc dust, allyl bromide, THF, sonication, 10–15 °C, 15 min, 86%; (b) Grubbs' 1st generation catalyst, C_6H_6, reflux, 2 h, 65%; (c) Grubbs' 1st generation catalyst, C_6H_6, reflux, 1 h, 88%.

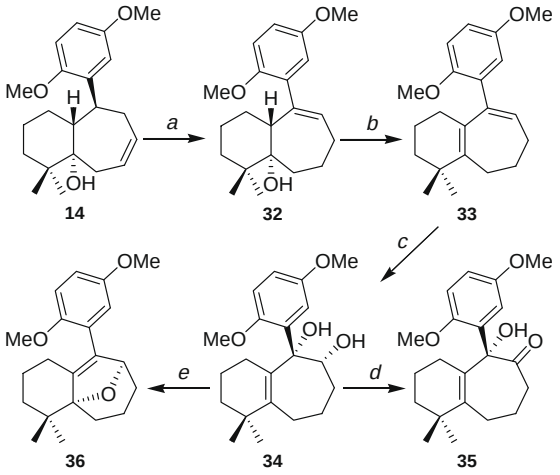


Scheme 5. Reagents and conditions: (a) zinc dust, allyl bromide, THF, sonication, 10–15 °C, 15 min, 74% based on recovered starting material (**20**), 64% based on recovered starting material (**21**); (b) Grubbs' 1st generation catalyst, C_6H_6, reflux, 2–4 h, 99% (**22**), 65% (**23**).

underwent smooth and efficient RCM reaction on exposure to Grubbs' I catalyst to furnish bicyclic compounds **22** and **23**, respectively, Scheme 5.[11] This sequence enabled a rapid five-step access to the basic bicyclic core of frondosins with functional variation



Scheme 6. Reagents and conditions: (a) $SOCl_2$, pyridine, −40 °C, 15 min, 72–75%; (b) $^1O_2$, TPP, CH_2Cl_2, rt, 8 h, quant.; (c) (i) zinc dust, AcOH, CH_2Cl_2, rt, 24 h, 92%; (ii) MnO_2, CH_2Cl_2, rt, 5 h, quant.; (d) PDC, ^{t}BuOOH, CH_2Cl_2, 0 °C to rt, 2 h, 20% or $Cr(CO)_6$, ^{t}BuOOH, MeCN, reflux, 2 h, 30%.



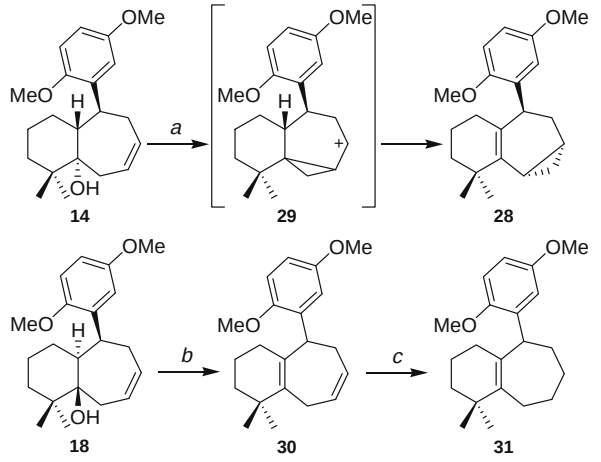
Scheme 8. Reagents and conditions: (a) ^{t}BuOK, DMSO, rt, 12 h, 60% based on recovered starting material; (b) $SOCl_2$, pyridine, −40 °C, 15 min, 80%; (c) OsO_4, 50% aq 4-methylmorpholine N-oxide, acetone–water (4:1), rt, 12 h, 60%; (d) DMP, CH_2Cl_2, 0 °C to rt, 5 h, 78%; (e) CF_3COOH, CH_2Cl_2, 0 °C, 30 min, 53%.

at the arene moiety from commercial starting materials and set the stage to explore further creation of diversity on the seven-membered ring of the bicyclic framework.

Towards this end, bicyclic tertiary alcohols **13** and **14**, on exposure to classical dehydration conditions, furnished smoothly cycloheptadiene derivative **24**, Scheme 6.

Oxyfunctionalization of **24** was achieved through singlet oxygen-mediated photooxygenation to furnish stereoselectively endoperoxide **25** through addition from the upper face, Scheme 6. Reductive peroxide cleavage of **25** to the 1,4-enediol and MnO_2 oxidation furnished a crystalline hemiketal **26**, the stereostructure of which was elucidated through single crystal X-ray structure determination. In an alternate oxyfunctionalization approach, diene **24** was subjected to direct allylic oxidation with either PDC/^{t}BuOOH or $Cr(CO)_6$/^{t}BuOOH,[14] which interestingly led to the transposed cycloheptadienone **27**, Scheme 6.[11]

It is interesting to note that the dehydration of bicyclic tertiary alcohols in Lewis acid medium takes a somewhat different course. For example, compound **14** on exposure to BF_3-etherate led to the cyclopropane-bearing tricycle **28** (stereostructure established through 2D NMR studies)[11] via the possible intermediacy of cyclopropylcarbinyl cation **29** and a 1,3-cyclopropane shift involving a cascade of cyclopropylcarbinyl–cyclobutyl cation rearrangements, Scheme 7. On the other hand, tertiary alcohol **18** on exposure to $BF_3{\cdot}OEt_2$ furnished the homoconjugated diene **30**, which could be partially reduced to furnish the frondosin prototype structure **31**, Scheme 7.



Scheme 7. Reagents and conditions: (a) cat. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 15 min, 58%; (b) cat. $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 15 min, 82%; (c) 10% Pd–C, H_2, EtOAc, rt, 5 min, quant.

In the context of further amplifying the substitution on the seven-membered ring, it was observed that the double bond in **14** could be relocated to give **32**[11] through exposure to a base, Scheme 8. Further, controlled dehydration in **32** furnished the cycloheptadiene **33**. Regioselective OsO_4-mediated dihydroxylation of **33** led to **34**, which could be oxidized to the α-hydroxyketone **35**.[11] Exposure of **34** to acid led to the tricyclic dihydrofuran derivative **36**, Scheme 8.[11]

In summary, we have delineated a concise route to the core structure of bioactive frondosins that is amenable to ready diversification of the arene moiety and enables functionalization of all the positions on the seven-membered ring.

Acknowledgements

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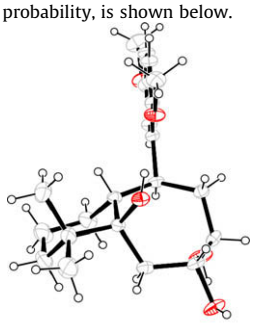
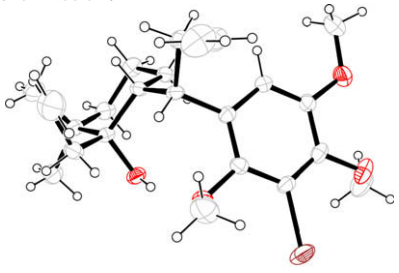
11. All new compounds reported here are racemic and characterized on the basis of spectroscopic data (IR, ^{1}H, ^{13}C NMR and mass). Spectral data of some key compounds follows: **9a** IR (neat): ν_{max} 2932, 1705, 1503, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 5.66–5.52 (m, 1H), 4.89–4.77 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.48–3.40 (m, 1H), 3.03–2.94 (m, 1H), 2.47–2.28 (m, 2H), 1.76–1.72 (m, 2H), 1.55–1.49 (m, 4H), 1.23 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.84, 153.42, 152.48, 137.32, 132.57, 116.22, 115.15, 111.68, 110.53, 56.09, 55.55, 50.18, 46.20, 42.74, 37.99, 33.81, 25.53, 24.51 [2C], 21.84; HRMS (ES): m/z calcd for $C_{20}H_{28}O_3$ (M+Na)$^+$: 339.1936, found: 339.1933; **10** IR (neat): ν_{max} 2934, 1710, 1642, 1592, 1500, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, J = 8.7 Hz, 1H), 6.69 (dd, J = 8.4, 2.7 Hz, 1H), 6.65 (d, J = 3.3 Hz, 1H), 5.70–5.59 (m, 1H), 5.00–4.86 (m, 2H), 3.75 (s, 6H), 2.95–2.85 (m, 1H), 2.43–2.32 (m, 2H), 2.06–1.99 (m, 1H), 1.78–1.36 (m, 6H), 1.15 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.74, 153.12, 151.59, 137.17, 133.41, 115.61, 115.22, 111.28, 110.02, 55.95, 55.58, 49.31, 45.61, 41.61, 35.38, 33.13, 29.25, 25.67, 25.28, 21.58; HRMS (ES): m/z calcd for $C_{20}H_{28}O_3$ (M+Na)$^+$: 339.1936, found: 339.1920; **13** IR (neat): ν_{max} 3573, 2934, 1499, 1465 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, J = 3.0 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.68 (dd, J = 9.0, 3.0 Hz, 1H), 5.93–5.86 (m, 1H), 5.56–5.50 (m, 1H), 3.75 (s, 6H), 3.08–2.96 (m, 2H), 2.75 (s, 1H), 2.69 (br s, 1 H), 2.47 (dd, J = 17.5, 7.6 Hz, 1H), 2.19–2.12 (m, 1H), 1.96 (dd, J = 16.4, 7.4 Hz, 1H), 1.57–1.52 (m, 1H), 1.37–1.25 (m, 5H), 1.06 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.68, 150.93, 137.67, 132.66, 126.17, 114.37, 111.93, 110.68, 78.13, 56.20, 55.62, 47.52, 39.73, 37.68, 34.96, 31.91, 29.99, 25.63, 23.36, 20.99 [2C]; HRMS (ES): m/z calcd for $C_{21}H_{30}O_3$ (M+Na)$^+$: 353.2093, found: 353.2088; **14** IR (neat): ν_{max} 3563, 2932, 1613, 1499, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, J = 8.7 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.67 (dd, J = 8.8, 3.0 Hz, 1H), 6.18–6.11 (m, 1H), 5.76–5.67 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.98 (br s, 1H), 2.62–2.40 (m, 3H), 2.11–2.04 (m, 2H), 1.90 (s, 1H), 1.75–1.65 (m, 1H), 1.34–1.15 (m, 3H), 1.05–0.97 (m, 2H), 1.02 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.72, 151.02, 137.50, 135.17, 127.91, 111.71 [2C], 109.85, 73.94, 56.18, 55.56, 38.72, 37.27, 35.26, 34.03 [2C], 27.91, 25.27, 22.73, 21.92, [2C]; HRMS (ES): m/z calcd for $C_{21}H_{30}O_3$ (M+Na)$^+$: 353.2093, found: 353.2073; **18** mp: 127–128 °C; IR (neat): ν_{max} 3434, 2929, 1615, 1494, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 8.7, 3.0 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.02–5.96 (m, 1H), 5.63–5.57 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.91–2.81 (m, 1H), 2.65–2.50 (m, 2H), 2.40 (s, 1H), 2.35–2.29 (m, 1H), 2.18 (dd, J = 17.6, 7.4 Hz, 1H), 1.79–1.69 (m, 1H), 1.54–1.41 (m, 2H), 1.26–1.16 (m, 2H), 1.08–0.99 (m, 1H), 0.96 (s, 3H), 0.94 (s, 3H), 0.96–0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.28, 150.89, 135.81, 134.10, 126.53, 115.80, 111.12, 110.09, 77.62, 56.13, 55.61, 42.54, 39.51, 38.97, 36.79, 33.56, 30.83, 25.08, 22.69, 22.41, 22.34; HRMS (ES): m/z calcd for $C_{21}H_{30}O_3$ (M+Na)$^+$: 353.2093, found: 353.2079; **19** IR (neat): ν_{max} 3558, 2934, 1592, 1493, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81–6.67 (m, 3H), 5.92–5.83 (m, 1H), 5.58–5.50 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.67–2.61 (m, 2H), 2.43 (dd, J = 16.8, 8.1 Hz, 1H), 2.22 (s, 1H), 2.17–2.02 (m, 2H), 1.48–1.26 (m, 6H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.29, 150.43, 137.14, 131.15, 126.78, 114.96, 111.04, 109.62, 76.29, 55.94, 55.65, 46.47, 40.13, 38.31, 32.89, 32.01, 27.94, 25.63, 23.27, 21.96, 21.86; HRMS (ES): m/z calcd for $C_{21}H_{30}O_3$ (M+Na)$^+$: 353.2093, found: 353.2117; **22** IR (neat): ν_{max} 3564, 3416, 2931, 1508, 1204, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.49 (s, 1H), 6.15–6.14 (m, 1H), 5.74–5.67 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 2.91 (br s, 1H), 2.66 (br s, 1H), 2.58 (dd, J = 14.1, 8.4 Hz, 1H), 2.48–2.41 (m, 1H), 2.12–2.04 (m, 2H), 1.74–1.64 (m, 2H), 1.35–1.23 (m, 2H), 1.20–1.05 (m, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 1.02–0.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.88, 147.42, 143.33, 135.27, 127.83, 111.92, 111.87, 98.25, 74.07, 56.88, 56.70, 56.11, 49.07, 38.77, 37.34, 35.46, 34.10, 28.06, 25.28 [2C], 22.81, 21.99; HRMS (ES): m/z calcd for $C_{22}H_{32}O_4$ (M+Na)$^+$: 383.2198, found: 383.2198; **23** IR (neat): ν_{max} 3493, 2928, 1512, 1203, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.20–6.13 (m, 1H), 5.79–5.72 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 2.93 (br s, 1H), 2.64–2.57 (m, 1H), 2.47–2.41 (m, 1H), 2.10–2.03 (m, 2H), 1.80 (s, 1H), 1.75–1.63 (m, 1H), 1.43–1.23 (m, 4H), 1.13–1.08 (m, 1H), 1.03 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.40, 148.56, 145.37, 137.29, 134.82, 128.45, 113.70, 109.88, 73.56, 61.18, 60.58, 56.75, 49.38, 38.90, 37.32, 36.19, 34.05, 28.67, 26.94, 25.27, 22.78, 21.91; HRMS (ES): m/z calcd for $C_{22}H_{31}BrO_4$ (M+Na)$^+$: 461.1303, found: 461.1313; **27** IR (neat): ν_{max} 2934, 1653, 1612, 1496, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82–6.72 (m, 3H), 6.43 (dd, J = 11.1, 6.6 Hz, 1H), 6.19–6.14 (m, 2H), 4.04 (t, J = 6.9 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.16–3.08 (m, 1H), 1.73–1.68 (m, 2H), 1.46–1.36 (m, 2H), 1.27–1.20 (m, 2H), 1.17 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.29, 168.14, 153.47, 151.08, 143.33, 133.25, 131.38, 124.79, 115.33, 112.01, 111.59, 55.90, 55.61, 44.14, 43.35, 41.85, 40.01, 34.47, 29.99, 27.39, 21.93; HRMS (ES): m/z calcd for $C_{21}H_{26}O_3$ (M+Na)$^+$: 349.1780, found: 349.1797; **28** IR (neat): ν_{max} 2927, 1697, 1506, 1489, 1455, 1219, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, J = 3.3 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.69 (dd, J = 9.0, 3.0 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.35 (t, J = 4.9 Hz, 1H), 2.14–2.05 (m, 1H), 1.75–1.45 (m, 7H), 1.22 (s, 3H), 1.16 (s, 3H), 0.93–0.84 (m, 3H), 0.17 (d, J = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.36, 151.76, 139.09, 134.22, 129.70, 114.60, 111.23, 110.89, 56.06, 55.47, 39.77, 37.42, 34.76, 31.59, 30.18, 28.96, 28.70, 19.74, 18.28, 10.65, 7.83; MS (ES): m/z 335 (M+Na)$^+$; **32** IR (neat): ν_{max} 3488, 2933, 1496, 1461, 1214, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81–6.71 (m, 2H), 6.55 (d, J = 2.7 Hz, 1H), 5.57–5.55 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.28 (d, J = 12.6 Hz, 1H), 2.46–2.22 (m, 3H), 1.79–1.57 (m, 5H), 1.44–1.35 (m, 2H), 1.17–1.11 (m, 1H), 1.08–0.98 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.39, 150.10, 138.82, 134.87, 131.40, 117.88, 111.89, 111.74, 56.59, 55.58, 41.01, 39.05, 37.14, 37.03, 30.53, 27.27, 25.41, 24.18, 21.99, 21.94 [2C]; HRMS (ES): m/z calcd for $C_{21}H_{30}O_3$ (M+Na)$^+$: 353.2093, found: 353.2086; **35** IR (neat): ν_{max} 3433, 2929, 2861, 1698, 1492, 1464, 1224 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.85 (s, 2H), 4.79 (s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.70–2.65 (m, 2H), 2.32–1.98 (m, 4H), 1.81–1.46 (m, 6H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.01, 153.80, 151.40, 144.16, 132.04, 130.79, 114.42, 114.31, 113.35, 83.43, 56.17, 55.58, 53.41, 41.19, 39.31, 36.76, 28.06 [2C], 27.70, 26.98, 19.67; HRMS (ES): m/z calcd for $C_{21}H_{28}O_4$ (M+Na)$^+$: 367.1885, found: 367.1874; **36** IR (neat): ν_{max} 2926, 1582, 1495, 1462, 1219, 1048 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85–6.76 (m, 3H), 5.05 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.58–2.52 (m, 1H), 2.08–1.96 (m, 2H), 1.69–1.39 (m, 6H), 1.35–1.20 (m, 2H), 1.17–1.11 (m, 1H), 0.98 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.20 [2C], 137.96, 130.17, 124.31, 116.69, 112.52, 112.48, 89.83, 81.75, 56.19, 55.66, 37.13, 36.16, 25.05, 24.53, 24.25 [2C], 23.09, 20.31, 17.75; HRMS (ES): m/z calcd for $C_{21}H_{28}O_3$ (M+Na)$^+$: 351.1936, found: 351.1948.
12. Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Satheesh, G. *Tetrahedron Lett.* **2002**, *43*, 9695–9697.
13. X-ray data were collected at 293 K on a SMART CCD–BRUKER diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å). Structures were solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. Compound **15**: CCDC 697875, $C_{21}H_{32}O_5$, MW = 364.47, crystal system: triclinic, space group: $P\bar{1}$, cell parameters: a = 8.0132 (55) Å, b = 11.3339 (78) Å, c = 12.1107 (83) Å, α = 66.434 (10)°, β = 83.514 (11)°, γ = 88.146 (11)°, V = 1001.62 (51) Å^3, Z = 2, ρ_{calcd} = 1.21 g cm^{-3}, F(0 0 0) = 396.0, μ = 0.085 mm^{-1}, number of l.s. parameters = 251, $R1$ = 0.061 for 2474 reflections with $I > 2\sigma(I)$ and 0.090 for all 3402 data, $wR2$ = 0.116, GOF = 1.135 for all data. An ORTEP diagram of **15**, drawn at 30% ellipsoid probability, is shown below.



ORTEP diagram of **15**

Compound **18**: CCDC 697874, $C_{21}H_{30}O_3$, MW = 330.45, crystal system: triclinic, space group: $P\bar{1}$, cell parameters: a = 7.3108 (70) Å, b = 9.3827 (88) Å, c = 13.6878 (13) Å, α = 89.473 (16)°, β = 81.928 (15)°, γ = 75.333 (15)°, V = 898.98 (45) Å^3, Z = 2, ρ_{calcd} = 1.22 g cm^{-3}, F(0 0 0) = 360.0, μ = 0.080 mm^{-1}, number of l.s. parameters = 222, $R1$ = 0.041 for 2806 reflections with $I > 2\sigma(I)$ and 0.047 for all 3255 data, $wR2$ = 0.107, GOF = 1.037 for all data; Compound **21**: CCDC 733793; $C_{24}H_{35}BrO_4$, MW = 467.4, crystal system: monoclinic, space group: $P21/n$, cell parameters: a = 17.0258 (49) Å, b = 7.4381 (20) Å, c = 19.0945 (56) Å, β = 104.623 (6)°, V = 2339.79 (40) Å^3, Z = 4, ρ_{calcd} = 1.33 g cm^{-3}, F(0 0 0) = 983.9, μ = 1.783 mm^{-1}, number of l.s. parameters = 268, $R1$ = 0.061 for 1949 reflections with $I > 2\sigma(I)$ and 0.176 for all 4321 data, $wR2$ = 0.076, GOF = 0.891 for all data. An ORTEP diagram of **21**, drawn at 30% ellipsoid probability, is shown below.



ORTEP diagram of **21**

Compound **26**: CCDC 733792; $C_{21}H_{28}O_4$, MW = 360.5, crystal system: triclinic, space group: $P\bar{1}$, cell parameters: a = 10.4326 (43) Å, b = 12.4180 (50) Å, c = 16.2569 (66) Å, α = 91.438 (8)°, β = 101.948 (8)°, γ = 93.388 (7)°, V = 2055.38 (14) Å^3, Z = 4, ρ_{calcd} = 1.16 g cm^{-3}, F(0 0 0) = 775.9, μ = 0.082 mm^{-1}, number of l.s. parameters = 479, $R1$ = 0.129 for 4799 reflections with $I > 2\sigma(I)$ and 0.167 for all 7181 data, $wR2$ = 0.374, GOF = 1.432 for all data.
14. (a) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907–3910; (b) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235–1238.