Tetrahedron Letters 49 (2008) 7113–7116

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A total synthesis of (±)-frondosins A and B

Goverdhan Mehta *, Nachiket S. Likhite

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

ARTICLE INFO

Article history:
Received 10 August 2008
Revised 14 September 2008
Accepted 22 September 2008
Available online 2 October 2008

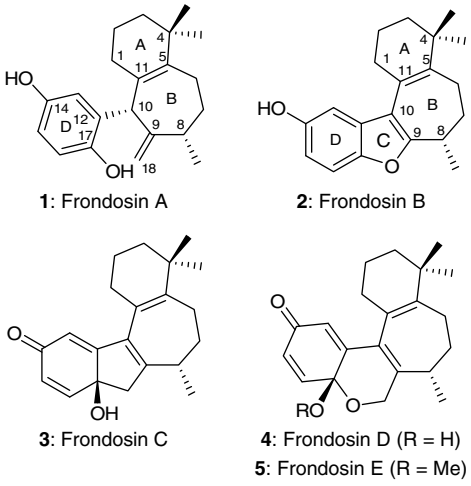
ABSTRACT

A total synthesis of the bioactive meroterpenoid natural products frondosin B and frondosin A (formal) from readily available cyclohexanone and gentisic aldehyde dimethyl ether, involving RCM as the key step to generate the bicyclic 6,7-fused core structure, is outlined.

During a high-throughput screening program on natural product extracts for bioactive compounds with therapeutical potential towards inflammatory diseases, Freyer et al. reported the isolation of five novel meroterpenoids from the marine sponge *Dysidea frondosa* collected from the sea around the Pacific island, Pohnpei, Federated States of Micronesia.[1] These natural products, designated frondosins A-E **1–5**, were shown to possess a novel carbon skeleton and their structures were secured through incisive two dimensional NMR studies. Quite promisingly, it was observed that all five frondosins **1–5** inhibited binding of interleukin-8 (IL-8) to its receptor and also protein kinase C in low micromolar range, with frondosin A being the most active.[1] This first report was quickly followed by the isolation of frondosins A and D from another sponge, *Euryspongia sp.*, interestingly in enantiomeric forms, by scientists at the National Cancer Institute (NCI).[2] It was shown that frondosins A and D also displayed HIV-inhibitory activity in anti-HIV assays.[2]

On account of their novel framework and excellent biological activity related to IL-8, a chemoattractant peptide for neutrophils and implicated in acute and chronic inflammatory disorders, tumour progression and metastasis among others,[3] frondosins **1–5** aroused widespread attention from practitioners of total synthesis. Several imaginative synthetic strategies have been pursued in this context. The first synthesis of a member of this family was that of frondosin B **2** by Danishefsky et al.,[4] which also established its absolute configuration. Subsequently, groups led by Trauner,[5] Flynn,[6] Ovaska[7] and Davies (formal)[8] have accomplished total syntheses of frondosin B. More recently, the synthesis of frondosin A **1** has been reported by Trost et al.[9] and Ovaska et al.[10] A sole synthesis of frondosin C **3** has emanated from the Ovaska group.[11] We describe here a *de novo* synthesis of frondosins A **1** and B **2** involving a late stage convergence with the Ovaska approach.[7]

The focus of our strategy towards frondosins was the rapid acquisition of the bicyclo[5.4.0]undecane-based AB-ring core **6** with an appropriate aromatic segment and functionalization, employing RCM as the pivotal step, for further elaboration to the natural products. The RCM precursor **7** of **6** was to be accessed from an arylidene-cyclohexenone **8** as shown retrosynthetically in Scheme 1.



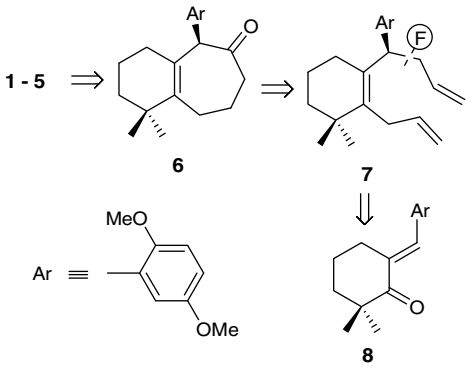
Implementation of the approach depicted in Scheme 1 required ready access to the precursor **8**.

Towards this end, cyclohexanone was condensed with the dimethyl ether of gentisic aldehyde **9** to furnish arylidene **10**, and further exhaustive methylation introduced the *gem*-dimethyl group present in **8**,[12] Scheme 2. Michael addition of the anion derived from nitromethane to **8** led to a diastereomeric mixture (1:1) of **11a** and **11b**, Scheme 2. Although the two diastereomers **11a,b** could be separated and characterized,[12] the mixture itself was quite serviceable for the next step.

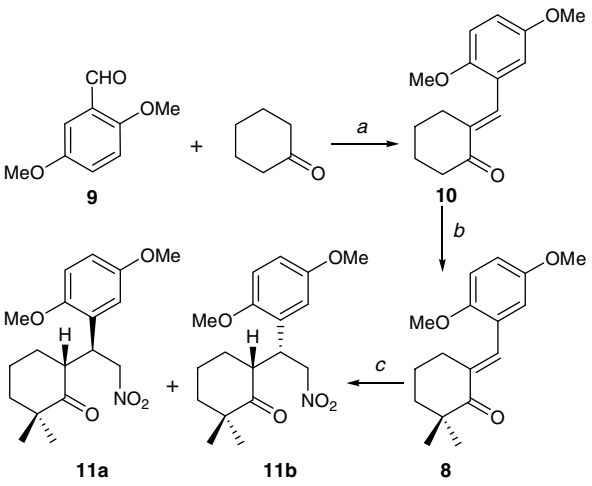
A Nef reaction[13] on **11a,b** was quite productive and led to aldehyde **12** as a single diastereomer[12] through equilibration under the reaction regime, Scheme 3. The stage was now set to introduce the

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

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.163



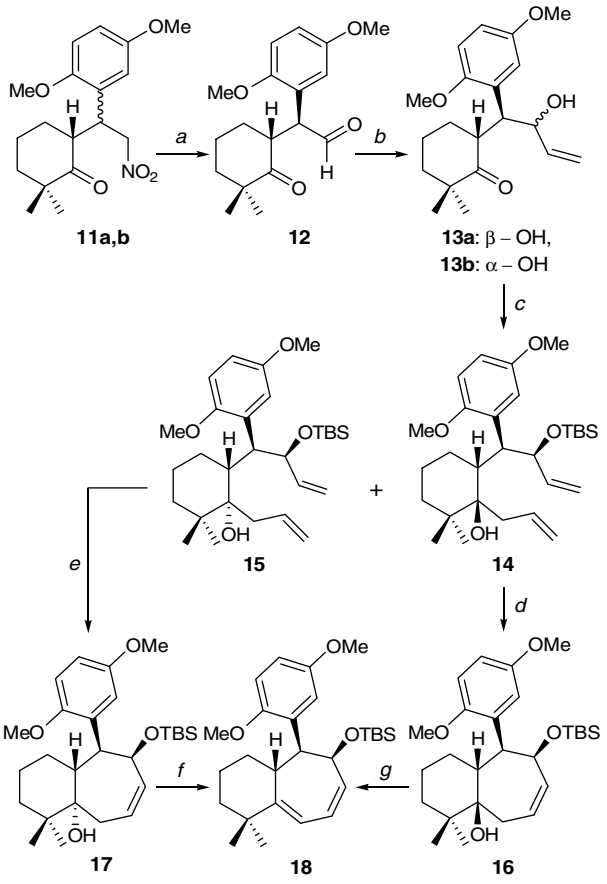
Scheme 1. Retrosynthetic strategy.



Scheme 2. Reagents and conditions: (a) 1 M NaOH, reflux, 12 h, 70%; (b) ^{t}BuOK, MeI, toluene, 0 °C to rt, 3 h, 85%; (c) DBU, $MeNO_2$, MeCN, reflux, 5 h, 96%.

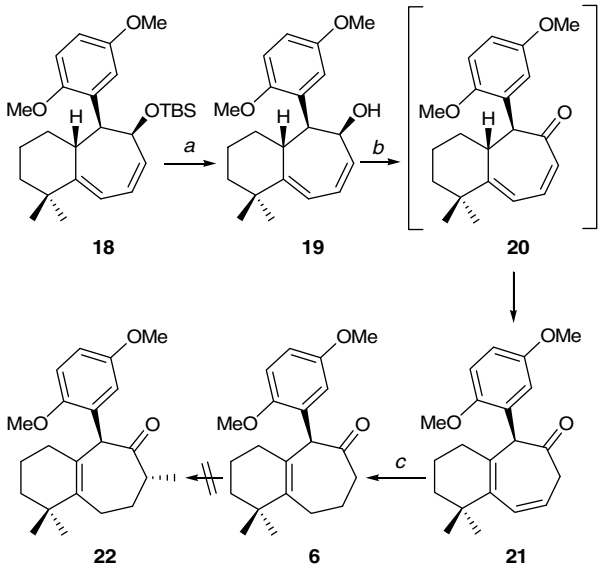
two alkenyl arms onto the ketone and aldehyde groups of **12** to set up the RCM precursor for construction of the seven-membered ring. Addition of vinylmagnesium bromide to **12** was chemoselective with moderate stereoselectivity and furnished diastereomeric vinyl alcohols **13a,b**, in which the β-hydroxy isomer predominated (2:1). The major β-hydroxy isomer **13a** was subjected to Barbier-type reaction in the presence of zinc to furnish a diastereomeric mixture of diols and the secondary hydroxyl groups were—OTBS protected to furnish a 3:1 mixture of tertiary alcohols **14** and **15**,[12] Scheme 3. The stereochemical assignments to **14** and **15** were deduced through X-ray single crystal structure determination[14] of the diastereomer **15**, Scheme 3. The preferred α-face addition of the allyl chain to the keto-carbonyl group in **13a** is understandable in terms of steric preference from the less hindered face. However, from tactical consideration, this lack of stereoselectivity during the Barbier addition to **13a** was inconsequential as the newly generated stereogenic centre bearing the tertiary hydroxyl group was destined to be destroyed during subsequent steps. Both the dialkenyl precursors **14** and **15** underwent smooth RCM in the presence of Grubbs' first generation catalyst to furnish bicyclic tertiary alcohols **16**[12] and **17**,[12] respectively, incorporating the AB rings of the targeted natural products.

At this stage, convergence was established between the two diastereomers **16** and **17** by dehydration into a single product **18**, Scheme 3. Thus, exposure of either of the tertiary alcohol **16** or **17** to thionyl chloride/pyridine led to dehydration to give the bicyclic 1,3-dienol derivative **18**[12] in fair yield.



Scheme 3. Reagents and conditions: (a) (i) Na, EtOH, 0 °C to rt, 2 h; (ii) HCl/EtOH/H_2O (1:8:10), 0 °C, 15 min, 88–90%; (b) Vinylmagnesium bromide, THF −78 °C, 1 h, 90–92%; (c) (i) Zn, allyl bromide, THF,)))), 10–15 °C, 15 min, 65–70%; (ii) Et_3N, TBDMSOTf, DCM, 0 °C, 1 h, 84%; (d) Grubbs' I, benzene, reflux, 12 h, 75%; (e) Grubbs' I, benzene, reflux, 16 h, 80%; (f) $SOCl_2$, pyridine, DCM, 0 °C, 15 min, 78%; (g) $SOCl_2$, pyridine, DCM, 0 °C, 15 min, 82%.

Deprotection of the TBS protective group in **18** furnished the dienol **19** and Dess–Martin periodinane (DMP) oxidation led to the isomerized dienone **21**[12] instead of the expected conjugated

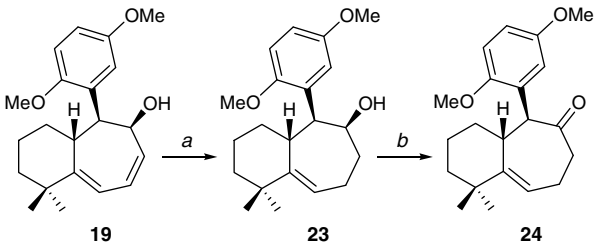


Scheme 4. Reagents and conditions: (a) *cat*. PTSA, MeOH, 0 °C, 3 h, 80%; (b) Dess–Martin periodinane, DCM, 0 °C, 1 h; 85%; (c) H_2, 10% Pd/C, ethyl acetate, rt, 5 min, quantitative.

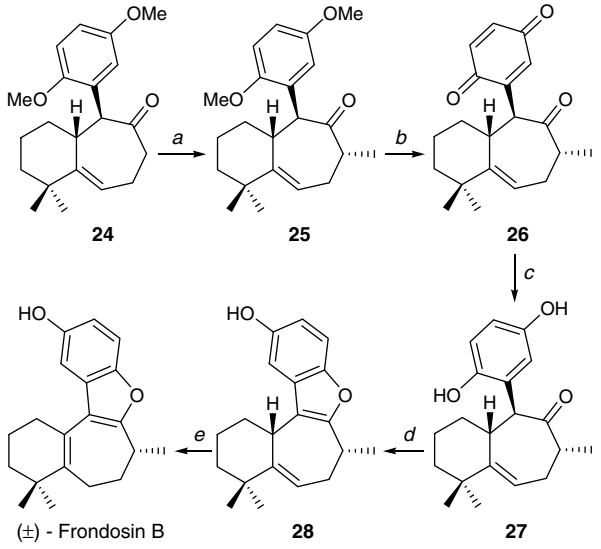
dienone **20**. Indeed, the formation of **20** could be detected by NMR but it rapidly isomerized to **21**, Scheme 4. Controlled catalytic hydrogenation of **21** smoothly delivered **6**,[12] an advanced precursor of frondosins (see retrosynthesis in Scheme 1), in which the C-8 methyl group was needed to be installed to access **22**. However, repeated attempts to introduce the methyl group at C-8, α to the C-9 carbonyl group, a seemingly straightforward manoeuvre, proved abortive. An alternative sequence was thus sought.

Selective catalytic hydrogenation of the less substituted double bond in **19** proved to be quite uneventful to deliver **23**, which was further oxidized with DMP to the enone **24**,[12] Scheme 5. Bicyclic enone **25** has been recently elaborated[7] to frondosin B, and we took recourse to this strategy to complete our total synthesis.

Enone **24** underwent α-methylation quite smoothly and in a regio- and stereoselective manner to furnish **25**[12] embodying the complete carbon framework of the frondosins. Aromatic methoxy group deprotection in **25** proved to be unexpectedly capricious, and therefore a more circuitous route involving CAN oxidation to quinone **26** followed by its reduction to the quinol **27** was implemented, Scheme 6. Exposure of **27** to the Lewis acid BF_3-etherate induced the furan cyclization to install the CD rings and deliver **28** with the complete framework of the frondosins. Lastly, the trisubstituted double bond in **28** was isomerized to the desired tetrasubstituted position to deliver frondosin B **2**, which was found to be spectroscopically (^{1}H and ^{13}C NMR) identical with the natural product.[1,7]



Scheme 5. Reagents and conditions: (a) Pd–$CaCO_3$ poisoned with lead, MeOH, rt, 12 h, 98%; (b) Dess–Martin periodinane, DCM, 0 °C to rt, 3 h, 90%.



Scheme 6. Reagents and conditions: (a) (i) KHMDS, THF, −78 °C, 30 min; (ii) MeI, −60 °C, 2 h, 92%; (b) CAN, MeCN/H_2O (2:1), rt, 30 min, 96%; (c) H_2, 10% Pd/C, $CHCl_3$, rt, 5 min; (d) $BF_3{\cdot}OEt_2$, DCM, 0 °C, 5 min, 95% for two steps; (e) *cat*. PTSA, benzene, reflux, 5 h, 70%.

Very recently, bicyclic enone **25** has also been formally elaborated to the natural product frondosin A **1**.[10] Therefore, our synthesis of **25** (Scheme 5) *en route* to frondosin B **2** constitutes a formal synthesis of frondosin A **1**.

In summary, we have accomplished a relatively simple synthesis of bioactive frondosins through a strategy which is inherently flexible. It is worth pointing out that the frondosin framework, particularly the bicylic AB core, displays deceptive reactivity in the sense that many of the seemingly obvious and predictable reactions do not run their normal course, thereby rendering the total synthesis of these natural products even more challenging.

Acknowledgements

We thank Professor Timo Ovaska for his help in providing spectral data for comparison. N.S.L. thanks CSIR for the award of a research fellowship. X-ray data were collected at the CCD facility at IISc, supported by DST, India, and we thank Mr. Saikat Sen for this help with crystal structure determination. This research was also supported by the CBU of JNCASR, Bangalore.

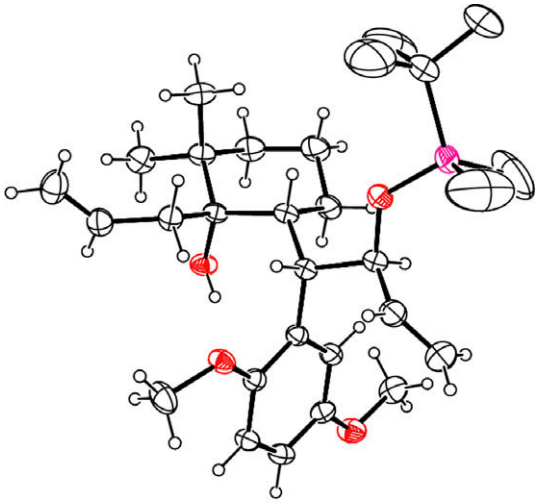
References and notes

1. Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047–5060.
2. Hallock, Y. F.; Cardellina, J. H., II.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153–160.
3. (a) Seitz, M.; Dewald, B.; Gerber, N.; Baggiolini, M. *J. Clin. Invest.* **1991**, *87*, 463–469; (b) Miller, E. J.; Cohen, A. B.; Nagao, D.; Griffith, R. J.; Maunder, R. J.; Martin, T. R.; Weiner-Kronish, J. P.; Sticherling, M.; Christophers, E.; Matthay, M. A. *Am. Rev. Respir. Dis.* **1992**, *146*, 427–432; (c) Brat, D. J.; Bellail, A. C.; Van Meir, E. G. *Neuro-oncology* **2005**, *7*, 122–133; (d) Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer* **2004**, *91*, 1970–1976.
4. (a) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761–764; (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878–1889.
5. (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569–1572; (b) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675–9686.
6. Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457–460.
7. Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, *9*, 3837–3840.
8. Oslon, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573–576.
9. Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781–11790.
10. Li, X.; Keon, A. E.; Sullivan, J. A.; Ovaska, T. V. *Org. Lett.* **2008**, *10*, 3287–3290.
11. Li, X.; Kyne, R. E.; Ovaska, T. V. *Tetrahedron* **2007**, *63*, 1899–1906.
12. All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR and mass). Spectral data for some of the key compounds follows: *Compound* **11a/b** IR (neat) 2931, 1700, 1589, 1502, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 8.7 Hz, 1H), 6.75–6.71 (m, 1H), 6.64 (d, J = 2.7 Hz, 1H), 4.82–4.68 (m, 2H), 3.93–3.85 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.25–3.16 (m, 1H), 1.78–1.60 (m, 2H), 1.60–1.45 (m, 3H), 1.22 (s, 3H), 1.18–1.13 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.07, 153.51, 151.81, 127.07, 117.27, 112.66, 111.92, 77.61, 55.88, 55.58, 46.12, 45.98, 42.19, 41.32, 33.77, 25.40, 24.56, 21.60; HRMS (ES) m/z calcd for $C_{18}H_{25}NO_5$ (M+Na$^+$): 358.1630; found: 358.1613; *Compound* **11a/b** IR (neat) 2935, 1702, 1554, 1496, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81–6.66 (m, 3H), 4.84–4.72 (m, 2H), 4.43–4.37 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.21–3.13 (m, 1H), 2.12–2.09 (m, 1H), 1.83–1.49 (m, 4H), 1.38–1.24 (m, 1H), 1.17 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.85, 153.41, 151.19, 128.39, 115.00, 112.01, 111.91, 75.39, 56.01, 55.62, 47.52, 45.79, 41.55, 36.37, 30.23, 25.41, 24.92, 21.48; HRMS (ES) m/z calcd for $C_{18}H_{25}NO_5$ (M+Na$^+$): 358.1630; found: 358.1613; *Compound* **12** IR (neat) 2931, 2712, 1722, 1700, 1502, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.84–6.75 (m, 2H), 6.63 (d, J = 3.0 Hz, 1H), 4.32 (d, J = 9.9 Hz, 1H), 3.75 (s, 6H), 3.52–3.45 (m, 1H), 1.85–1.75 (m, 2H), 1.62–1.47 (m, 4H), 1.31 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.51, 199.25, 153.70, 152.18, 124.03, 116.57, 113.09, 111.86, 56.03, 55.67, 51.88, 46.34, 45.70, 42.01, 31.89, 25.43, 24.61, 21.58; HRMS (ES) m/z calcd for $C_{18}H_{24}O_4$ (M+Na$^+$): 327.1572; found: 327.1571; *Compound* **14** IR (neat) 3580, 2930, 1496, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73–6.65 (m, 3H), 6.02–5.88 (m, 1H), 5.62–5.50 (m, 1H), 4.92–4.75 (m, 4H), 4.29–4.17 (m, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 2.82 (s, 1H), 2.69–2.65 (m, 1H), 2.44 (d, J = 6.9 Hz, 1H), 2.24 (dd, J = 15.6, 6.0 Hz, 1H), 1.92 (dd, J = 15.7, 7.6 Hz, 1H), 1.52–1.23 (m, 5H), 0.97 (s, 3H), 0.94 (s, 9H), 0.92 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H); HRMS (ES) m/z calcd for $C_{29}H_{48}O_4Si$ (M+Na$^+$): 511.3220; found: 511.3227; *Compound* **15** IR (neat) 3583, 3493, 2931, 1497, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 8.9 Hz, 1H), 6.73 (d, J = 2.9 Hz, 1H), 6.67 (dd, J = 8.8, 3.0 Hz, 1H), 6.31–6.20 (m, 1H), 5.53–5.44 (m, 1H), 5.12–4.78 (m, 4H), 4.27 (t, J = 8.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.68 (d, J = 9.9 Hz, 1H), 2.83–2.68 (m, 4H), 1.85 (s, 1H), 1.69–1.34 (m, 5H), 1.01 (s, 3H), 0.96 (s, 9H), 0.93 (s, 3H), 0.14 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.93, 151.20, 140.64, 138.05, 130.14, 118.44, 115.75, 115.03, 111.95, 110.77, 78.02, 75.86, 56.17, 55.63 (2C), 41.79, 40.75,

39.95, 38.90, 37.93, 25.93, 25.89, 25.63, 24.95, 24.46, 21.98, 18.10, −3.85, −4.70; HRMS (ES) *m*/*z* calcd for $C_{29}H_{48}O_4Si$ (M+Na$^+$): 511.3220; found: 511.3227; *Compound* **16** IR (neat) 3440, 1588, 1495, 1464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8, 2.9 Hz, 1H), 5.84–5.72 (m, 2H), 5.56 (br s, 1H), 4.01 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.29 (d, J = 9.6 Hz, 1H), 2.56–2.45 (m, 3H), 1.49–1.39 (m, 3H), 1.29–1.21 (m, 6H), 1.22 (s, 3H), 1.00 (s, 3H), 0.89 (s, 9H), −0.09 (s, 3H), −0.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.40, 151.31, 134.56, 131.07, 130.24, 116.25, 111.05, 110.13, 75.40, 72.94, 56.21, 55.66, 46.89, 43.90, 39.53, 37.46, 32.42, 30.55, 25.90 (3C), 25.86, 23.61, 20.97, 17.89, −4.12, −6.00; HRMS (ES) *m*/*z* calcd for $C_{27}H_{44}O_4Si$ (M+Na$^+$): 483.2907; found: 483.2910; *Compound* **17** IR (neat) 3534, 1590, 1496, 1462 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, J = 3.0 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.68–6.64 (m, 1H), 6.16 (t, J = 8.5 Hz, 1H), 5.75 (dd, J = 14.8, 9.1 Hz, 1H), 4.00 (d, J = 6.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.39 (d, J = 10.5 Hz, 1H), 3.06 (dd, J = 13.9, 5.5 Hz, 1H), 2.63 (dd, J = 16.0, 10.0 Hz, 1H), 2.39 (dd, J = 13.6, 8.5 Hz, 1H), 1.91 (br s, 1H), 1.72–1.63 (m, 1H), 1.42–1.23 (m, 3H), 1.14–1.01 (m, 2H), 1.02 (s, 6H), 0.88 (s, 9H), −0.13 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.47, 151.24, 137.26, 135.31, 129.85, 116.25, 111.17, 109.78, 75.42, 72.44, 55.29, 55.68, 42.18, 40.05, 39.02, 37.39, 33.47, 29.69, 27.67, 25.92 (2C), 25.48, 22.80, 22.06, 18.06, −4.34, −5.53; HRMS (ES) *m*/*z* calcd for $C_{27}H_{44}O_4Si$ (M+Na$^+$): 483.2907; found: 483.2914; *Compound* **18** IR (neat) 2950, 1613, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 3.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.65 (dd, J = 8.7, 3.0 Hz, 1H), 5.95–5.83 (m, 2H), 5.82 (d, J = 5.2 Hz, 1H), 4.35 (t, J = 4.3 Hz, 1H), 3.81 (dd, J = 10.1, 2.8 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.92–2.86 (m, 1H), 1.54–1.38 (m, 6H), 1.19 (s, 3H), 1.13 (s, 3H), 0.82 (s, 9H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.34, 153.48, 151.57, 136.28, 135.26, 126.37, 117.02, 114.47, 110.94, 110.90, 72.50, 56.13, 55.66, 50.23, 42.29, 41.87, 38.39, 33.75, 31.82, 27.83, 25.86, 25.48, 21.87, 18.18, −4.29, −4.91; HRMS (ES) *m*/*z* calcd for $C_{27}H_{42}O_3Si$ (M+Na$^+$): 465.2001; found: 465.2817; *Compound* **21** IR (neat) 2929, 1708, 1497, 1221 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84–6.73 (m,3H), 6.25 (d, J = 10.5 Hz, 1H), 5.50–5.43 (m, 1H), 4.42 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.10 (d, J = 5.4 Hz, 1H), 2.08 (t, J = 6.1 Hz, 1H), 1.63–1.47 (m, 6H), 1.17 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.12, 153.43, 152.11, 140.33, 130.66, 129.46, 126.27, 122.11, 114.80, 112.58, 111.64, 60.06, 56.06, 55.52, 43.82, 38.61, 34.38, 31.94, 29.02, 28.44, 19.43; HRMS (ES) *m*/*z* calcd for $C_{21}H_{26}O_3$ (M+Na$^+$): 349.1780; found: 349.1767; *Compound* **6** IR (neat) 2925, 1715, 1497, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 9.0 Hz, 1H), 6.79–6.75 (m, 1H), 6.66 (d, J = 3.0 Hz, 1H), 4.23 (s, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.70–2.61 (m, 1H), 2.46–2.36 (m, 1H), 2.21–2.04 (m, 4H), 1.96–1.68 (m, 2H), 1.64–1.50 (m, 4H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.31, 153.72, 152.46, 141.48, 129.24, 127.20, 114.14, 112.43, 111.66, 61.06, 56.13, 55.48, 39.97, 39.21, 35.74, 32.44, 28.19, 27.82, 26.78, 26.22, 19.80; HRMS (ES) *m*/*z* calcd for $C_{21}H_{28}O_3$ (M+Na$^+$): 351.1936; found: 351.1920; *Compound* **24** IR (neat) 2926, 1716, 1497, 1463 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, J = 3.0 Hz, 1H), 6.78–6.73 (m, 2H), 5.64 (dd, J = 8.8, 4.9 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.94–2.87 (m, 1H), 2.79 (t, J = 11.3 Hz, 1H), 2.70–2.65 (m, 1H), 2.61–2.55 (m, 1H), 2.22–2.15 (m, 1H), 1.78–1.75 (m, 1H), 1.62–1.48 (m, 3H), 1.28–1.16 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.09, 153.57, 151.63, 150.38, 128.51, 117.42, 115.51, 111.26, 110.91, 56.07, 55.68, 49.62, 45.27, 42.42, 42.36, 38.51, 34.13, 30.36, 25.99, 22.69, 20.88; HRMS (ES) *m*/*z* calcd for $C_{21}H_{28}O_3$ (M+Na$^+$): 351.1936; found: 351.1926; *Compound* **25** IR (neat) 2926, 1716, 1498, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 2.4 Hz, 1H), 6.78–6.73 (m, 2H), 5.59 (dd, J = 9.2, 4.0 Hz, 1H), 5.08 (d, J = 11.2 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.75 (t, J = 12.0 Hz, 1H), 2.70–2.63 (m, 2H), 2.17–2.11 (m, 1H), 1.69–1.66 (m, 1H), 1.56–1.51 (m, 1H), 1.50–1.46 (m, 2H), 1.25–1.19 (m, 2H), 1.10 (d, J = 6.6 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.80, 153.64, 151.61, 150.56, 128.37, 116.55, 115.87, 111.49, 110.97, 55.99, 55.74, 50.59, 46.08, 44.02, 42.47, 38.46, 33.99, 30.29, 29.69, 25.95, 22.75, 17.88; HRMS (ES) *m*/*z* calcd for $C_{22}H_{30}O_3$ (M+Na$^+$): 365.2093; found: 365.2086; *Compound* **2** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.7 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 8.6, 2.5 Hz, 1H), 4.53 (br s, 1H, OH), 3.21–3.15 (m, 1H), 2.55 (t, J = 5.7 Hz, 2H), 2.17–2.06 (m, 3H), 1.72–1.69 (m, 2H), 1.62–1.55 (m, 3H), 1.34 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.23, 150.70, 149.10, 144.37, 129.62, 123.76, 116.46, 111.06, 110.88, 107.26, 39.52, 38.56, 35.70, 34.67, 30.52, 28.92, 27.88, 26.05, 20.02, 19.73.

13. Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792.

14. X-ray data were collected at 291 K on a Bruker Kappa APEX II diffractometer with graphite monochromated MoKα radiation (λ = 0.7107 Å). The crystal structure was solved by direct methods (SIR92) and refined by full-matrix least-squares method on F^2 using SHELXL-97. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 697873. *Compound* **15**: $C_{29}H_{48}O_4Si$, M_W = 488.33, crystal system: monoclinic, space group: $P21/n$, cell parameters: a = 20.1001(7) Å, b = 7.2963(2) Å, c = 22.5767(8) Å, β = 116.108(2)°, V = 2973.18(17) Å^3, Z = 4, ρ_{calc} = 1.072 g cm^{-3}, $F(000)$ = 1036, μ = 0.107 mm^{-1}, number of l.s. parameters = 324, R_1 = 0.0678 for 3665 reflections with $I > 2\sigma(I)$ and 0.1062 for all 5501 data. wR_2 = 0.2465, GOF = 1.086 for all data. An ORTEP diagram of **15**, drawn at 30% ellipsoidal probability, is shown below.



ORTEP diagram of **15**