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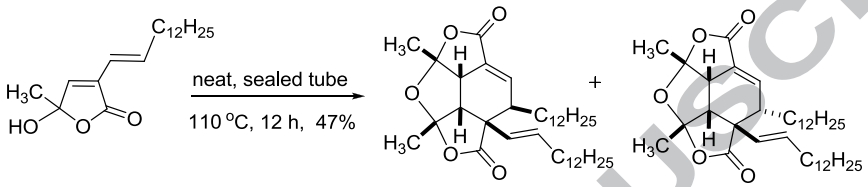

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Total synthesis of a novel oxa-bowl natural product paracaseolide A *via* a 'putative' biomimetic pathway

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ABSTRACT

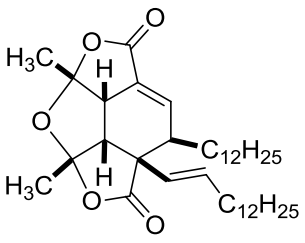
A total synthesis of bioactive tetracyclic natural product paracaseolide A, embodying an architecturally unusual oxa-bowl framework, has been accomplished from commercially available 5-methyl-2-furfural. The key step involving a thermal [4+2]-dimerization of an appropriately crafted 5-methyl-3-alkenylbutenolide is shown to proceed in a stepwise manner.

In 2011, Guo and co-workers reported[1] the isolation and structure determination of a novel natural product, paracaseolide A **1** from the stem bark of *Sonneratia paracaseolaris*, an endemic mangrove species found in China. In structural terms, tetracyclic **1** is an unusual construct that features oxa-bowl architecture and embodies a 3-alkenylbutenolide substructure reminiscent of many bioactive natural products.[2] The five oxygen atoms present in **1** essentially dot the rim of its bowl-like framework and the additional presence of two long linear hydrophobic chains on its convex surface impart the natural product a dipolarofacial character. Indeed, **1** can be formally derived through a [4+2]-type dimerization of a 3-alkenylbutenolide precursor **2**.

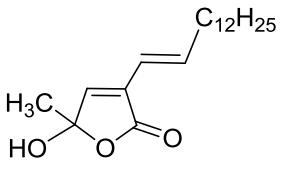
Paracaseolide **1** has been shown to exhibit impressive inhibitory activity against dual-specificity phosphatase CDC25B with an IC_{50} value of 6.44 μM. This is a potentially significant bioactivity attribute as CDC25B is a proto-oncogene in humans and shown to be over expressed in a number of cancers and is implicated in cell cycle progression in tumors.[3]

Both, on account of its complex and unusual molecular structure and its bioactivity profile, natural product **1** presents a challenging and interesting target for total synthesis. We were instantly drawn to a synthesis of **1** in view of our long standing interest in the oxa-bowl like constructs.[4] While our own efforts towards **1** were underway, two total syntheses of **1** from the groups of Vassilikogiannakis[5] and Kraus[6] have appeared in the very recent past. Herein we report a total synthesis of **1**, essentially along the proposed biosynthetic route[1,5] involving the [4+2]-dimerization of a butenolide precursor **2**. Such a biomimetically patterned approach to **1** involving the [4+2]-dimerization was successfully implemented in the first synthesis of the natural product by Vassilikogiannakis *et al.*[5] However, our access to the key precursor **2** is shorter, well differentiated and the outcome of the dimerization protocol is somewhat different, which in turn sheds some light on the nature of the [4+2]-type dimerization leading to the natural product.

In our quest for **1**, we initially carried out a model study in which a sibling 3-alkenylbutenolide **3** was deployed to probe the



Paracaseolide A (**1**)



3-alkenylbutenolide (**2**)

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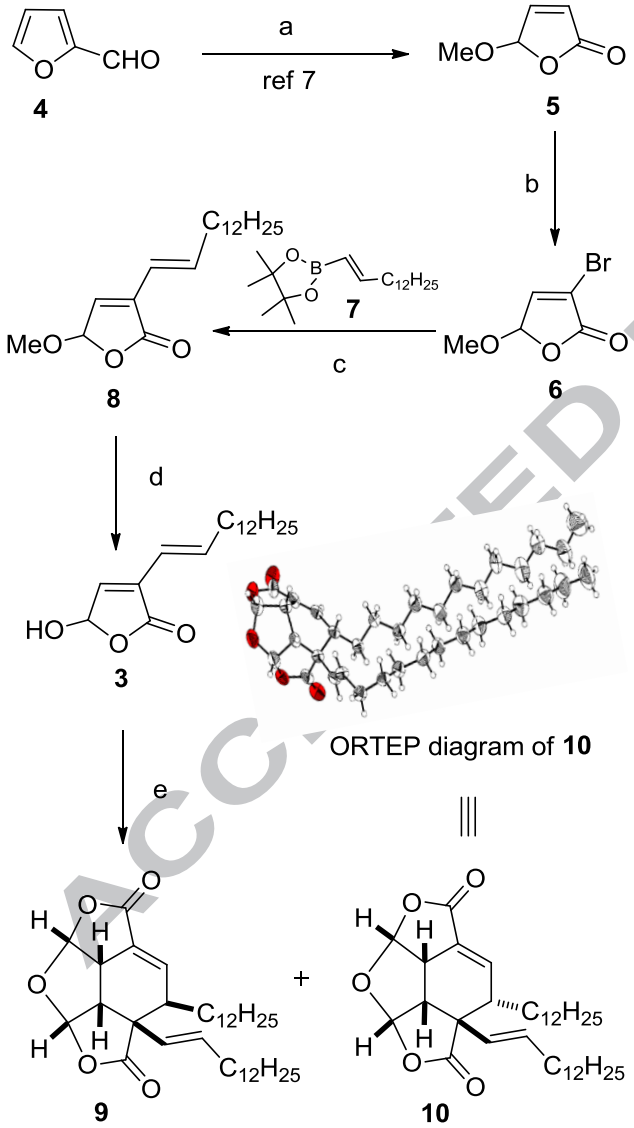
key dimerization process. Commercially available furfural **4** was elaborated to butenolide **5** *via* a known[7] protocol involving dye sensitized photo-oxygenation as the key step, Scheme 1. Bromine addition[8] to **5** and *in situ* dehydrobromination led to 3-bromo-butenolide **6**. Pd-mediated Suzuki cross-coupling[9] between **6** and vinylicboronate **7** delivered 3-alkenylbutenolide **8** and further 5-methoxy deprotection[10] led to the requisite 3-alkenylbutenolide **3**.[11] Heating (neat, sealed tube, 100 °C) **3** triggered the tandem [4+2]-type dimerization and concomitant dehydration to furnish a mixture (40:60) of two diastereomeric dimers **9** and **10** in 52% isolated yield. Stereo-structures of **9** and **10** were derived through incisive analyses of their 2D NMR (COSY, HMBC and ROESY) studies and the key connectivities are displayed in Figure 1. In addition, structure of one of the diastereomers **10** was further verified by a single crystal X-ray structure determination and an ORTEP[12] is shown in Scheme 1. Interestingly, in **9** both the alkenyl and the alkyl hydrophobic



Scheme 1. *Reagents and conditions*. (a) (i) $^1O_2$, MeOH; (ii) MeOH, reflux, 3 d; (b) 1.2 equiv Br_2, 0.08 equiv PBr_3, CCl_4, 0 °C-rt, 12 h; py, 0 °C-rt, 4 h 65%; (c) 1.5 equiv **7**, 3 mol% $PdCl_2$dppf, 4 equiv CsF, 1 equiv TBAB, THF/H_2O (4:1), μW, 100 °C, 4 min, 41%; (d) TFA/acetone/H_2O (1:1:1), 0 °C-rt, 2 h, 59%; (e) neat, sealed tube, 100 °C, 14.5 h 52% (9:10 = 2:3).

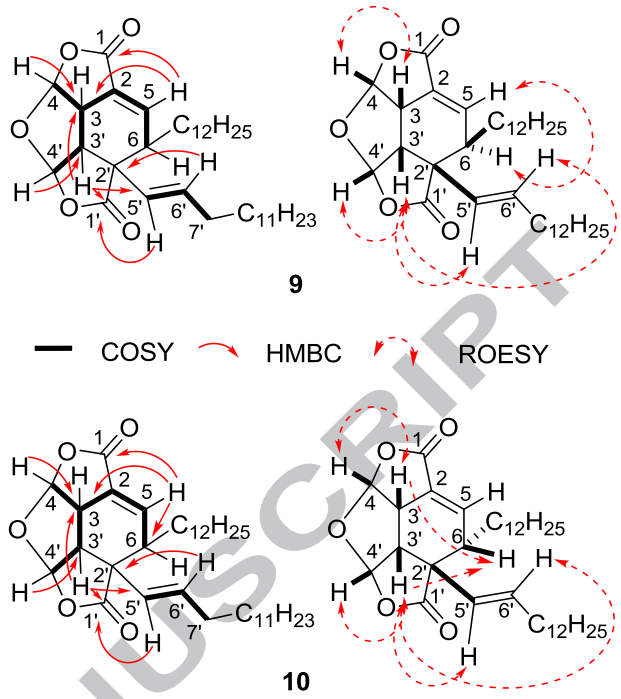
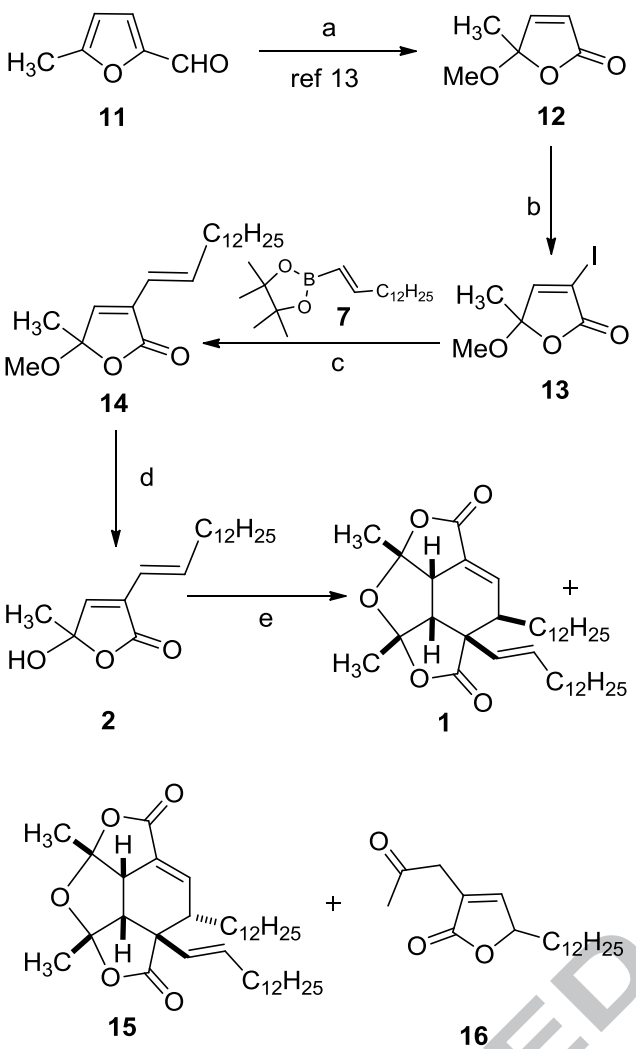


Figure 1. Key HMBC, COSY, ROESY connectivities of compound **9**, **10**.

chains are *cis* disposed and located on convex surface as present in the natural product **1**, but in the diastereomer **10** the two chains are *trans* with the alkyl chain protruding towards the cavity of the oxa-bowl. In separate experiments, it was shown that under the conditions of thermal activation employed to effect dimerization, both **9** and **10** were stable and did not interconvert. This clearly established that **9** and **10** were independently produced during the [4+2]-dimerization protocol.

Having demonstrated the viability of the 3-alkenylbutenolide dimerization in **3**, it was decided to extend the protocol to 5-methyl-3-alkenylbutenolide **2** to target the natural product **1**. Towards this end, 5-methyl-2-furfural **11** was photooxygenated[13] to 5-methylbutenolide **12** (Scheme 2). Single pot iodination-dehydroiodination in **12** led to 5-methyl-3-iodobutenolide **13**. Pd-mediated Suzuki cross-coupling between **13** and vinylic boronate **7** delivered **14** in which methoxy deprotection[10] was smoothly implemented to furnish the desired 5-methyl-3-alkenylbutenolide **2**. Thermal activation (neat, sealed tube, 110 °C) of **2** led to the formation of two diastereomeric dimers **1**, **15** and a ring opened compound **16**[5] in 66% yield and in a ratio of 4.9:1:2.4. While it was pleasing to establish the identity of the major dimeric product with the natural product paracaseolide A **1** through appropriate spectral comparison, the structure of the minor product **15** had to be deduced from 2D NMR studies (COSY, HMBC, ROESY) and the connectivities are displayed in Figure 2. Once again, we observed that subjecting either **1** or **15** to prolonged thermal activation did not provide any evidence of interconversion among them. Thus, indicating an independent origin of both the natural product **1** and its epimer **15** during the dimerization process.



Scheme 2. Synthesis of diastereomeric dimers paracaseolide A (**1**), **15,** and **16**; *Reagents and conditions*. (a) (i) $^1O_2$, MeOH; (b) 4 equiv I_2, Py/CCl_4(1:1), 0 ^oC-rt, 24 h, 50%; (c) 1.5 equiv **7**, 3 mol% $PdCl_2$dppf, 4 equiv CsF, 1 equiv TBAB, THF/H_2O (4:1), µW, 120 ^oC, 40 min, 60%; (d) TFA/acetone/H_2O (1:1:1), 0 ^oC-rt, 13 h, 82%; (e) neat, sealed tube, 110 ^oC, 12 h, 66% (**1**:**15**:**16** = 4.9:1:2.4).

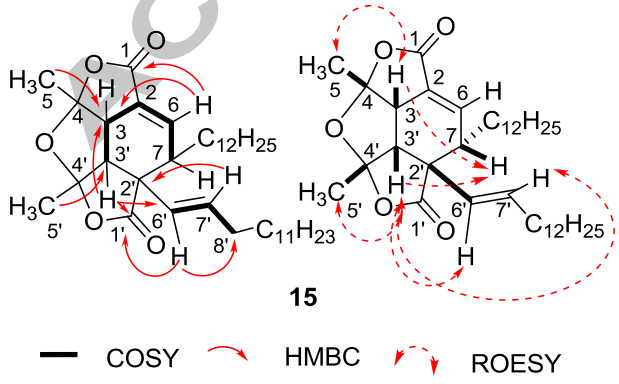
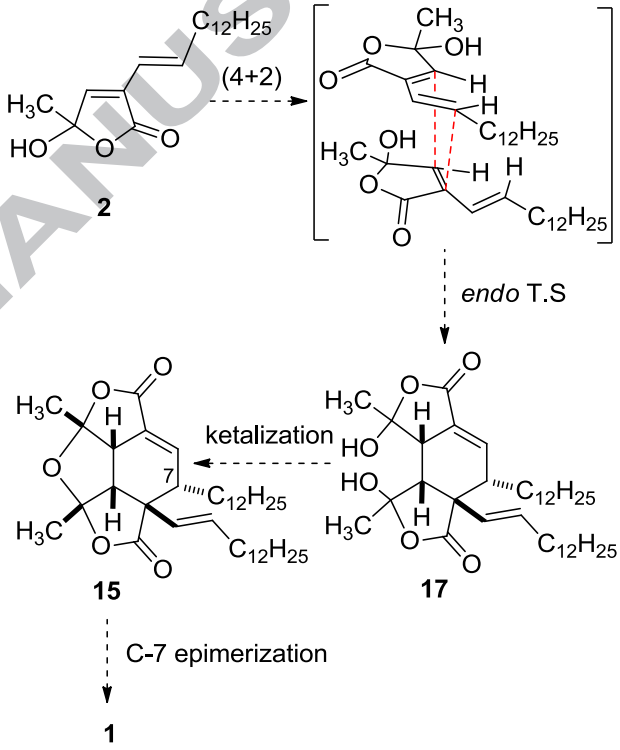


Figure 2. Key HMBC, COSY, ROESY connectivities of compound **15**.

During their synthesis of paracaseolide A **1**, involving the dimerization of **2**, Vassilikogiannakis *et al.*[5] hypothesized initial formation of a Diels-Alder dimer **17** in a stereoselective manner through a concerted *endo*-transition state. Intramolecular dehydration in **17** could led to a tetracycle **15** (unknown prior to the present work). An epimerization of the sp^3 anchored alkyl side arm in **15** was proposed to account for the generation of the requisite *cis* stereochemistry of the alkyl and alkenyl arms to eventuate in the natural product (Scheme 3). As it turned out, the earlier authors[5] observed the formation of only one diastereomer, namely natural product **1**, during the thermal activation of **2**, contrary to our observation of formation of **1** and **15** under essentially the same conditions. While the reasons for this discrepancy remain unclear at the moment, formation of two non-interconvertible diastereomers during the dimerization of 3-alkenylbutenolides **2** and **3** in the present study is indicative of the involvement of a step-wise process involving [4+2]-dimerization. We intend to probe this issue further employing experimental and quantum mechanical approaches to delineate the mechanistic contours of the dimerization process.



Scheme 3. Proposed route[5] for the dimerization of **2** to deliver the natural product **1**

In short, we have outlined a concise approach to the bioactive natural product paracaseolide A from commercially available 5-methyl-2-furfural through a 'putative' biomimetic approach that involves [4+2]-dimerization of a suitably crafted 5-methyl-3-alkenylbutenolide **2**.

Acknowledgments

One of us (LV) thanks CSIR, India for the award of a research fellowship. F.A.K. acknowledges CSIR for financial support. G.M. acknowledges the research support from Eli Lilly and Jubilant-Bhartia Foundations and the facilities extended by the University of Hyderabad. We thank Dr. Saikat Sen for determining the X-ray crystal structure.

Supplementary Material

Supplementary data (experimental procedures and copies of ^{1}H and ^{13}C NMR, HMBC, HSQC, COSY, ROESY spectra), associated with this article can be found in the online version, at

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11. 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: **8** IR (Neat) 2923, 2853, 1772, 1662, 1465, 1366, 1341, 1210, 1124, 1089, 1028, 981, 939 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.86 (dt, *J* = 15.9, 7.5 Hz, 1H), 6.76 (s, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 5.75 (s, 1H), 3.55 (s, 3H), 2.16 (q, *J* = 7.5 Hz, 2H), 1.45-1.39 (m, 2H), 1.25 (br s, 18H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 141.3, 138.8, 133.2, 117.9, 102.0, 56.7, 33.5, 31.9, 29.7, 29.64, 29.56, 29.45, 29.36, 29.2, 28.6, 22.7, 14.1; HRMS (+APCI) m/z calcd for $C_{19}H_{33}O_3$ $(M + H)^+$ 309.2430, found 309.2417; **3** mp. 40-42 ºC; IR (Neat) 3369, 2956, 2922, 2852, 1767, 1662, 1466, 1282, 1206, 1090, 1012, 973, 925, 873 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.85 (s, 1H), 6.86-6.81 (m, 1H), 6.11 (s, 1H), 6.08 (d, *J* = 16.5 Hz, 1H), 4.10 (br s, 1-OH), 2.16 (q, *J* = 7.1 Hz, 2H), 1.44-1.40 (m, 2H), 1.25 (br s, 18H), 0.87 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 141.3, 140.5, 132.7, 117.7, 96.5, 33.5, 31.9, 29.68, 29.67, 29.66, 29.59, 29.5, 29.4, 29.3, 28.6, 22.7, 14.1; HRMS (+APCI) m/z calcd for $C_{18}H_{31}O_3$ $(M + H)^+$ 295.2273, found 295.2257; **9** IR (Neat) 2923, 2853, 1779, 1671, 1461, 1352, 1302, 1207, 1167, 1118, 1010, 933, 894 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 7.6, 3.3 Hz, 1H), 6.21 (d, *J* = 5.8 Hz, 1H), 6.00 (d, *J* = 5.5 Hz, 1H), 5.79 (dt, *J* = 15.7, 6.8 Hz 1H), 5.47 (d, *J* = 15.7 Hz, 1H), 3.65-3.60 (m, 1H), 3.52 (dd, *J* = 9.9, 5.5 Hz, 1H), 3.14-3.10 (m, 1H), 2.10 (q, *J* = 6.8 Hz, 2H), 1.73-1.65 (m, 1H), 1.39-1.20 (m, 41H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.3, 166.5, 146.0, 135.2, 127.2, 126.0, 106.6, 106.3, 57.5, 46.8, 44.6, 40.9, 32.7, 31.9, 29.69, 29.66, 29.63, 29.5, 29.41, 29.36, 29.1, 28.9, 28.2, 28.1, 22.7, 14.1; HRMS (+APCI) m/z calcd for $C_{36}H_{59}O_5$ $(M + H)^+$ 571.4363, found 571.4351; **10** IR (Neat) 2921, 2852, 1775, 1670, 1466, 1349, 1208, 1004, 929, 890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (t, *J* = 3.8, 1H), 6.21 (d, *J* = 5.7 Hz, 1H), 5.90 (d, *J* = 5.5 Hz, 1H), 5.65 (dt, *J* = 15.7, 6.8 Hz 1H), 5.44 (d, *J* = 15.7 Hz, 1H), 3.54-3.49 (m, 1H), 3.43 (dd, *J* = 10.2, 5.5 Hz 1H), 2.26-2.22 (m, 1H), 2.12-2.02 (m, 2H), 1.79-1.76 (m, 1H), 1.38-1.20 (m, 41H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 166.1, 145.6, 135.2, 128.2, 126.3, 106.5, 106.1, 59.1, 52.2, 45.8, 41.7, 32.6, 31.9, 29.69, 29.66, 29.64, 29.60, 29.59, 29.44, 29.40, 29.37, 29.1, 28.9, 28.6, 27.5, 22.7, 14.1; HRMS (+APCI) m/z calcd for $C_{36}H_{59}O_5$ $(M + H)^+$ 571.4363, found 571.4333; **14** IR (Neat) 2923, 2853, 1774, 1720, 1463, 1376, 1362, 1281, 1178, 1125, 1070, 1032, 1006, 947 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.86 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.71 (s,1H), 6.09 (d, *J* = 15.8 Hz, 1H), 3.21 (s, 3H), 2.17 (q, *J* = 6.9 Hz, 2H), 1.63 (s, 3H), 1.45-1.40 (m, 2H), 1.25 (br s, 18H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 142.9, 141.0, 132.4, 117.8, 106.8, 51.2, 33.5, 31.9, 29.67, 29.65, 29.64, 29.56, 29.5, 29.4, 29.3, 28.6, 24.0, 22.7, 14.1; HRMS (+APCI) m/z calcd for $C_{20}H_{35}O_3$ $(M + H)^+$ 323.2581, found 323.2586; **2** mp. 40-42 ºC; IR (Neat) 3371, 2922, 2853, 1745, 1659, 1460, 1372, 1260, 1171, 1106, 1055, 971, 930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.83 (s, 1H), 6.76 (dt, *J* = 15.9, 7.2 Hz, 1H), 6.02 (d, *J* = 15.9 Hz, 1H), 4.12 (br s, 1-OH), 2.13 (q, *J* = 7.2 Hz, 2H), 1.68 (s, 3H), 1.43-1.39 (m, 2H), 1.25 (br s, 18H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 144.1, 140.9, 130.7, 117.8, 104.1, 33.5, 31.9, 29.68, 29.66, 29.64, 29.58, 29.5, 29.4, 29.3, 28.7, 24.8, 22.7, 14.1; HRMS (+APCI) calcd for $C_{19}H_{33}O_3$ $(M + H)^+$ 309.2424, found 309.2414; **1** IR (Neat) 2922, 2853, 1772, 1671, 1460, 1388, 1351, 1310, 1276, 1197, 1155, 1124, 1055, 983, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (dd, *J* = 7.7, 3.2 Hz, 1H), 5.83 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.48 (d, *J* = 15.8 Hz, 1H), 3.37 (dd, *J* = 9.5, 3.2 Hz, 1H), 3.30 (d, *J* = 9.5 Hz, 1H), 3.07-3.01 (m, 1H), 2.11 (q, *J* = 6.9 Hz, 2H), 1.75 (s, 3H), 1.69-1.65 (m, 1H), 1.62 (s, 3H), 1.39-1.15 (m, 41H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 166.2, 144.7, 135.1, 129.3, 126.3, 115.4, 113.8, 58.3, 50.3, 46.7, 45.1, 32.7, 31.9, 29.68, 29.66, 29.64, 29.55, 29.42, 29.36, 29.1, 29.0, 28.2, 28.0, 26.6, 25.7, 22.7, 14.1; HRMS (+APCI) calcd for $C_{38}H_{63}O_5$ $(M + H)^+$ 599.4670, found 599.4646; **15** IR (Neat) 2922, 2853, 1771, 1673, 1460, 1387, 1311, 1273, 1237, 1121, 1057, 973, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (t, *J*= 3.7 Hz, 1H), 5.69 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.43 (d, *J* = 15.7 Hz, 1H), 3.27 (d, *J* = 9.6 Hz, 1H), 3.19 (d, *J* = 9.6 Hz, 1H), 2.14-1.96 (m, 3H), 1.74 (s, 3H), 1.59 (s, 3H), 1.38-1.15 (m, 42H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:173.2, 165.8, 144.3, 135.3, 130.3, 127.3, 114.7, 113.7, 59.9, 55.3, 47.4, 45.9, 32.6, 31.9, 29.68, 29.66, 29.6, 29.44, 29.40, 29.37, 29.2, 29.0, 28.6, 27.5, 26.7, 25.6, 22.7, 14.1; HRMS (+APCI) calcd for $C_{38}H_{66}NO_5$ $(M + NH_4)^+$ 616.4936, found 616.4917; **16** IR (Neat) 2923, 2853, 1757, 1725, 1465, 1357, 1163, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, *J* = 1.3 Hz, 1H), 5.00-4.97 (m, 1H), 3.45 (s, 2H), 2.25 (s, 3H), 1.74-1.67 (m, 2H), 1.46-1.24 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}CNMR$ (100 MHz, $CDCl_3$) δ: 203.1, 173.5, 152.2, 126.6, 82.1, 38.9, 33.4, 31.9, 30.3, 29.7, 29.63, 29.59, 29.5, 29.4, 29.34, 29.31, 25.0, 22.7, 14.1; HRMS(+APCI) m/z calcd for $C_{19}H_{33}O_3$ $(M + H)^+$ 309.2430, found 309.2422.
12. Single crystal X-ray diffraction data was collected on a Bruker AXS SMART APEX CCD diffractometer. The X-ray generator was operated at 45 KV and 30 mA using MoK_{α} radiation. The data was collected with a ω scan width of 0.3°. A total of 600 frames per set were collected using SMART in three different settings of φ (0°, 90° and 180°), keeping the sample to detector distance of 6.023 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 were used to determine the space group. The crystal structure was solved by direct methods using SIR92 and refined by full-matrix least-squares method using SHELXL97. Crystal data for **10** $C_{36}H_{58}O_5$, MW = 570.82, monoclinic, space group $P2_1/n$, cell parameters a = 6.0635(13), b = 71.972(15), c = 8.1928(17) Å, β = 99.310(4)°, V = 3528.3(13) $Å^3$, Z = 4, ρ_{calcd} = 1.075 g/cm^3, 15564 reflections measured, 5795 unique (R_{int} = 0.1131), $R1$ = 0.1187 and $wR2$ = 0.2768 for 1967 observed relections. Crystallographic data (excluding structure factors) for the structure in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 923267. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
13. Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1983**, *24*, 1193.