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Towards a Biomimetic Synthesis of the Marine Alkaloids Papuamine and Haliclonadiamine: Model Studies

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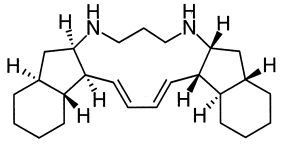
Abstract—A plausible biosynthetic pathway for the isomeric marine alkaloids papuamine and haliclonadiamine via the double tandem ene cyclisation of a tetraenediimine is proposed. Initial model studies directed toward the biomimetic synthesis of these alkaloids are described which illustrate that the Lewis acid-promoted ene cyclisation of methyl-2-(methoxycarbonyl)dodeca-2,8-dienoate is critically dependent on the Δ-8 geometry.

Papuamine **1**,[1] a C_2-symmetric antifungal alkaloid, and haliclonadiamine **2**,[2] an unsymmetrical diastereomer of **1**, were isolated from apparently identical sponges of the genus *Haliclona* collected from Papua New Guinea and Palau, respectively.



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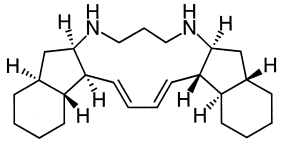

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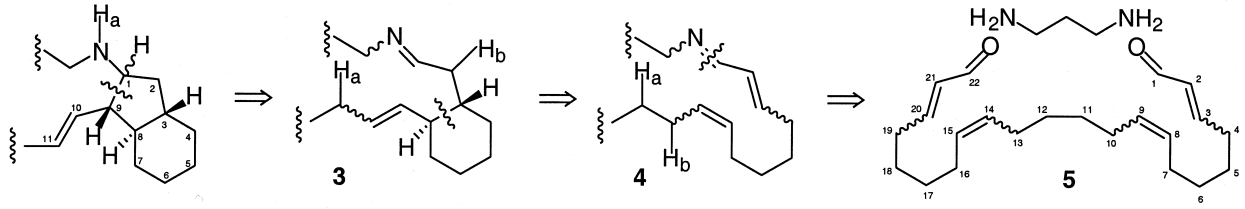
Whilst it has been noted that **1** is formally derivable from an unbranched C_{22} hydrocarbon and 1,3-diaminopropane,[1] nothing is known about the biosynthesis of these alkaloids. In this paper a plausible biosynthetic pathway to **1** and **2** is advanced and the results of initial studies directed towards a biomimetic synthesis of these alkaloids are reported.

Retrosynthetic analysis suggests that both **1** and **2** may be biosynthesised from a macrocyclic diimine via a pair of tandem ene reaction cascades. Thus disconnection of the C-1, C-9 and C-14, C-22 bonds in **1** or **2** via a pair of imino–ene reactions gives the tricyclic intermediate **3**, which on further disconnection across the C-3, C-8 and C-15, C-20 bonds via a pair of all-carbon ene reactions gives the macrocyclic diimine **4**. Finally, disconnection of the imines in **4** gives the dialdehyde **5**, which could be of either polyketide or fatty acid origin, and 1,3-diaminopropane (Scheme 1).

A key issue in the application of this analysis to the synthesis of **1** and **2** is the effect of Δ-7 geometry on the intramolecular ene reaction of disubstituted 1,7-dienes bearing an electron withdrawing group at C-1. Tietze has shown that the Knoevenagel adducts from condensation of trisubstituted-1,6-enals, such as citronellal, with dimethyl malonate undergo a thermal or Lewis acid promoted



3 **4** **5**

Scheme 1.

Keywords: dienes; enals; ene reactions; steric and strain effects.

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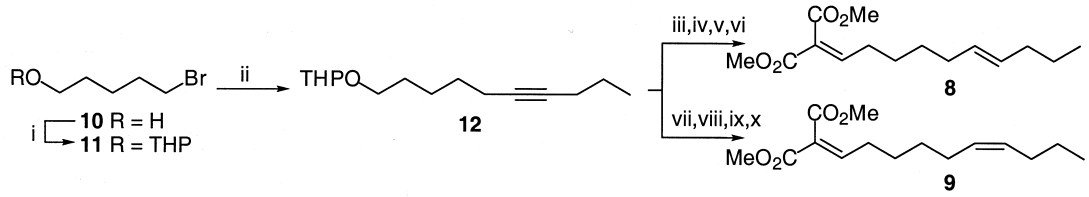
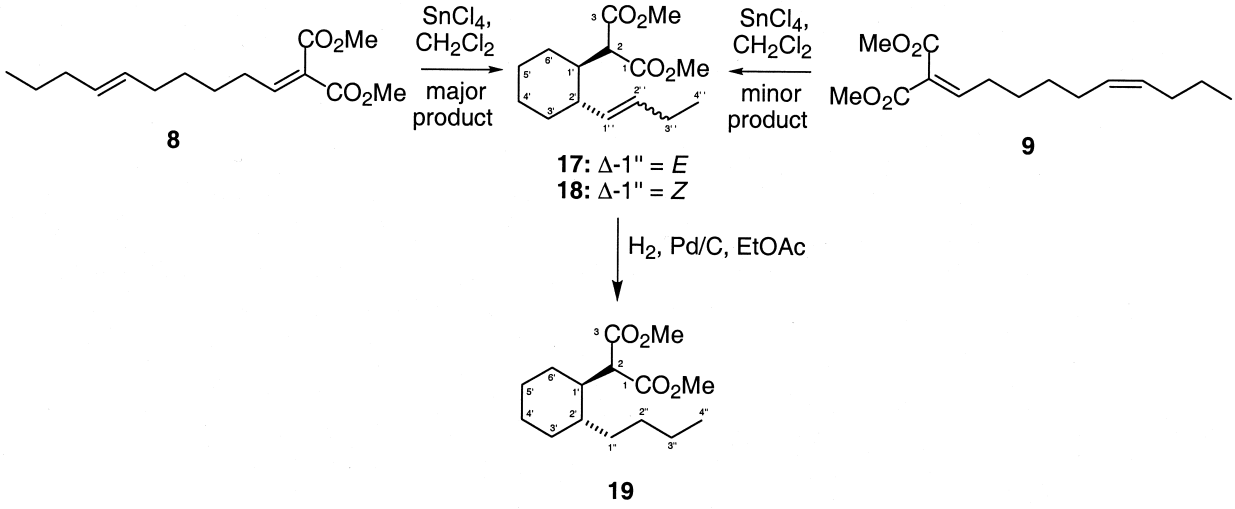


Scheme 2. Reagents and conditions: (i) 3,4-dihydro-2*H*-pyran, $TsOH \cdot H_2O$, CH_2Cl_2, 0–25°C, 78%; (ii) 1-pentyne, *n*-BuLi, THF, DMPU, −78 to 20°C, 78%; (iii) Na, NH_3(l), Et_2O, −33°C, ca. 88% (**13**); (iv) Amberlyst H-15®, MeOH, 45°C, 94% (**14**); (v) DMP, CH_2Cl_2, 0°C, ca. 94% (**6**); (vi) $CH_2(CO_2Me)_2$, piperidinium acetate, CH_2Cl_2, 25°C, ca. 51%; (vii) Lindlar's catalyst, quinoline, CH_2Cl_2, 20°C, 89% (**15**); (viii) Amberlyst H-15®, MeOH, 45°C, 90% (**16**); (ix) DMP, CH_2Cl_2, 0°C, ca. 97% (**7**); (x) $CH_2(CO_2Me)_2$, piperidine, AcOH, CH_2Cl_2, 0–25°C, 40%.



Scheme 3.

intramolecular ene reaction to yield *trans*-1,2-disubstituted cyclohexanes as the major product.[3] It was therefore decided to investigate the ene reaction of the corresponding Knoevenagel adducts derived from the disubstituted isomeric enals (*E*)- and (*Z*)-6-decenal, **6** and **7**.

(*E*)- and (*Z*)-Knoevenagel adducts **8** and **9** were synthesised according to the routes outlined in Scheme 2. Thus 5-bromopentan-1-ol **10**[4] was protected as the THP‡ ether **11**[5] which was reacted with lithium pentynylide in THF/DMPU[6] to give the acetylene **12**. Reduction of this acetylene with sodium in liquid ammonia[7] gave the (*E*)-alkene **13** which was deprotected with Amberlyst H-15® in methanol[8] to give (*E*)-decen-1-ol **14**. Oxidation with the Dess–Martin periodinane[9] gave (*E*)-6-decenal **6**. Similarly, reduction of **12** with Lindlar's catalyst[10] followed by deprotection and oxidation gave (*Z*)-decenal **7**. Condensation of these aldehydes with dimethyl malonate was carried out using modification of the conditions reported by Tietze[3] to avoid aldol condensation of the aldehyde with itself.

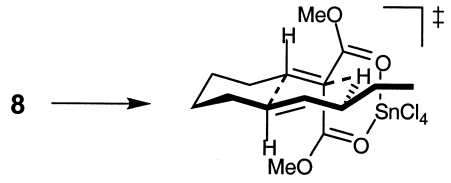
With a synthetic route to the desired isomeric Knoevenagel adducts established, the effect of the Δ-8 double bond geometry on the intramolecular ene reaction of these compounds was examined next. Reaction of methyl (*E*)-2-(methoxycarbonyl)dodeca-2,8-dienoate **8** with tin tetrachloride (1.3 equiv.) in dichloromethane at 0–25°C for 16 h afforded the *trans*-1,2-disubstituted cyclohexane intramolecular ene adduct as the major product after aqueous workup, which could be isolated by chromatography as an inseparable mixture of geometrical isomers **17** and **18** (*E*:*Z* 7:1) in up to 48% yield. Reaction at −30°C for three days gave yields of up to 53% but no change in the ratio of *E* to *Z* isomers. In contrast, reaction of methyl (*Z*)-2-(methoxycarbonyl)dodeca-2,8-dienoate **9** under the same sets of conditions gave crude mixtures containing **17** and **18** as only a minor component (ca. 10%), along with a number of other products that could not be unambiguously identified but that lacked alkenyl hydrogens and as such appeared not to derive from an intramolecular ene reaction (Scheme 3).

The relative stereochemistry of the ring substituents in **17** could not be determined directly due to overlap of the H-1′ and H-2′ resonances in the ^{1}H NMR spectrum of this compound. Therefore **17** and **18** were hydrogenated over palladium on carbon to give the 1″,2″-dihydro derivative **19**.[11] The signal due to H-1′ appeared as a complex multiplet in the NMR spectrum of this compound, which upon homonuclear decoupling of the H-2 resonance collapsed to an apparent triplet of doublets. This splitting pattern is consistent with the coupling of H-1′ to two axial hydrogens (H-2′ and H-6′$_{ax}$, J=10 Hz) and one equatorial hydrogen

‡ Abbreviations: DMP, Dess–Martin periodinane; DMPU, *N*,*N*′-dimethyl-*N*,*N*′-propylene urea; THF, tetrahydrofuran; THP, tetrahydropyranyl; Ts, toluene-4-sulfonyl; ax, axial; eq, equatorial.

(H-6′$_{eq}$, J=3 Hz), and thus the *trans*-orientation of the substituents on the cyclohexane ring.

The reduced tendency toward intramolecular ene reaction of **9** compared with **8** can be rationalised by considering the transition state conformations for concerted cyclisation of these isomeric substrates. Whilst **8** can undergo cyclisation via the *trans*-decalin-like transition state **20**, the cyclisation of **9** to give **17** requires the reaction to proceed via the much more strained chair/twist boat transition state **21**.[12] Thus the intramolecular ene reaction of **9** is much less facile than that of **8**, allowing other reactions to compete. These results suggest that the geometry of the Δ-8 and Δ-14 double bonds in the proposed biosynthetic precursor **5** is (*E*).



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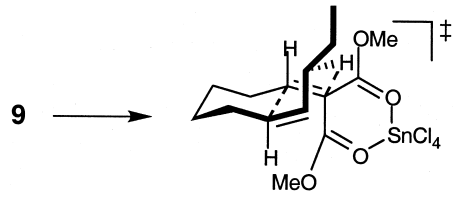

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It is interesting to compare these results with those reported for the tin tetrachloride-promoted reaction of the *E*- and *Z*-allylsilanes **22** and **23**.[13] Whilst the *Z*-allylsilane **23** gave in 80% yield almost exclusively the *trans*-1,2-disubstituted cyclohexane **24** (*trans*:*cis* >96:4), the *E*-allylsilane **22** reacted with lower overall diastereoselectivity, but (presumably) still gave **24** as the major product (Scheme 4). However, the presence of the allylsilyl group means that the cyclisation mechanism probably differs from the cases described in this paper.

Investigation of the imino–ene reaction is now in progress. Ultimately we hope to produce a perhydroindane unit with the same stereochemistry as half of papuamine thus demonstrating the chemical feasibility of the biogenetic hypothesis. This methodology, if then applied to the ene reactions of dialdehyde **5**, may allow simultaneous construction of both halves of papuamine in a very concise manner.

Experimental

General experimental details are as previously published[14] with the following amendments:

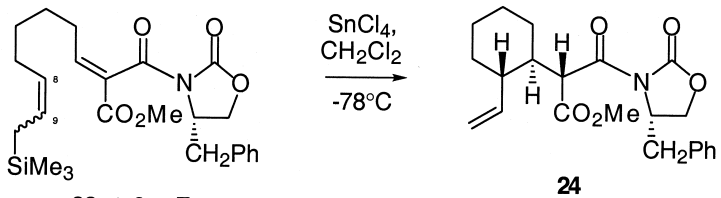
Proton magnetic resonance spectra (^{1}H NMR) recorded at 300 MHz were obtained using a Bruker WH 300 spectrometer.

Low resolution mass spectra (*m*/*z*) were recorded on a Micromass Platform APCI (APCI) or VG Mass Lab Trio-1 (GCMS) spectrometer by chemical ionisation (CI^+). High resolution mass spectra were recorded on a VG AutoSpec spectrometer by ammonia chemical ionisation in the Dyson Perrins Laboratory.

The Dess–Martin periodinane was prepared according to a literature method.[15] The fractions of light petroleum ether boiling between 30 and 40°C and between 40 and 60°C are referred to as ‘pentanes’ and ‘hexanes’, respectively.

2-(6′-Decynyloxy)tetrahydropyran (12). Following a standard procedure,[6] from 2-(5′-bromopentyloxy)tetrahydropyran (**11**) (12.13 g, 48.3 mmol) was obtained 2-(6′-decynyloxy)tetrahydropyran (**12**) (8.99 g, 78%) as a colourless oil; R_f 0.2 in 1:19 ether/hexanes; ν_{max} (film)/cm^{-1} 2937s, 2869s (C–H), 1455m, 1137m, 1120s, 1078s and 1036s; δ_H (300 MHz; $CDCl_3$) 0.97 (3H, t, J=7.5 Hz, 10′-H$_3$), 1.45–1.83 (14H, m, 3-H$_2$, 4-H$_2$, 5-H$_2$, 2′-H$_2$, 3′-H$_2$, 4′-H$_2$ and 9′-H$_2$), 2.09–2.19 (4H, m, 5′-H$_2$, 8′-H$_2$), 3.36–3.53 (2H, m, 1′-H$_2$), 3.70–3.87 (2H, m, 6-H$_2$) and 4.59 (1H, t, J=3.5 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 13.27 (C10′), 18.53, 19.46, 20.58, 22.36, 25.36, 28.86, 29.16, 30.62 (C3, C4, C5, C2′, C3′, C4′, C5′, C8′ and C9′ (two CH_2 coincident), 62.21, 67.44 (C6 and C1′), 80.13 (C6′ and C7′) and 98.86 (C2); *m*/*z* (GCMS, CI^+) 256 (MNH_4^+, 0.6%), 239 (MH^+, 0.7), 172 (3), 155 (1), 137 (1), 102 (32), 85 (100) and 55 (6); *m*/*z* (accurate) found 239.2010 for MH^+, $C_{15}H_{27}O_2$ requires 239.2011.

(*E*)-2-(6′-Decenyloxy)tetrahydropyran (13). Following a standard procedure,[7] from 2-(6′-decynyloxy)tetrahydropyran (**12**) (7.10 g, 29.8 mmol) was obtained (*E*)-2-(6′-decenyloxy)tetrahydropyran (**13**) (7.02 g, 98%; >90% pure, the remainder being the alkyne (**12**)) as a colourless oil; R_f 0.25 in 1:19 ether/hexanes; ν_{max} (film)/cm^{-1} 2936s, 2871s (C–H), 1455w, 1353w, 1120m, 1078m and 1035s; δ_H (300 MHz; $CDCl_3$) 0.89 (3H, distorted t, J=7.5 Hz, 10′-H3), 1.30–1.86 (14H, m, 3-H$_2$, 4-H$_2$, 5-H$_2$, 2′-H$_2$, 3′-H$_2$, 4′-H$_2$ and 9′-H$_2$), 1.99 (4H, mc, 5′-H$_2$, 8′-H$_2$), 3.35–3.54 (2H, m, 1′-H$_2$), 3.70–3.91 (2H, m, 6-H$_2$), 4.58 (1H, t,



22: Δ-8 = *E*
23: Δ-8 = *Z*

24

Scheme 4.

J=3.5 Hz, 2-H) and 5.40 (2H, mc, 6′-H and 7′-H); δ_C (50 MHz; $CDCl_3$) 13.44 (C10′), 19.48, 22.57, 25.38, 29.59, 29.31, 29.47, 30.62, 32.39, 34.59 (C3, C4, C5, C2′, C3′, C4′, C5′, C8′ and C9′), 62.17, 67.56 (C6 and C1′), 98.83 (C2) and 130.42 (C6′ and C7′); *m/z* (GCMS, CI^+) 258 (MNH_4^+, 2%), 241 (MH^+, 0.5), 174 (2), 138 (1), 103 (4), 102 (61), 86 (5), 85 (100) and 84 (5).

(*Z*)-2-(6′-Decenyloxy)tetrahydropyran (15). Following a standard procedure,[10] from 2-(6′-decynyloxy)tetrahydropyran (**12**) (0.240 g, 1.00 mmol) was obtained (*Z*)-2-(6′-decenyloxy)tetrahydropyran (**15**) (0.213 g, 89%) as a colourless oil; R_f 0.3 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 2938s, 2870m (C–H), 1138m, 1120m, 1078m, 1036m and 668m; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, t, J=7.5 Hz, 10′-H_3), 1.31–1.86 (14H, m, 3-H_2, 4-H_2, 5-H_2, 2′-H_2, 3′-H_2, 4′-H_2 and 9′-H_2), 1.98–2.05 (4H, m, 5′-H_2 and 8′-H_2), 3.35–3.54 (2H, m, 1′-H_2), 3.70–3.92 (2H, m, 6-H_2), 4.59 (1H, t, J=3.5 Hz, 2-H) and 5.37 (2H, mc, 6′-H and 7′-H); δ_C (50 MHz; $CDCl_3$) 13.62 (C10′), 19.50, 22.72, 25.38, 25.78, 27.02, 29.16, 29.45, 29.53, 30.65 (C3, C4, C5, C2′, C3′, C4′, C5′, C8′ and C9′), 62.21, 67.56 (C6 and C1′), 98.87 (C2) and 130.02 (C6′ and C7′); *m/z* (GCMS, CI^+) 258 (MNH_4^+, 2%), 103 (6), 102 (100) and 85 (71).

(*E*)-6-Decen-1-ol (14). To a solution of (*E*)-2-(6′-decenyloxy)tetrahydropyran (**13**) (0.601 g, 2.50 mmol) in methanol (5 ml) was added Amberlyst H-15® (75 mg). The mixture was stirred at 45°C for 2 h. The catalyst was removed by filtration and the solvent removed in vacuo. The crude material was purified by flash chromatography (SiO_2, 1:1 ether/hexanes) to yield (*E*)-6-decen-1-ol (**14**) (0.368 g, 94%) as a colourless oil with experimental data consistent with that already published.[16]

(*Z*)-6-Decen-1-ol (16). Following the procedure used to prepare **14**, from (*Z*)-2-(6′-decenyloxy)tetrahydropyran (**15**) (0.935 g, 3.90 mmol) was obtained (*Z*)-6-decen-1-ol (**16**) (0.547 g, 90%) as a colourless oil with experimental data consistent with that already published.[16]

(*E*)-6-Decenal (6). Following a standard procedure[9] and after purification by solution in 1:4 ether/pentanes and filtration through a plug of silica to remove *o*-iodobenzoic acid, from (*E*)-6-decen-1-ol (**14**) (0.398 g, 2.55 mmol) was obtained (*E*)-6-decenal (**6**) (ca. 0.37 g, ca. 94%, the contaminant being residual ether) as a pungent volatile colourless oil; R_f 0.3 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 2958s, 2930s, 2860m (C–H), 1727s (C=O), 1458m, 969m and 735m; δ_H (300 MHz; $CDCl_3$) 0.89 (3H, distorted t, J=7.5 Hz, 10-H_3), 1.30–1.45 and 1.59–1.73 (4H and 2H 2×m, 3-H_2, 4-H_2 and 9-H_2), 1.93–2.40 (4H, m, 5-H_2 and 8-H_2), 2.43 (2H, td, J=7.5 and 2 Hz, 2-H_2), 5.40 (2H, mc, 6-H and 7-H) and 9.77 (1H, t, J=2 Hz, 1-H); δ_C (50 MHz; $CDCl_3$) 13.44 (C10), 21.34, 22.51, 29.16, 32.11, 34.55, 43.65 (C2, C3, C4, C5, C8 and C9), 129.76, 131.00 (C6 and C7) and 203.15 (C1); *m/z* (GCMS, CI^+) 172 (MNH_4^+, 81%), 110 (65), 81 (89), 67 (99) and 58 (100); *m/z* (accurate) found 153.1277 for $[M-H]^+$, $C_{10}H_{17}O$ requires 153.1279.

(*Z*)-6-Decenal (7). Following a standard procedure[9] with purification as for (**6**), from (*Z*)-6-decen-1-ol (**16**) (0.156 g, 1.00 mmol) was obtained (*Z*)-6-decenal (**7**) (ca. 0.15 g, ca. 97%, the contaminant being residual ether) as a pungent volatile colourless oil; R_f 0.3 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 3006m, 2931s, 2862s, 2718w (C–H), 1727s (C=O), 1460w and 1072w; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, distorted t, J=7.5 Hz, 10-H_3), 1.34–1.45 and 1.60–1.71 (4H and 2H, 2×m, 3-H_2, 4-H_2 and 9-H_2), 1.97–2.11 (4H, m, 5-H_2 and 8-H_2), 2.44 (2H, td, J=7.5 and 1.5 Hz, 2-H_2), 5.37 (2H, m, 6-H and 7-H) and 9.77 (1H, t, J=1.5 Hz, 1-H); δ_C (50 MHz; $CDCl_3$) 13.59 (C10), 21.49, 22.67, 26.72, 29.05, 43.68 (C2, C3, C4, C5, C8 and C9 (two CH_2 coincident)), 129.27, 130.46 (C6 and C7) and 203.14 (C1); *m/z* (GCMS, CI^+) 172 (MNH_4^+, 41%), 136 (100), 121 (22), 112 (30), 107 (32), 98 (41), 95 (36), 81 (70), 67 (39), 58 (29) and 54 (45); *m/z* (accurate) found 155.1430 for MH^+, $C_{10}H_{19}O$ requires 155.1436 found 153.1274 for $[M-H]^+$, $C_{10}H_{17}O$ requires 153.1279.

Methyl (*E*)-2-(methoxycarbonyl)dodeca-2,8-dienoate (8). To a stirred solution of dimethyl malonate (183 μl, 1.60 mmol) and piperidinium acetate (48 mg, 0.17 mmol) in dry CH_2Cl_2 (1 ml) under argon was added a solution of (*E*)-6-decenal (**6**) (0.250 g, 1.62 mmol) in CH_2Cl_2 (1 ml) dropwise over 2 h. After 2 h stirring at 25°C the solvent was removed in vacuo and the crude material purified by flash chromatography (SiO_2, 1:9 ether/hexanes) to yield methyl (*E*)-2-(methoxycarbonyl)dodeca-2,8-dienoate (**8**) (0.233 g, 57%, ca. 90% purity by ^1H NMR, the contaminant being residual dimethyl malonate) as a colourless oil; R_f 0.15 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 2954s, 2929s, 2858m (C–H), 1730s (C=O), 1644m (C=C), 1437s, 1259s, 1225s and 1063m; δ_H (300 MHz; $CDCl_3$) 0.89 (3H, distorted t, J=7.5 Hz, 12-H_3), 1.30–1.58 (6H, m, 5-H_2, 6-H_2 and 11-H_2), 1.92–2.03 (4H, m, 7-H_2 and 10-H_2), 2.30 (2H, q, J=7.5 Hz, 4-H_2), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.29 (2H, mc, 8-H and 9-H) and 7.04 (1 H, t, J=7.5 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 13.47 (C12), 22.53, 27.54, 28.94, 29.56, 32.05, 34.55 (C4, C5, C6, C7, C10 and C11), 52.14, 52.23 (2×OCH_3), 128.09 (C2), 129.90, 130.93 (C8 and C9), 150.73 (C3), 164.67 and 166.21 (C1 and 2-CO_2CH_3); *m/z* (APCI, CI^+) 291 (MNa^+, 7%), 269 (MH^+, 46), 237 (59), 205 (90), 177 (33) and 137 (100); *m/z* (accurate) found 269.1741 for MH^+, $C_{15}H_{25}O_4$ requires 269.1753.

Methyl (*Z*)-2-(methoxycarbonyl)dodeca-2,8-dienoate (9). To a cooled (0°C) solution of (*Z*)-6-decenal (**7**) (36 mg, 0.23 mmol) and dimethyl malonate (34 mg, 0.26 mmol) in CH_2Cl_2 (1 ml) were added piperidine (2.3 μl, 0.023 mmol) and glacial acetic acid (1.3 μl, 0.023 mmol). The mixture was stirred at room temperature for 1 h after which piperidine (2.3 μl, 0.023 mmol) and glacial acetic acid (1.3 μl, 0.023 mmol) were added. After a further 2.5 h the solvent was removed in vacuo and the residue dissolved in ether (10 ml). The organic phase was washed with water (2 ml), saturated aqueous $NaHCO_3$ (2 ml), water (2 ml), saturated aqueous NaCl (2 ml) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude material purified by flash chromatography (SiO_2, 1:19 ether/hexanes) to yield methyl (*Z*)-2-(methoxycarbonyl)dodeca-2,8-dienoate (**9**) (25 mg, 40%) as a colourless oil; R_f 0.2 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 3005m, 2955s, 2861m (C–H), 1728s (C=O) 1644m (C=C), 1436s, 1372m, 1259s, 1224s and 1062m;

δ_H (300 MHz; $CDCl_3$) 0.90 (3H, distorted t, J=7.5 Hz, 12-H_3), 1.31–1.58 (6H, m, 5-H_2, 6-H_2 and 11-H_2), 1.96–2.08 (4H, m, 7-H_2 and 10-H_2), 2.29 (2H, q, J=7.5 Hz, 4-H_2), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.36 (2H, mc, 8-H and 9-H) and 7.04 (1H, t, J=8.0 Hz, 3-H); δ_C (50 MHz; $CDCl_3$) 13.62 (C12), 22.68, 26.65, 27.67, 29.05, 29.60 (C4, C5, C6, C7, C10 and C11 (two CH_2 coincident)), 52.16, 52.24 (2×OCH_3), 128.05 (C2), 129.36, 130.35 (C8 and C9), 150.65 (C3) and 164.63 (C1 and 2-CO_2CH_3 coincident); m/z (APCI, CI^+) 291 (MNa^+, 5%), 269 (MH^+, 21), 237 (13), 205 (100), 177 (12) and 137 (85); m/z (accurate) found 269.1748 for MH^+, $C_{15}H_{25}O_4$ requires 269.1753.

Dimethyl (*E*)- and (*Z*)-1′,2′-*trans*-2-(2′-but-1″-enylcyclohex-1′-yl)propane-1,3-dioate (17 and 18). *Method 1:* To a cooled (0°C) solution of methyl (*E*)-2-(methoxycarbonyl)-dodeca-2,8-dienoate (**8**) (2.10 g, 7.83 mmol) in CH_2Cl_2 (100 ml) was added dropwise $SnCl_4$ (10 ml of 1.0 M solution in CH_2Cl_2, 10 mmol). The reaction mixture was stirred at 25°C for 16 h then saturated aqueous $NaHCO_3$ (50 ml) was added followed by ether (500 ml). The layers were separated and the organic layer was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ (100 ml), water (100 ml), saturated aqueous NaCl (100 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude material purified by flash chromatography (SiO_2, 1:9 CH_2Cl_2/hexanes) to yield a 7:1 mixture of dimethyl (*E*)- and (*Z*)-1′,2′-*trans*-2-(2′-buten-1″-ylcyclohex-1′-yl)-propane-1,3-dioate (**17** and **18**) (1.00 g, 48%) as a colourless oil; R_f 0.2 in 1:9 ether/hexanes; ν_{max} (film/cm^{-1} 2930m, 2855w (C–H), 1736s (C=O), 1435m, 1222m, 1153m, 1019m and 973m; δ_H (500 MHz; C_6D_6) for **17**: 0.98 (3H, t, J=7.5 Hz, 4″-H_3), 1.01–1.42 (4H, m, 3′-H_{ax}, 4′-H_{ax}, 5′-H_{ax} and 6′-H_{ax}), 1.61–1.76 (4H, m, 3′-H_{eq}, 4′-H_{eq}, 5′-H_{eq} and 6′-H_{eq}), 1.98 (2H, mc, 3″-H_2), 2.06 (1H, m, 1′-H), 2.15 (1H, m, 2′-H), 3.39 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.90 (1H, d, J=4 Hz, 2-H), 5.22 (1H, ddt, J=15.5, 9 and 1.5 Hz, 1″-H) and 5.56 (1H, dt, J=15.5 and 6.5 Hz, 2″-H); for **18**: 0.98 (3H, t, J=7.5 Hz, 4″-H_3), 1.01–1.42 (4H, m, 3′-H_{ax}, 4′-H_{ax}, 5′-H_{ax} and 6′-H_{ax}), 1.61–1.76 (4H, m, 3′-H_{eq}, 4′-H_{eq}, 5′-H_{eq} and 6′-H_{eq}), 1.98 (2H, mc, 3″-H_2), 2.06 (1H, m, 1′-H), 2.15 (1H, m, 2′-H), 3.51 (3H, s, OCH_3), 3.53 (3H, s, OCH_3), 3.88 (1H, d, J=4 Hz, 2-H), 5.12 (1H, tt, J=10.5 and 2 Hz, 1″-H) and 5.44 (1H, dt, J=10.5 and 5.5 Hz, 2″-H); δ_C (50 MHz; $CDCl_3$) for **17** (and **18**): 15.58 (C4″), 25.38, 25.53, 26.03, 28.14, 33.93 (C3′, C4′, C5′, C6′ and C3″), 42.32, 45.48 (C1′ and C2′), 51.84, 52.17 (2×OCH_3), 54.49 (C2), 132.61, 133.45 (C1″ and C2″), 169.58 and 170.45 (C1 and C3); m/z (APCI, CI^+) 270 (2%), 269 (MH^+, 24), 237 (13), 209 (9), 205 (8), 167 (12) and 137 (100); m/z (accurate) found 269.1743 for MH^+, $C_{15}H_{25}O_4$ requires 269.1753.

Method 2: To a cooled (0°C) solution of methyl (*Z*)-2-(methoxycarbonyl)dodeca-2,8-dienoate (**9**) (56 mg, 0.21 mmol) in CH_2Cl_2 (2 ml) was added dropwise $SnCl_4$ (0.25 ml of 1.0 M solution in CH_2Cl_2, 0.25 mmol). The reaction mixture was stirred at 25°C for 22 h then water (2 ml) was added followed by CH_2Cl_2 (10 ml). The layers were separated and the organic layer was washed with water (2 ml) and saturated aqueous NaCl (2 ml) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude material purified by flash chromatography (SiO_2, 1:9 ether/hexanes) to yield a mixture of compounds with R_f 0.2 (50 mg). Separation by preparative thin layer chromatography (1:9 ether/hexanes, multiple elutions) was partially successful and yielded an approximately 10:1 mixture of dimethyl (*E*)- and (*Z*)-1′,2′-*trans*-2-(2′-buten-1″-ylcyclohex-1′-yl)propane-1,3-dioate (**17** and **18**) (4 mg, 7%) as a colourless oil with spectral data as above.

Dimethyl 1′,2′-*trans*-2-(2′-butylcyclohex-1′-yl)propane-1,3-dioate (19). To a solution of dimethyl (*E*)- and (*Z*)-1′,2′-*trans*-2-(2′-but-1″-enylcyclohex-1′-yl)propane-1,3-dioate (**17** and **18**) (22 mg, 0.082 mmol) in ethyl acetate (2 ml) was added 10% Pd on activated carbon (15 mg). The reaction mixture was stirred under an atmosphere of hydrogen for 20 h then the catalyst removed by filtration. The solvent was removed in vacuo to yield dimethyl 1′,2′-*trans*-2-(2′-butylcyclohex-1′-yl)propane-1,3-dioate (**19**) (22 mg, 99%) as a colourless oil; R_f 0.2 in 1:9 ether/hexanes; ν_{max} (film)/cm^{-1} 2930s, 2858s (C–H), 1738s (C=O), 1435s, 1217s, 1147s and 1020s; δ_H (300 MHz; C_6D_6) 0.87 (3H, t, J=7.0 Hz, 4″-H_3), 1.11–1.26, 1.44–1.51, 1.61–1.72 (14H, 3×m, 2′-H, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_{ax}, 1″-H_2, 2″-H_2 and 3″-H_2), 1.94 (1H, mc, 6′-H_{eq}), 2.10 (1H, mc, 1′-H), 3.33 (3H, s, OCH_3), 3.35 (3H, s, OCH_3) and 3.88 (1H, d, J=5.5 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 13.91 (C4″), 22.79, 25.10, 25.42, 27.61, 28.20, 30.66, 32.47 (C3′, C4′, C5′, C6′, C1″, C2″ and C3″), 38.52 (C1′), 41.90 (C2′), 51.95, 52.28 (2×OCH_3), 53.11 (C2), 169.55 and 170.54 (C1 and C3), m/z (CI^+) 293 (MNa^+, 35%), 271 (MH^+, 7), 239 (37), 237 (100), 205 (33), 139 (15) and 137 (64); m/z (accurate) found 271.1907 for MH^+, $C_{15}H_{27}O_4$ requires 271.1909.

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