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# Synthesis of Plaunotol Derivatives and their Antibacterial Activities Against *Helicobacter pylori*

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**Abstract**—Plaunotol, a known antiulcer drug, has antibacterial activities against *Helicobacter pylori*. Plaunotol thiourea derivatives **2**–**4** and diol derivatives **6**–**10** were designed in search for a compound with high antibacterial activities. Thiourea derivatives **2**–**4** were synthesized regioselectively using our effective synthetic route for plaunotol (**1**), and diol derivatives **6**–**10** were also synthesized. Their antibacterial activities against *H. pylori* are described and we found that the most potent antibacterial agent was C1-thiourea derivative **2c**. 

## Introduction

*Helicobacter pylori* was first discovered in human stomach tissue in 1982,[1] and it has been demonstrated to be a major causative agent in gastritis,[2] gastric ulcer,[3] and duodenal ulcer.[4] The World Health Organization (WHO) labeled *H. pylori* as a class 1 carcinogen, since chronic infection is known to be associated with the development of gastric adenocarcinoma, one of the most common types of cancer in humans.[5] Thus, an effective antibiotic therapy to eliminate *H. pylori* would reduce the risk of ulcer recurrence and gastric cancers. *H. pylori* is a spiral-shaped, gram negative bacteria which inhabits the area between the muscus layer and the gastric epithelium. While most bacteria cannot survive in acidic environments such as that in the stomach, *H. pylori* is able to thrive in the mucus layer since the bacteria produces ammonia by urease. Urease is an enzyme that helps cleave urea into ammonia, a substance which neutralizes stomach acid and causes cellular damage.

Plaunotol (**1**),[6] the most important component of Thai folk medicine -*Plau-noi*, is a known cytoprotective antiulcer drug which stays in the mucus layer. Recently, Koga et al. reported that plaunotol (**1**) has antibacterial activity against *H. pylori,* and they suggested that the bactericidal effects of plaunotol (**1**) may be the main cause of membrane fluidity alteration.[7] The antibacterial mechanism of plaunotol is interesting, since there are few currently available antibiotics which act on the membrane of bacteria.

In view of the above fact, we designed two series of plaunotol derivatives, thiourea derivatives **2**–**4** and diol derivatives **6**–**10** (Scheme 1). Since thiourea is known to inhibit urease activity,[8] we designed several plaunotol thiourea derivatives **2**–**4**, which are expected to possess higher antibacterial activities against *H. pylori* than plaunotol (**1**). For diol derivatives **6**–**10** of plaunotol (**1**), if plaunotol (**1**) interacts with the cell membrane of *H. pylori,* then, the activities of the diol derivatives would not be markedly different from that of plaunotol (**1**).

In our previous studies,[9] we developed effective routes to synthesize plaunotol (**1**) via trisubstituted olefins which are synthesized highly stereoselectively. Here, we describe the synthesis of thiourea and diol derivatives of plaunotol using the developed synthetic routes, and reported their antibacterial activities against *H. pylori*.

## Results and Discussion

Plaunotol (**1**) has two allylic hydroxyl groups, the C-1 hydroxyl group and C-18 hydroxyl group, that have similar chemical behavior; hence, it is difficult to modify each of the two groups individually. Modification of each group individually using direct regioselective synthesis from **1** would be highly laborious. By using the key intermediate **5** which is derived from geraniol in our synthetic route for **1**,[9a,b] it becomes feasible to modify each group regioselectively (Scheme 1).

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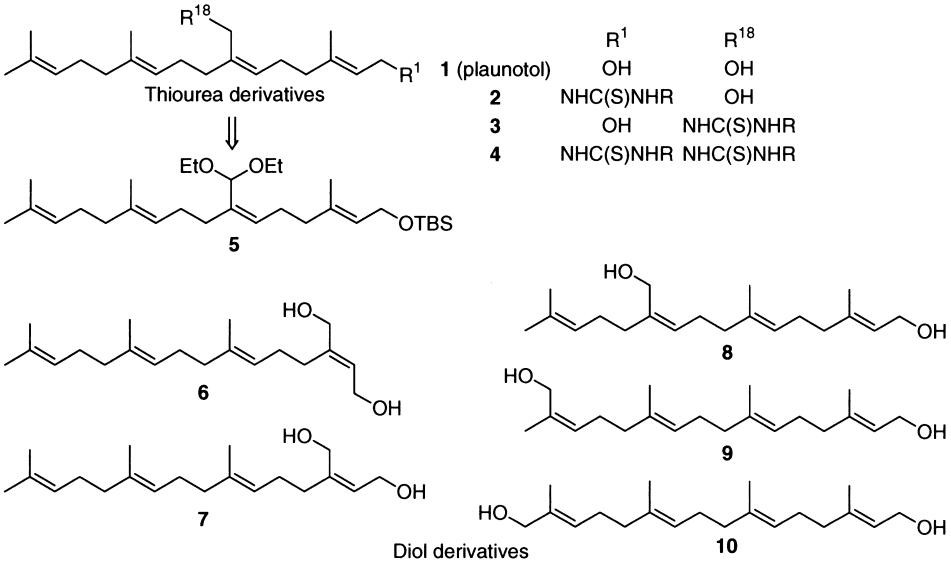
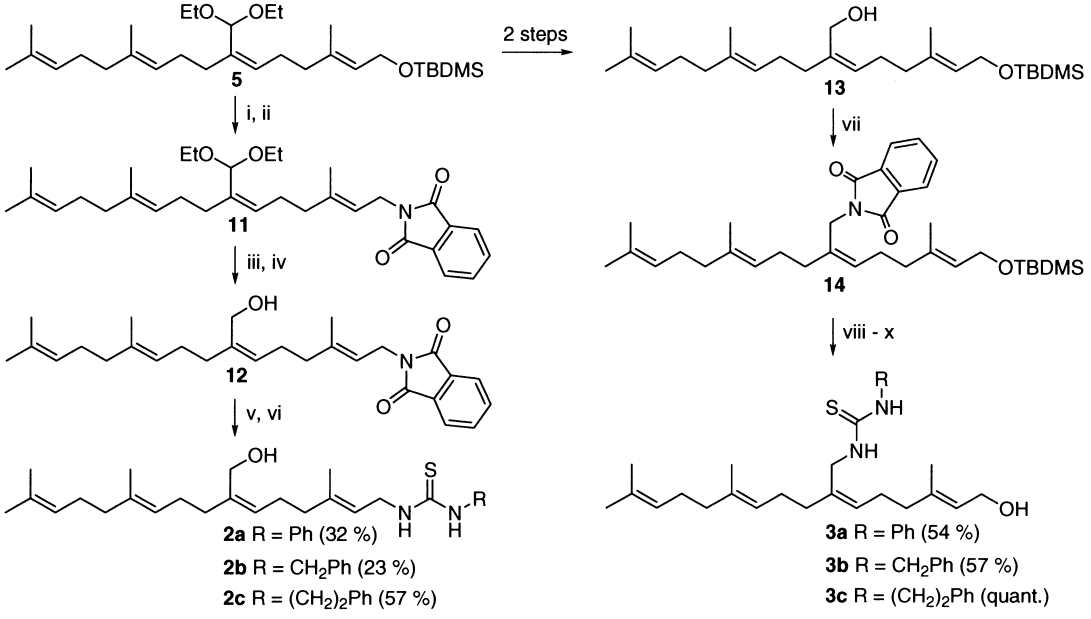
C-1 thiourea derivatives were prepared from common precursor **5** by the following procedure (Scheme 2). Deprotection of the *O*-TBDMS group of **5** and subsequent Mitsunobu reaction[10] with phthalimide yielded **11**, and then, treatment of the phthalimide derivative **11** with 50% aqueous acetic acid produced an aldehyde. Although treatment with other metal hydrides (sodium borohydride and diisobutylalminium hydride) caused partial reduction of imide carbonyl groups, selective reduction of the aldehyde was achieved by treatment with zinc borohydride in ether to give alcohol **12** in 89% yield. Alcohol **12** was treated with *n*-$BuNH_2$ to produce amine, and the amine was transformed to C-1 thiourea derivatives **2a**–**c** by treatment with phenyl, benzyl and phenetyl isothiocyanate, respectively. C-18 thiourea derivatives were prepared by the method shown in Scheme 2. C-18 hydroxyl derivative **13**, [9a,b] easily prepared from precursor **5**, was converted to phthalimide **14** by Mitsunobu reaction as shown in Scheme 2. A reaction with phthalimide **14** led to corresponding C-18 thiourea derivatives **3a**–**c** using a similar procedure to obtain C-1 thiourea derivatives.

C-1, 18-dithiourea derivatives were synthesized from **1** as shown in Scheme 3. Plaunotol (**1**) was subjected to Mitsunobu reaction with four equivalents of phthalimide and subsequent treatment with $NH_2NH_2 \cdot H_2O$ to give diamine **10**. Diamine **10** was converted to corresponding C-1, 18-dithiourea derivatives **4a**–**c**. In addition, C-1 thiourea derivatives **2d**–**g**, which have




**Scheme 1.**




**Scheme 2.** Reagents and conditions: (i), TBAF, THF, 99%; (ii) phthalimide, $PPh_3$, DEAD, THF, 89%; (iii), 50% AcOH aq, THF, rt 92%; (iv), $Zn(BH_4)_2$, $Et_2O$, 89%; (v), *n*-$BuNH_2$, EtOH, 74%; (vi), RNCS, EtOH; (vii), phthalimide, $PPh_3$, DEAD, THF, 59%; (viii), *n*-$BuNH_2$, EtOH, 68%; (ix), TBAF, AcOH, THF, 67%; (x), RNCS, EtOH.

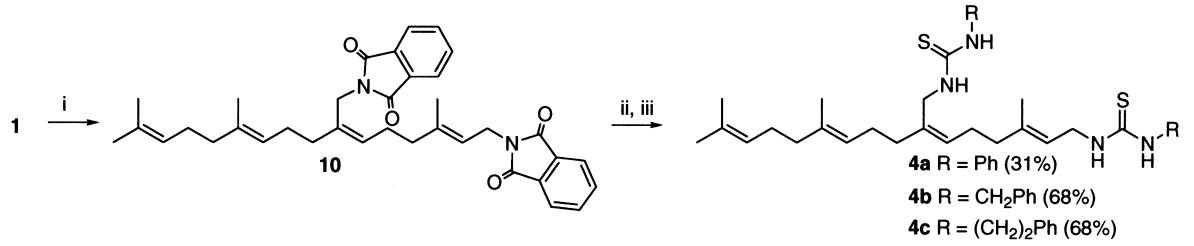
substituted phenethyl thiourea, were synthesized by reacting their corresponding phenethylamine with di-2-pyridylthiocarbonate instead of thioisocyanate.[11]

Diol derivatives **6** and **7** were regarded as reduced compounds of schizostatin and its *Z*-isomer, respectively, which are inhibitors of squalene synthase.[12] We have already achieved the total synthesis of schizostatin and its *Z*-isomer,[12] and thus **6** and **7** were readily prepared using the intermediates of this route.

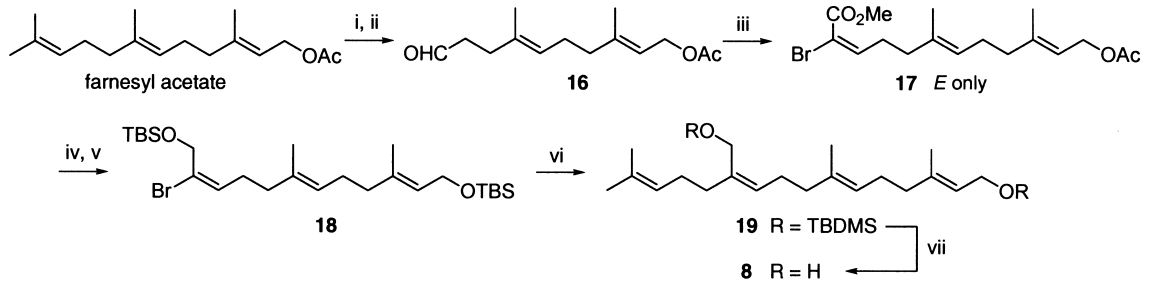
Compound **8** was synthesized via (*E*)-α-bromoacrylate **17** as shown in Scheme 4.[9c] The HWE reaction of our reagent, methyl bis(2,2,2-trifluoroethyl)bromophosphonoacetate[13] and aldehyde **16**[14] gave only the *E*-isomer (*Z*-isomer could not be detected by $^1$H NMR). The precursor of the coupling reaction, **18**, was obtained by a subsequent reduction and sililation reaction. Suzuki-coupling[15] of **18** with a boron reagent, which was derived from commercially available 2-methylpent-2,4-diene (Fluka Co., Ltd), produced **19**. Finally, **8** was obtained by the deprotection of **19** (35% yield from **18**).

Derivatives **9** and **10** were synthesized as shown in Scheme 5. The HWE reaction of aldehyde **21**, which was synthesized from geranylgeraniol,[16] gave *E*/*Z* mixutre of **22**. Interestingly, the stereoselectivity of this HWE reaction was reversed by the addition of 18-crown-6 ether. *E*/*Z* isomers of **22** were able to be separated by flash column chromatography. Treatment of *E*-**22** and *Z*-**22** with DIBAL-H produced **9** and **10**, respectively.

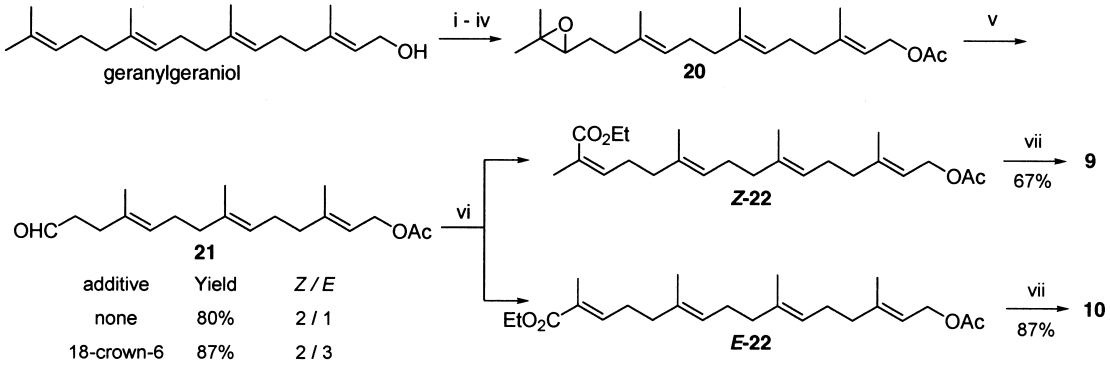
The antibacterial activities of these synthesized compounds against three strains[7] of *H. pylori*—one standard strain (NCTC 11637) and two clinical isolates (CPY 2052 and No.7)—are summarized in Table 1. C-1 monothiourea derivatives **2a**–**c** showed higher activities than plaunotol (**1**) and other thiourea derivatives. Among the three types of *N*-alkyl substituents—phenyl, benzyl and phenethyl groups—*N*-phenethyl derivatives showed higher activities than the other analogues, and compound **2c** showed the most potent antibacterial activity. The antibacterial activities of C-1 phenethyl thiourea derivatives **2d**–**f** are shown in Table 2. While




**Scheme 3.** Reagents and conditions: (i), phthalimide, $PPh_3$, DEAD, THF, 82%; (ii), $H_2N$-$NH_2$ aq, EtOH, 85%; (iii), RNCS, EtOH.

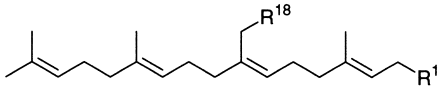



**Scheme 4.** Reagents and conditions: (i), m-CPBA, $CH_2Cl_2$; (ii), $HIO_4$, THF–$H_2O$, 33% (two steps), (iii), $(CF_3CH_2O)_2P(O)CHBrCO_2Me$, 18-C-6, *t*-BuOK, THF, 95%; (iv), DIBAL-H, $CH_2Cl_2$; (v), TBS-Cl, $Et_3N$, $CH_2Cl_2$, 77% (2 steps); (vi), 4-methylpenta-1,3-diene, 9-BBN, THF, then **18**, $PdCl_2$(dppf), $Ph_3As$, $Cs_2CO_3$, DMF; (vii), cat. *p*-TsOH, MeOH, 35% (two steps).




**Scheme 5.** Reagents and conditions: (i), $Ac_2O$, Py., 81%; (ii), NBS, $H_2O$; (iii), $K_2CO_3$, MeOH; (iv), $Ac_2O$, Py., 43% (three steps); (v), $HIO_4$, 84%; (vi), $(EtO)_2P(O)CHMeCO_2Et$, *t*-BuOK, additive, THF; (vii), DIBAL-H, THF.

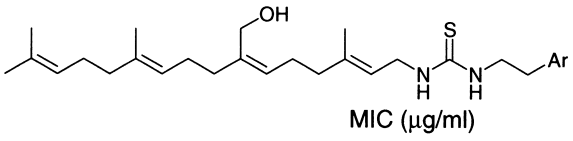
**Table 1.** Minimum inhibitory concentration (MIC) values (μg/mL) of plaunotol thiourea derivatives against three strains of *Helicobacter pylori*[a]



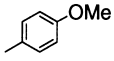

| Compound | $R^1$ | $R^{18}$ | MIC (μg/mL) NCTC 11637 | CPY 2052 | No. 7 |
|---|---|---|---|---|---|
| **1** (synthesized) | OH | OH | 3.13 | 6.25 | 6.25 |
| **2a** | NHC(S)NHPh | OH | 6.25 | 1.56 | 1.56 |
| **2b** | $NHC(S)NHCH_2Ph$ | OH | 1.56 | 0.39 | 0.39 |
| **2c** | $NHC(S)NH(CH_2)_2Ph$ | OH | ≤0.10 | ≤0.10 | ≤0.10 |
| **3a** | OH | NHC(S)NHPh | 100 | 25 | 12.5 |
| **3b** | OH | $NHC(S)NHCH_2Ph$ | 25 | 12.5 | 12.5 |
| **3c** | OH | $NHC(S)NH(CH_2)_2Ph$ | 25 | 1.56 | 1.56 |
| **4a** | NHC(S)NHPh | NHC(S)NHPh | >100 | 6.25 | 100 |
| **4b** | $NHC(S)NHCH_2Ph$ | $NHC(S)NHCH_2Ph$ | 100 | 6.25 | 12.5 |
| **4c** | $NHC(S)NH(CH_2)_2Ph$ | $NHC(S)NH(CH_2)_2Ph$ | 6.25 | 0.78 | 6.25 |
| Amoxycillin | | | 0.025 | 0.05 | 0.10 |

[a]For details on in vitro assay, see ref 7.

**Table 2.** Minimum inhibitory concentration (MIC) values (μg/mL) of plaunotol 1-phenthylthiourea derivatives against three strains of *Helicobacter pylori*[a]




MIC (μg/ml)

| Compound | Ar | MIC (μg/mL) NCTC 11637 | CPY 2052 | No. 7 |
|---|---|---|---|---|
| **2c** |  | ≤0.10 | ≤0.10 | ≤0.10 |
| **2d** |  | ≤0.10 | 0.20 | ≤0.10 |
| **2e** |  | 0.78 | 3.13 | 1.56 |
| **2f** |  | 0.20 | 0.78 | 0.39 |
| **2g** |  | ≤0.10 | 0.39 | 0.20 |

[a]For details on in vitro assay, see ref 7.

**Table 3.** Minimum inhibitory concentration (MIC) values (μg/mL) of plaunotol diol derivatives against three strains of *Helicobacter pylori*[a]

| Compound | MIC (μg/mL) NCTC 11637 | CPY 2052 | No. 7 |
|---|---|---|---|
| **1** (plaunotol) | 3.13 | 6.25 | 6.25 |
| **6** | 3.13 | 6.25 | 3.13 |
| **7** | 6.25 | 6.25 | 6.25 |
| **8** | 3.13 | 6.25 | 3.13 |
| **9** | 6.25 | 6.25 | 6.25 |
| **10** | 3.13 | 3.13 | 3.13 |

[a]For details on in vitro assay, see ref 7.

*para*-substituted phenethyl thiourea possessed similar antibacterial activities against *H. pylori* to **2c**, *ortho*-substitution reduced the activity. In the end, the most potent antibacterial agent turned out to be **2c** and its activity is comparable to that of amoxycillin, a known antibiotic which is used in clinical therapy.

As shown in Table 3, the activity of diol derivatives **6**–**10** was almost the same as that of synthesized plaunotol, regardless of the position of the hydroxymethyl groups. This result indicates that plaunotol (**1**) and its diol derivatives **6**–**10** would interact with the cell membrane of *H. pylori,* and the alter membrane fluidity. This alteration is thought to be the main cause of the bactericidal effects of plaunotol (**1**).

## Conclusion

In conclusion, we designed and synthesized plaunotol thiourea derivatives **2**–**4** from **5** and diol derivatives **6**–**10**, regioselectively. C-1 thiourea derivatives possessed higher antibacterial activities against *H. pylori* than plaunotol and other derivatives. The activity of the diol derivatives was almost equivalent to that of plaunotol. Among the synthesized derivatives, C-1 thiourea derivative **2c** was the most potent against *H. pylori,* and the activity of **2c** was similar to that of amoxycillin.

## Experimental

### General methods

Unless otherwise noted, all reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane ($CH_2Cl_2$) was distilled from calcium hydride. All other dry solvents were purchased from Aldrich in SureSeal™ con-

tainers. All other commercially obtained reagents were used as received. $^1$H NMR and $^{13}$C NMR spectra were recorded on a JEOL JNM-EX-270 or Varian 400 spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infra-red spectra were recorded on a JASCO FT-IR-8900 spectrometer. Mass spectra were obtained on a JEOL HX-100, an SX-102A or a JMS-AX-505H mass spectrometer. Analytical TLC was performed on 0.25 mm pre-coated Merck silica gel 60 $F_{254}$ plates. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh).

**(2*E*,6*Z*,10*E*)-7-Diethoxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraen-1-ol.** A solution of tetra-*n*-butylammoium fluoride (1.0 M in THF, 0.95 mL) was added to a solution of **5** (235 mg, 0.48 mmol) in THF (4 mL) at 0 °C, and the reaction mixture was stirred at rt for 1.5 h. After water was mixed in, the organic material was extracted with *n*-hexane, and the combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 4:1) furnished 178 mg (99% yield) of alcohol as a pale yellow oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 3613, 2978, 2931, 2881, 1668, 1602, 1482, 1447, 1383, 1347, 1332, 1152, 1107, 1060, 994 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22 (6H, t, $J$ = 7.0 Hz), 1.60 (6H, s), 1.68 (3H, s), 1.69 (3H, s), 1.95–1.97 (2H, m), 2.03–2.16 (8H, m), 2.27 (2H, q, $J$ = 7.5 Hz), 3.40–3.48 (2H, m), 3.56–3.66 (2H, m), 4.15 (2H, d, $J$ = 6.8 Hz), 5.06–5.16 (3H, m), 5.36 (1H, t, $J$ = 7.4 Hz), 7.54 (1H, t, $J$ = 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 15.3, 16.1, 16.3, 17.7, 25.7, 26.8, 27.5, 31.0, 39.66, 39.74, 59.3, 62.1, 100.3, 124.0, 124.45, 124.51, 128.8, 131.3, 134.9, 137.3, 139.0; HRMS (FAB) calcd for $C_{24}H_{42}O_3Na$ $(M+Na)^+$ 401.3032, found 401.3023.

**2-[(2*E*,6*Z*,10*E*)-7-Diethoxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]isoindole-1,3-dione (11).** Diethyl azadicarboxylate (95 μL, 0.58 mmol) was added dropwise to a mixture of alcohol (178 mg, 0.47 mmol), phthalimide (90 mg, 0.61 mmol), and triphenylphosphine (160 mg, 0.61 mmol) in THF (4 mL) at 0 °C, and the reaction mixture was stirred at rt for 35 min. Water was added, the organic material was extracted with ether, and the combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 8:1) furnished 216 mg (89% yield) of phthalimide **11** as a pale yellow oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2978, 2931, 1771, 1713, 1469, 1433, 1396, 1326, 1172, 1158, 1111, 1087, 1061, 1002, 948 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22 (6H, t, $J$ = 7.0 Hz), 1.57 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 1.84 (3H, s), 1.92–2.05 (10H, m), 2.23 (2H, q, $J$ = 7.7 Hz), 3.38–3.45 (2H, m), 3.55–3.62 (2H, m), 4.28 (2H, d, $J$ = 6.8 Hz), 5.07–5.11 (3H, m), 5.29 (1H, t, $J$ = 6.8 Hz), 5.32 (1H, t, $J$ = 7.7 Hz), 7.68–7.72 (2H, m), 7.81–7.86 (2H, m); HRMS (FAB) calcd for $C_{32}H_{45}NO_4K$ $(M+K)^+$ 546.2986, found 546.2990.

**(5*E*)-2-(*Z*)-[(4*E*)-6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-4-methylhex-4-enylidene]-6,10-dimethylundeca-5,9-dienal.** Aqueous acetic acid (50%, 2 mL) was added to a solution of phthalimide **11** (215 mg, 0.42 mmol) in THF (3m6) at rt and the reaction mixture was stirred for 30 min at this temperature. Water was added, the organic material was extracted with ether, and the combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 8:1) furnished 167 mg (92% yield) of aldehyde as a colorless wax.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2971, 2928, 2858, 1771, 1714, 1672, 1617, 1469, 1433, 1397, 1366, 1326, 1172, 1147, 1112, 1087, 949, 859 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 1.86 (3H, s), 1.92–2.06 (6H, m), 2.15 (4H, q, $J$ = 8.2 Hz), 2.66 (2H, t, $J$ = 7.5 Hz), 4.28 (2H, d, $J$ = 7.1 Hz), 5.01–5.10 (2H, m), 5.31 (1H, t, $J$ = 7.5 Hz), 6.38 (1H, t, $J$ = 8.2 Hz), 7.68–7.73 (2H, m), 7.81–7.86 (2H, m), 10.06 (1H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.4, 17.7, 24.9, 25.7, 26.8, 27.1, 30.3, 35.7, 39.2, 39.7, 119.5, 123.2, 123.4, 124.3, 131.4, 132.3, 133.9, 135.8, 138.9, 140.1, 148.2, 168.1, 190.7; HRMS (EI) calcd for $C_{28}H_{35}NO_3$ $(M)^+$ 433.2617, found 433.2626.

**2-[(2*E*,6*Z*,10*E*)-7-Hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]isoindole-1,3-dione (12).** $ZnCl_2$ (1.0 M in ether, 2.5 mL) was added to a suspension of $NaBH_4$ (190 mg 5.0 mmol) in THF (10 mL), and then the mixture was stirred at rt for 2 h to prepare $Zn(BH_4)_2$ solution. The $Zn(BH_4)_2$ (0.2 M in ether, 2.5 mL) was added to a solution of aldehyde (10 mg, 0.023 mmol) in ether (1 mL) at rt, and the reaction mixture was stirred at this temperature for 3 h. Water was added, the organic material was extracted with ether, and the combined organic extracts were washed with 2 N HCl, a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 2:1) furnished 8 mg (76% yield) of alcohol **12** as a colorless oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2969, 2929, 2857, 1771, 1741, 1713, 1469, 1433, 1397, 1367, 1326, 1111, 1087, 998, 949 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.55 (3H, s), 1.59 (3H, s), 1.67 (3H, s), 1.83 (3H, s), 1.87–2.14 (10H, m), 2.18 (2H, q, $J$ = 7.4 Hz), 4.10 (2H, d, $J$ = 4.1 Hz), 4.27 (2H, d, $J$ = 7.2 Hz), 5.04–5.12 (2H, m), 5.19–5.26 (2H, m), 7.68–7.72 (2H, m), 7.81–7.85 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.0, 16.4, 17.7, 25.7, 26.7, 26.9, 35.0, 35.8, 39.6, 39.7, 60.3, 118.5, 123.2, 124.0, 124.3, 127.8, 131.3, 132.3, 133.8, 135.3, 138.7, 140.0, 168.2; HRMS (FAB) calcd for $C_{28}H_{37}NO_3Ma$ $(M+Na)^+$ 458.2671, found 458.2670.

**(5*E*)-3-(*Z*)-[(4*E*)-6-Amino-4-methylhex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-diene-1-ol.** *n*-Buthylamine (9.1 mL, 92 mmol) was added to a solution of **12** (10.1 g, 23 mmol) in ethanol (50 mL) at rt, and then the reaction mixture was stirred at rt overnight. After the solvent

was removed in vacuo, the residue was dissolved in ether and extracted with 0.5 N HCl. Ammonia was added to the water layer and the organic material was extracted with $CHCl_3$. The organic layer was concentrated in vacuo to obtain 4.1 g of amino-alcohol. The amino-alcohol was used without further purification.

**1-[(2*E*,6*Z*,10*E*)-7-Hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-3-phenylthiourea (2a).** Phenyl isothiocyanate (137 μL, 1.1 mmol) was added dropwise to a solution of aminoalcohol (116 mg, 0.38 mmol) in ethanol (2 mL) at rt, and the mixture was stirred at rt for 5h. The reaction mixture was poured into ice water and the organic material was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 3:1) furnished 54 mg (32% yield) of thiourea **2a** as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3281, 2921, 1537, 1498, 1451, 1381, 1354 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.59 (6H, s), 1.66 (3H, s), 1.68 (3H, s), 1.95–2.18 (12H, m), 4.08 (2H, s), 4.22–4.24 (2H, m), 5.08–5.11 (2H, m), 5.20–5.25 (2H, m), 7.21–7.30 (3H, m), 7.39–7.44 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.7, 17.7, 25.7, 25.9, 26.7, 26.9, 35.1, 39.4, 39.7, 43.7, 60.2, 119.5, 123.9, 124.3, 125.2, 127.2, 127.9, 130.2, 131.4, 135.5, 136.2, 138.7, 140.2; HRMS (FAB) calcd for $C_{27}H_{41}N_2OS$ $(M+H)^+$ 441.2940, found 441.2941.

**1-Benzyl-3-[(2*E*,6*Z*,10*E*)-7-hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]thiourea (2b).** Using a similar procedure to above, compound **2b** was obtained in 23% yield from aminoalcohol and benzyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3278, 2922, 1549, 1496, 1454, 1375, 1352, 1272 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, s), 1.60 (3H, s), 1.61 (3H, s), 1.68 (3H, s), 1.95–2.18 (12H, m), 3.96 (2H, s), 4.09 (2H, s), 4.67 (2H, d, $J=4.3$ Hz), 5.07–5.11 (2H, m), 5.20–5.26 (2H, m), 7.27–7.37 (5H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.0, 26.7, 26.9, 35.1, 39.2, 39.7, 42.3, 48.8, 60.1, 119.5, 123.9, 124.3, 127.7, 127.88, 127.92, 128.9, 131.4, 135.6, 137.2, 138.6, 140.9, 181.9; HRMS (FAB) calcd for $C_{28}H_{43}N_2OS$ $(M+H)^+$ 455.3096, found 455.3095.

**1-[(2*E*,6*Z*,10*E*)-7-Hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-3-phenethylthiourea (2c).** Using a similar procedure to above, compound **2c** was obtained in 23% yield from aminoalcohol and phenethyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3278, 2924, 1552, 1497, 1454, 1381, 1354, 1333, 1274 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.60 (6H, s), 1.61 (3H, s), 1.68 (3H, s), 1.96–2.19 (12H, m), 2.91 (2H, t, $J=6.8$ Hz), 3.78 (2H, t, $J=5.4$ Hz), 3.85 (2H, s), 4.07 (2H, s), 5.07–5.11 (2H, m), 5.18, (1H, t, $J=6.1$ Hz), 5.24 (1H, t, $J=7.4$Hz), 7.21–7.34 (5H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.7, 26.9, 35.1, 35.2, 39.1, 39.7, 45.5, 53.4, 60.1, 119.5, 123.8, 124.3, 126.7, 127.9, 128.7, 128.8, 131.4, 135.6, 138.5, 138.6, 140.8, 181.7; HRMS (FAB) calcd for $C_{29}H_{45}N_2OS$ $(M+H)^+$ 469.3253, found 469.3240.

**2-{(5*E*)-2-(*Z*)-[(4*E*)-6-(*tert*-Butyldimethylsilyloxy)-4-methylhex-4-enylidene]-6,10-dimethylundeca-5,9-dienyl}isoindole-1,3-dione (14).** A solution of diethyl azadicarboxylate (2.3 mL, 15 mmol) in THF (6 mL) was added dropwise to a mixture of alcohol **13** (5.0 g, 12 mmol), phthalimide (2.2 g, 15 mmol), and triphenylphosphine (3.9 g, 15 mmol) in THF (30 mL) at 0 °C, and the reaction mixture was stirred at rt for 3 h. After water was added, the organic material was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 8:1) furnished 3.9 g (59% yield) of phthalimide **14** as a colorless oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2957, 2929, 2857, 1771, 1713, 1603, 1470, 1432, 1393, 1363, 1329, 1256, 1235, 1226, 1204, 1196, 1109, 1068, 1056, 1004, 943, 837, 812 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.91 (9H, s), 1.57 (6H, s), 1.66 (3H, s), 1.68 (3H, s), 1.91–1.96 (4H, m), 2.00–2.05 (2H, m), 2.10–2.15 (4H, m), 2.43 (2H, q, $J=7.6$ Hz), 4.21 (2H, d, $J=6.1$ Hz), 4.32 (2H, s), 5.04–5.08 (2H, m), 5.35–5.40 (2H, m), 7.69–7.73 (2H, m), 7.81–7.85 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ −5.0, 16.0, 16.4, 17.7, 18.4, 25.7, 26.0, 26.1, 26.66, 26.73, 34.7, 37.1, 39.5, 39.7, 60.3, 123.2, 123.7, 124.4, 124.8, 129.6, 131.2, 132.1, 133.1, 133.9, 135.3, 136.6, 168.3; HRMS (FAB) calcd for $C_{34}H_{50}NO_3Si$ $(M-H)^+$ 548.3560, found 548.3571.

**(2*E*,6*Z*,10*E*)-7-Aminomethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraen-1-ol.** *n*-Buthylamine (2.8 mL, 28 mmol) was added to a solution of **14** (3.9 g, 7.0 mmol) in ethanol (10 mL) at rt, and then the reaction mixture was stirred at rt overnight. After the solvent was removed in vacuo, Phtaloyl derivatives were removed by flash chromatography ($SiO_2$,$CHCl_3$–MeOH 9:1) and 2.0 g (68% yield) of amine was obtained. Acetic acid (142 μL, 2.5 mmol) was added to a solution of tetra-*n*-butylammoium fluoride (1.0 M in THF, 7.4 mL) at 0 °C, and then the amine (1.0 g, 2.4 mmol) was added to the mixure. The reaction mixture was stirred at rt overnight. After EtOAc was added, the organic material was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Silyl derivatives were removed by flash chromatography ($SiO_2$,$CHCl_3$–MeOH 3:1) and 485 mg (67% yield) of aminoalcohol was obtained. The aminoalcohol was used without further purification.

**1-[(5*E*)-2-(*Z*)-[6-(4*E*)-Hydroxy-4-methylhex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl]-3-phenylthiourea (3a).** Phenyl isothiocyanate (59 μL, 0.49 mmol) was added dropwise to a solution of aminoalcohol (100 mg, 0.33 mmol) in ethanol (2 mL) at rt, and the mixture was stirred at rt for 5 h. The reaction mixture was poured into ice water and the organic material was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by

flash chromatography ($SiO_2$, *n*-hexane–AcOEt 3:1) furnished 78 mg (54% yield) of thiourea **3a** as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3287, 2923, 1534, 1498, 1451, 1314 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s), 1.60 (3H, s), 1.65 (3H, s), 1.68 (3H, s), 1.92–2.21 (12H, m), 4.12 (2H, d, $J=6.8$ Hz), 4.22 (2H, d, $J=4.7$ Hz), 5.02–5.10 (2H, m), 5.30–5.39 (2H, m), 7.23–7.29 (3H, m), 7.39–7.43 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.3, 17.7, 25.7, 26.1, 26.70, 26.73, 36.1, 39.3, 39.7, 44.8, 59.2, 123.4, 123.9, 124.2, 124.9, 127.0, 129.7, 130.0, 131.4, 134.8, 135.8, 136.5, 139.1, 180.8; HRMS (FAB) calcd for $C_{27}H_{41}N_2OS$ $(M+H)^+$ 441.2940, found 441.2933.

**1-Benzyl-3-{(5*E*)-2-(*Z*)-[(4*E*)-6-hydroxy-4-methylhex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl}thiourea (3b).** Using a similar procedure to above, compound **3b** was obtained in 57% yield from aminoalcohol and benzyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3286, 2921, 1549, 1454, 1375, 986 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, s), 1.60 (3H, s), 1.63 (3H, s), 1.68 (3H, s), 1.95–2.18 (12H, m), 3.98 (2H, s), 4.07 (2H, d, $J=7.2$ Hz), 4.72 (2H, d, $J=4.7$ Hz), 5.07–5.10 (2H, m), 5.29–5.33 (2H, m), 7.26–7.36 (5H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 17.7, 25.7, 26.0, 26.66, 26.73, 36.0, 38.9, 39.7, 43.6, 48.8, 58.9, 123.6, 124.1, 124.2, 127.7, 128.8, 129.6, 131.4, 135.7, 182.6; HRMS (FAB) calcd for $C_{28}H_{43}N_2OS$ $(M+H)^+$ 455.3096, found 455.3078.

**1-{(5*E*)-2-(*Z*)-[(4*E*)-6-Hydroxy-4-methylhex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl}-3-phenethylthiourea 3c.** Using a similar procedure to above, compound **3c** was obtained in quantative yield from aminoalcohol and phenethyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3286, 2923, 1549, 1454, 1381, 1356 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, s), 1.60 (3H, s), 1.61 (3H, s), 1.68 (3H, s), 1.94–2.17 (12H, m), 2.91 (2H, t, $J=6.8$ Hz), 3.84 (2H, dd, $J=6.3$, 12.2 Hz), 3.90 (2H, s), 4.00 (2H, d, $J=7.1$ Hz), 5.06–5.10 (2H, m), 5.27 (2H, t, $J=7.6$ Hz), 7.21–7.34 (5H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.3, 17.7, 25.7, 25.9, 26.67, 26.71, 35.1, 35.9, 38.8, 39.7, 43.2, 45.4, 58.7, 123.6, 124.1, 124.2, 126.5, 128.6, 128.9, 129.5, 131.4, 135.6, 139.0, 182.5; HRMS (FAB) calcd for $C_{29}H_{45}N_2OS$ $(M+H)^+$ 469.3253, found 469.3237.

**Bis-*N*-phthaloyl-(2*Z*,5*E*)-2-[(4*E*)-4,8-dimethylnona-3,7-dienyl]-6-methylocta-2,6-diene-1,8-diamine 10.** Diethyl azadicarboxylate (1.0 mL, 6.5 mmol) was added dropwise to a mixture of plaunotol (**1**) (500 mg, 1.63 mmol), phthalimide (960 mg, 6.52 mmol), and triphenylphosphine (1.71 mg, 6.52 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at rt for 3 h. Water was added, the organic material was extracted with ether, and the combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 3:1) furnished 757 mg (82% yield) of phthalimide **10** as a pale yellow oil.

IR (liquid film) $\upsilon_{max}$ 2922, 1771, 1714 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, s), 1.58(3H, s), 1.65(3H, s), 1.89–2.14 (13H, m), 2.39–2.45 (2H, m), 4.29 (2H, s), 4.30 (2H, d, $J=6.8$ Hz), 4.99–5.08 (2H, m), 5.33 (2H, t, $J=7.2$ Hz), 7.68–7.71 (4H, m), 7.81–7.83 (4H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.0, 16.4, 17.7, 25.7, 26.0, 26.7, 34.6, 35.8, 37.0, 39.4, 39.7, 1184, 123.1, 123.2, 123.7, 124.4, 129.3, 131.2, 132.1, 132.4, 123.7, 124.4, 129.3, 131.2, 132.1, 132.2, 132.4, 133.8, 133.9, 135.2, 140.3, 167.1 168.3; HRMS (FAB) calcd for $C_{36}H_{41}N_2O_4$ $(M+H)^+$ 565.3066, found 565.3067.

**(2*Z*,6*E*)-2-[(3*E*)-4,8-Dimethylnona-3,7-dienyl]-6-methylocta-2,6-diene-1,8-diamine.** Hydradine monohydarate (8 mL, 165 mmol) was added to a solution of **10** (2.0 g, 3.5 mmol) in ethanol (40 mL), and then the reaction mixture was refluxed for 1 h. The mixture was cooled and resulting solid was removed by filtration (three times). The filtrate was poured into 10% aqueous NaOH solution and the organic material was extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration and 912 mg (85% yield) of diamine was obtained. The diamine was used without further purification.

**1-{(5*E*)-2-(*Z*)-[(4*E*)-4-Methyl-6-(3-phenylthioureid)hex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl}-3-phenylthiourea (4a).** Phenyl isothiocyanate (300 μL, 2.5 mmol) was added dropwise to a solution of diamine (304 mg, 1.0 mmol) in ethanol (5 mL) at rt, and the mixture was stirred at rt for 5 h. The reaction mixture was poured into ice water and the organic material was extracted with ether. The combined organic layers were washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 3:1) furnished 180 mg (31% yield) of thioure a **4a** as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3244, 2923, 1537, 1533, 1497, 1354, 1314, 1298 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.56 (3H, s), 1.60 (3H, s), 1.63 (3H, s), 1.68 (3H, s), 1.91–2.04 (12H, m), 4.21 (2H, d, $J=7.2$ Hz), 4.22 (2H, s), 5.02 (1H, t, $J=6.5$ Hz), 5.05–5.08 (1H, m), 5.15–5.18 (1H, m), 5.28 (1H, t, $J=7.0$ Hz), 7.13–7.22 (4H, m), 7.29–7.30 (2H, m), 7.40–7.44 (4H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.1, 26.69, 26.72, 36.0, 39.2, 39.6, 43.6, 44.8, 119.6, 123.2, 124.2, 125.4, 125.1, 127.2, 129.6, 130.1, 130.2, 131.4, 134.7, 135.8, 136.1, 136.2, 139.8, 180.3, 180.6; HRMS (FAB) calcd for $C_{34}H_{47}N_4S_2$ $(M+H)^+$ 575.3242, found 575.3236.

**1-Benzy-3-{(5*E*)-2-(*Z*)-[(4*E*)-6-(3-benzylthioureid)-4-methylhex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl}-thiourea (4b).** Using a similar procedure to above, compound **4b** was obtained in 68% yield from diamine and benzyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3259, 2923, 1558, 1538, 1375, 1352, 1273 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.58 (9H, s), 1.68 (3H, s), 1.94–2.15 (12H, m), 3.98 (4H, brs), 4.63 (4H, d, $J=14.0$ Hz), 5.03–5.10 (2H, m), 5.17 (1H, t,

$J = 6.7$ Hz), 5.28 (1H, t, $J = 7.2$ Hz), 7.28–7.36 (10H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.8, 17.7, 25.7, 26.1, 26.6, 26.7, 35.7, 38.6, 39.7, 42.2, 73.9, 48.6, 48.8, 120.1, 123.3, 124.2, 127.7, 127.9, 128.9, 129.9, 131.5, 134.7, 135.9, 137.0, 137.2, 181.7, 182.0; HRMS (FAB) calcd for $C_{36}H_{51}N_4S_2$ $(M+H)^+$ 603.3555, found 603.3565.

**1-{(5*E*)-2-(*Z*)-[(4*E*)-4-Methyl-6-(3-phenethylthioureid)hex-4-en-1-ylidene]-6,10-dimethylundeca-5,9-dienyl}-3-phenethylthiourea (4c).** Using a similar procedure to above, compound **4c** was obtained in 68% yield from diamine and phenetyl isothiocyanate as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3259, 2925, 1549, 1381, 1354, 1275 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s), 1.68 (3H, s), 1.94–2.13 (12H, m), 3.74–3.87 (4H, brs), 4.63 (4H, d, $J = 14.0$ Hz), 5.03–5.10 (2H, m), 5.17 (1H, t, $J = 6.7$ Hz), 5.28 (1H, t, $J = 7.2$ Hz), 7.28–7.36 (10H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.7, 17.7, 25.7, 26.1, 26.6, 35.16, 35.23, 35.8, 38.6, 39.7, 41.9, 43.25, 43.33, 45.7, 123.3, 124.2, 126.66, 126.70, 128.7, 130.0, 131.4, 134.6, 138.4, 138.5, 181.6, 181.9; HRMS (FAB) calcd for $C_{38}H_{55}N_4S_2$ $(M+H)^+$ 631.3867, found 631.3868.

**1-[(2*E*,6*Z*,10*E*)-7-Hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-3-[2-(4-methoxyphenyl)ethyl]-thiourea (2d).** 4-Methoxyphenethylamine (293 μL, 2.0 mmol) was added to a solution of di-2-pyridyl-thiocarbonate (418 mg, 1.8 mmol) in acetonitrile (1.5 mL) and the resulting mixture was stirred at rt for 5 min. A solution of 1-aminoalcohol (200 mg, 0.69 mmol) in acetonitrile (1.5 mL) was added to the reaction mixture and stirring was continued for 10 min at rt. Ether was added to the mixture, and solid was removed by filtration. The filtrate was washed with 2 N HCl, a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $Na_2SO_4$ and concentrated in vacuo after filtration. Purification by flash chromatography ($SiO_2$, *n*-hexane–AcOEt 3:2) furnished 137 mg (40% yield) of thiourea **2d** as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3280, 2925, 1612, 1550, 1513, 1274, 1004 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (6H, s), 1.61 (3H, s), 1.68 (3H, s), 1.96–2.19 (12H, m), 2.85 (2H, t, $J = 6.8$ Hz), 3.73 (2H, d, $J = 5.4$ Hz), 3.79 (3H, s), 3.84 (2H, brs), 4.08 (2H, s), 5.07–5.11 (2H, m), 5.19, (1H, dd, $J = 5.9$, 7.0 Hz), 5.24 (1H, t, $J = 7.4$Hz), 5.66 (1H, brs), 5.90 (1H, brs), 6.85 (2H, d, $J = 8.6$ Hz), 7.13 (2H, d, $J = 8.6$ Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.0, 26.7, 26.9, 34.2, 35.1, 39.2, 39.7, 45.7, 55.3, 114.2, 119.4, 123.8, 124.3, 127.9, 129.8, 130.4, 131.4, 135.6, 138.6, 140.9, 158.4, 181.7; HRMS (FAB) calcd for $C_{30}H_{47}N_2O_2S$ $(M+H)^+$ 499.3358, found 499.3366.

**1-[(2*E*,6*Z*,10*E*)-7-Hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-3-[2-(2-methoxyphenyl)ethyl]-thiourea (2e).** Using a similar procedure to above, compound **2e** was obtained in 40% yield from 1-aminoalcohol and 2- methoxyphenethylamine as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3286, 2924, 1551, 1494, 1377, 1353, 1224 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (6H, s), 1.66 (3H, s), 1.68 (3H, s), 1.96–2.22 (12H, m), 2.91 (2H, t, $J = 6.8$ Hz), 3.61 (2H, brs), 3.61 (2H, brs), 3.85(3H, s), 3.94 (2H, brs), 5.07–5.11 (2H, m), 5.25, (1H, dd, $J = 7.4$, 14.9 Hz), 5.88 (1H, brs), 6.06 (1H, brs), 6.90 (2H, m), 7.14 (1H, dd, $J = 1.5$, 7.4 Hz), 7.14 (1H, dt, $J = 1.5$, 7.7 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.0, 26.7, 26.9, 29.9, 35.1, 39.4, 39.7, 42.7, 44.2, 55.5, 60.2, 110.6, 121.0, 123.9, 124.3, 127.9, 128.2, 130.8, 131.4, 135.6, 138.7, 157.3, 181.3; HRMS (FAB) calcd for $C_{30}H_{47}N_2O_2S$ $(M+H)^+$ 499.3358, found 499.3354.

**1-(2-Benzo[1.3]dioxol-5-ylethyl)-3-[(2*E*,6*Z*,10*E*)-7-hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-thiourea (2f).** Using a similar procedure to above, compound **2f** was obtained in 39% yield from 1-aminoalcohol and 3,4-methylenedioxyphenethylamine as a colorless oil. IR (liquid film) $\upsilon_{max}$ 3280, 2923, 1551, 1247, 1041, 1005 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (6H, s), 1.63 (3H, s), 1.68 (3H, s), 1.98–2.18 (12H, m), 2.83 (2H, t, $J = 6.8$ Hz), 3.71 (2H, d, $J = 5.4$ Hz), 3.87 (2H, brs), 4.10 (2H, s), 5.07–5.12 (2H, m), 5.19 (1H, t, $J = 6.0$ Hz), 5.25 (1H, t, $J = 7.5$ Hz), 5.66 (1H, brs), 5.92 (1H, brs), 5.93 (2H, s), 6.66 (1H, dd, $J = 1.5$, 7.8 Hz), 6.70 (1H, d, $J = 1.5$ Hz), 6.75 (1H, d, $J = 7.8$ Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.0, 26.7, 26.9, 34.9, 35.1, 39.2, 39.7, 42.1, 45.7, 60.1, 101.1, 108.4, 109.4, 119.4, 121.7, 123.8, 124.3, 127.9, 131.4, 132.2, 135.6, 138.6, 140.9, 146.3, 147.9, 181.7; HRMS (FAB) calcd for $C_{30}H_{45}N_2O_3S$ $(M+H)^+$ 513.3151, found 513.3132.

**1-[2-(4-Chlorophenyl-ethyl]-3-[(2*E*,6*Z*,10*E*)-7-hydroxymethyl-3,11,15-trimethylhexadeca-2,6,10,14-tetraenyl]-thiourea (2g).** Using a similar procedure to above, compound **2g** was obtained in 51% yield from 1-aminoalcohol and 4-chlorophenethylamine as a colorless oil.

IR (liquid film) $\upsilon_{max}$ 3280, 2924, 1551, 1493, 1443, 1381, 1354, 1004 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.60 (6H, s), 1.63 (3H, s), 1.68 (3H, s), 1.96–2.20 (12H, m), 2.89 (2H, t, $J = 6.9$ Hz), 3.76 (2H, dd, $J = 6.2$, 12.2 Hz), 3.86 (2H, brs), 4.09 (2H, s), 5.07–5.11 (2H, m), 5.19, (1H, t, $J = 6.3$ Hz), 5.25 (1H, t, $J = 7.4$Hz), 5.68 (1H, brs), 6.00 (1H, brs), 7.15 (2H, d, $J = 8.3$ Hz), 7.28 (2H, d, $J = 8.3$ Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 16.1, 16.6, 17.7, 25.7, 26.0, 26.7, 26.9, 34.6, 35.1, 39.1, 39.7, 42.2, 45.5, 60.1, 119.4, 123.8, 124.3, 128.0, 128.7, 130.2, 131.4, 132.5, 137.1, 138.5, 140.9, 181.9; HRMS (FAB) calcd for $C_{29}H_{44}ClN_2O_2S$ $(M+H)^+$ 503.2863, found 503.2854.

## Diol derivatives

**(2*Z*)-[(3*E*,7*E*)-4,8,12-Trimethyltrideca-3,7,11-trienyl]but-2-ene-1,4-diol (7).** DIBAL-H (1.0 M in $CH_2Cl_2$, 3.3 mL) was added to a solution of dimethyl (1*Z*,5*E*,9*E*)-6,10,4-trimethyl-1,5,9,13-pentadecatetraene-1,2-dicarboxylate (200 mg, 0.55 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C, then the reaction mixture was stirred at 0 °C for 1 h. After

$NaSO_4 \cdot 10H_2O$ (1.2 g) was added to the mixture, stirring was continued for 30 min. The solid was removed by filtration and the filtrate was concentrated in vacuo. Purification by Lobar chromatography (RP-18, MeOH–$H_2O$ 4:1) furnished 25 mg (15% yield) of diol **7** as a colorless oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 4214, 3693, 3613, 3459, 2969, 2929, 2857, 1732, 1664, 1603, 1450, 1384, 1331, 1248, 1233, 1224, 1201, 1152, 1107, 1081, 1002, 930, 838, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.60 (9H, s), 1.63 (2H, br), 1.68 (3H, s), 1.93–2.10 (8H, m), 2.17 (2H, brs), 4.17 (2H, s), 4.21 (2H, d, $J=7.0$ Hz), 5.08–5.15 (3H, m), 5.64 (1H, t, $J=7.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 17.7, 25.7, 26.6, 26.7, 26.8, 35.8, 39.67, 39.71, 58.6, 60.9, 123.5, 124.1, 124.4, 126.7, 131.3, 135.0, 135.9, 143.7; HRMS (FAB) calcd for $C_{20}H_{34}O_2K$ $(M+K)^+$ 345.2196, found 345.2190.

**(2*E*,6*E*,10*E*)-12-Acetoxy-2-bromo-6,10-dimethyldodeca-2,6,10-trienoic acid methyl ester (17).** A solution of Methyl bis(trifluoroethyl)bromophosphonoacetate (830 mg, 2.1 mmol) and 18-C-6/$CH_3CN$ (692 mg, 2.3 mmol) in THF (15 mL) was cooled to −78 °C. Then 1.0 M of potassium *tert*-butoxide solution in THF (2.0 mL, 2.0 mmol) was added to the solution. After stirring for 30 min at −78 °C, aldehyde **16** (450 mg, 1.9 mmol) was added to the reaction mixture and the stirring was continued for 2 h. When the reaction was completed, saturated aqueous $NH_4Cl$ was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography (*n*-hexane–AcOEt 10:1) to afford bromoacrylate **17** (672 mg, 95%yield).

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2983, 2953, 2932, 2853, 1723, 1670, 1612, 1437, 1384, 1366, 1352, 1305, 1253, 1180, 1101, 1076, 1023, 953, 909, 878, 806 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.71 (3H, s), 2.06 (3H, s), 2.08–2.14 (6H, m), 2.62 (2H, q, $J=7.5$ Hz), 3.82 (3H, s), 4.59 (2H, d, $J=7.1$ Hz), 5.12–5.15 (1H, m), 5.30–5.37 (1H, m), 6.66 (1H, t, $J=7.5$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 15.8, 16.4, 21.0, 29.8, 38.3, 39.4, 52.8, 61.4, 110.5, 118.4, 125.2, 133.7, 142.0, 149.0, 163.3, 171.1; HRMS (FAB) calcd for $C_{17}H_{25}BrO_4K$ $(M+K)^+$ 411.0573, found 411.0566.

**(2*E*,6*E*,10*Z*)-2-Bromo-1,12-bis(*tert*-butyldimethylsilanyloxy)-6,10-dimethyldodeca-2,6,10-triene (18).** DIBAL-H (1.0 M in $CH_2Cl_2$, 9.0 mL) was added to a solution of bromoacrylate **17** (660 mg, 1.8 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C, then the reaction mixture was stirred at −60 °C for 1 h. After $NaSO_4 \cdot 10H_2O$ (3.2 g) was added to the mixture, stirring continued for 30 min. The solid was removed by filtration and the filtrate was concentrated in vacuo. The crude diol and triethylamine (5 mL) was dissolved in $CH_2Cl_2$ (10 mL) and cooled to 0 °C. *tert*-Butyldimethylsilylchloride (800 mg, 15 mmol) was added to the mixture then the reaction mixture was stirred at rt overnight. Water was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography (*n*-hexane–AcOEt 50:1) to afford bromide **18** (724 mg, 77 % yield from **17**).

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2956, 2930, 2898, 2886, 2853, 1668, 1644, 1471, 1464, 1407, 1388, 1363, 1256, 1229, 1212, 1184, 1108, 1095, 1058, 1006, 975, 938, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.09 (6H, s), 0.88 (9H, s), 0.90 (9H, s), 1.57 (3H, s), 1.61 (3H, s), 1.97–2.11 (6H, m), 2.19 (2H, q, $J=7.7$ Hz), 4.17 (2H, d, $J=6.2$ Hz), 4.31 (2H, s), 5.11 (1H, t, $J=7.0$ Hz), 5.29 (1H, t, $J=6.2$ Hz), 5.92 (1H, t, $J=7.7$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ –5.1, –5.0, 15.9, 16.4, 18.4,26.0, 26.3, 28.2, 38.9, 39.4, 60.3, 63.4, 124.2, 124.5, 125.2 133.7, 134.1, 136.8; HRMS (FAB) calcd for $C_{26}H_{50}BrO_2Si_2$ $(M-H)^+$ 529.2533, found 529.2446.

**(2*Z*,6*E*,10*E*)-6,10-Dimethyl-2-(4-methylpent-3-enyl)dodeca-2,6,10-triene-1,12-diol (8).** A solution of 2-methylpenta-2,4-diene (51 mg, 0.62 mmol) in THF (1 mL) was cooled to 0 °C and to the solution was added 0.5 M of 9-BBN in THF (2.5 mL, 1.3 mmol). Then the reaction mixture was stirred at rt for 4 h. After addition of water (0.1 mL), the resulting mixture was concentrated in vacuo to give a boron reagent. Compound **18** (166 mg, 0.31 mmol), $Cs_2CO_3$ (183 mg, 0.56 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (13 mg, 3 mol%), and $Ph_3As$ (10 mg, 6 mol%) were dissolved in DMF (3 mL) and stirred at rt for 10 min. Then, to the mixture was added the boron reagent and stirred at 50 °C for 5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography (*n*-hexane–$Et_2O$ 50:1) to furnished compound **19**. The product was dissolved in MeOH (2 mL) and added catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction mixture was stirred at rt for 30 min, then diluted with AcOEt. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated in vacuo after filtration. The residue was purified by Lobar column chromatography (RP-18, MeOH–$H_2O$ = 80:20) to give **8** as a light yellow oil (30 mg, 32% yield).

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 3692, 3675, 3613, 3521, 2929, 2857, 1666, 1603, 1595, 1471, 1449, 1384, 1363, 1255, 1219, 1207, 1087, 992, 952, 920, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.26 (2H, br), 1.61 (6H, s), 1.68 (3H, s), 1.69 (3H, s), 2.00–2.23 (12H, m), 4.11 (2H, s), 4.15 (2H, d, $J=6.8$ Hz), 5.10–5.13 (2H, m), 5.30 (1H, t, $J=7.3$ Hz), 5.42 (1H, t, $J=6.8$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 16.3, 17.7, 25.7, 26.2, 26.3, 27.1, 35.8, 39.4, 39.8, 59.4, 60.4, 123.5, 124.1, 124.4, 128.6, 131.8, 134.9, 138.4, 139.5; HRMS (FAB) calcd for $C_{20}H_{34}O_2K$ $(M+K)^+$ 345.2196, found 345.2198.

**(2*Z*,6*E*,10*E*,14*E*)-16-Acetoxy-2,6,10,14-tetramethyhexadeca-2,6,10,14-tetraenoic acid ethyl ester *Z*-22.** A solution of ethyl diethylbromophosphonoacetate (328 mg, 1.4 mmol) and 18-C-6/$CH_3CN$ (500 mg, 1.6 mmol) in

THF (10 mL) was cooled to −78 °C. Then 1.0 M of potassium *tert*-butoxide solution in THF (1.4 mL, 1.4 mmol) was added to the solution. After stirring for 30 min at −78 °C, aldehyde **21** (352 mg, 1.2 mmol) was added to the reaction mixture at 0 °C and the stirring was continued for 20 min. When the reaction was completed, saturated aqueous $NH_4Cl$ was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography (*n*-hexane–AcOEt 20:1) to afford compound ***Z*-22** (173 mg).

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2982, 2959, 2928, 2855, 1723, 1711, 1646, 1453, 1447, 1382, 1372, 1333, 1255, 1227, 1214, 1185, 1131, 1094, 1024, 953, 864, 844, 804 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, $J=7.0$ Hz), 1.595 (3H, s), 1.598 (3H, s), 1.71 (3H, s), 1.88 (3H, s), 1.96–2.13 (10H, m), 2.05 (3H, s), 2.55 (2H, q, $J=7.1$ Hz), 4.20 (2H, q, $J=7.0$ Hz), 4.59 (2H, d, $J=6.9$ Hz), 5.08–5.14 (2H, m), 5.35 (1H, t, $J=6.9$ Hz), 5.90 (1H, dt, $J=1.0$, 7.1 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 14.3, 15.9, 16.0, 16.5, 20.6, 21.1, 26.2, 26.6, 28.0, 39.1, 39.5, 39.7, 60.0, 61.4, 118.3, 123.6, 124.8, 127.1, 134.2, 135.5, 142.3, 142.6, 168.1, 171.1; HRMS (FAB) calcd for $C_{24}H_{38}O_4K$ $(M+K)^+$ 429.2407, found 429.2416.

**(2*E*,6*E*,10*E*,14*E*)-16-Acetoxy-2,6,10,14-tetramethyhexadeca-2,6,10,14-tetraenoic acid ethyl ester *E*-22.** A solution of ethyl diethylbromophosphonoacetate (168 mg, 0.71 mmol) in THF (5 mL) was cooled to 0 °C. Then 1.0 M of potassium *tert*-butoxide solution in THF (0.70 mL, 0.70 mmol) was added to the solution. After stirring for 30 min at 0 °C, aldehyde **21** (180 mg, 0.59 mmol) was added to the reaction mixture at 0 °C and the stirring was continued for 30 min. When the reaction was completed, saturated aqueous $NH_4Cl$ was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. The residue was purified by silica gel flash chromatography (*n*-hexane–AcOEt 20:1) to afford compound ***E*-22** (107 mg) and ***Z*-22** (51 mg).

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 2983, 2931, 2854, 1726, 1703, 1648, 1445, 1385, 1368, 1330, 1271, 1227, 1214, 1207, 1183, 1126, 1084, 1024, 982, 953, 866, 805 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, t, $J=7.0$ Hz), 1.60 (3H, s), 1.61 (3H, s), 1.71 (3H, s), 1.83 (3H, s), 1.88–2.14 (10H, m), 2.05 (3H, s), 2.26 (2H, t, $J=7.3$ Hz), 4.18 (2H, q, $J=7.0$ Hz), 4.59 (2H, d, $J=7.4$ Hz), 5.08–5.16 (2H, m), 5.35 (1H, dt, $J=1.1$, 7.4 Hz), 6.74 (1H, dt, $J=1.3$, 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 12.4, 14.3, 15.97, 16.04, 16.5, 21.1, 26.2, 26.7, 27.4, 38.3, 39.5, 39.6, 60.4, 61.4, 118.3, 123.7, 125.0, 127.7, 133.9, 135.4, 141.9, 142.2, 168.2, 171.1; HRMS (FAB) calcd for $C_{24}H_{38}O_4K$ $(M+K)^+$ 429.2407, found 429.2416.

**(2*Z*,6*E*,10*E*,14*E*)-2,6,10,14-Tetramethylhexadeca-2,6,10,14-tetraene-1,16-diol (9).** 1.0 M DIBAL-H in THF (3.0 mL, 3.0 mmol) was added to a solution of ***Z*-22** (173 mg, 0.44 mmol) in THF (2 mL) at 0 °C, then the reaction mixture was stirred at 0 °C for 1 h. When the reaction was completed, 10% aqueous HCl was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. Purification by Lobar chromatography (RP-18, MeOH–$H_2O$ 5:1) furnished 117 mg (87% yield) of diol **9** as a colorless oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 3615, 2921, 2856, 1666, 1449, 1384, 1242, 1219, 1199, 1191, 1183, 1152, 1093, 995, 946 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.32 (2H, br), 1.60 (6H, s), 1.68 (3H, s), 1.79 (3H, s), 1.97–2.17 (12H, m), 4.11 (2H, s), 4.15 (2H, d, $J=6.9$ Hz), 5.08–5.11 (2H, m), 5.28 (1H, t, $J=6.9$ Hz), 5.42 (1H, t, $J=7.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.0, 16.1, 16.3, 21.3, 26.3, 26.5, 39.56, 39.61, 39.9, 59.4, 61.1, 123.4, 123.9, 124.7, 128.2, 134.4, 134.5, 135.2, 139.7; HRMS (FAB) calcd for $C_{20}H_{34}O_2Na$ $(M+Na)^+$ 329.2456, found 329.2448.

**(2*E*,6*E*,10*E*,14*E*)-2,6,10,14-Tetramethylhexadeca-2,6,10,14-tetraene-1,16-diol (10).** 1.0 M DIBAL-H in THF (2.4 mL, 2.4 mmol) was added to a solution of ***E*-22** (97 mg, 0.25 mmol) in THF (1.5 mL) at −78 °C, then the reaction mixture was stirred at 0 °C for 3.5 h. When the reaction was completed, 10% aqueous HCl was added to the solution and the organic material was extracted with AcOEt. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo after filtration. Purification by Lobar chromatography (RP-18, MeOH–$H_2O$ 4:1) furnished 51 mg (67% yield) of diol **10** as a colorless oil.

IR ($CHCl_3$ soln.) $\upsilon_{max}$ 3671, 3612, 3463, 2979, 2925, 2858, 1666, 1447, 1384, 1244, 1228, 1219, 1212, 1201, 1187, 1154, 1095, 1057, 1032, 992, 951, 845, 805 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.31 (2H, br), 1.61 (6H, s), 1.67 (3H, s), 1.68 (3H, s), 1.97–2.13 (12H, m), 3.99 (2H, s), 4.15 (2H, d, $J=7.0$ Hz), 5.10–5.13 (2H, m), 5.37–5.44 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 13.7, 15.97, 16.01, 16.3, 26.2, 26.3, 26.6, 39.3, 39.5, 39.7, 59.4, 69.0, 123.4, 123.8, 124.5, 126.1, 134.6, 134.7, 135.3, 139.8; HRMS (FAB) calcd for $C_{20}H_{34}O_2Na$ $(M+Na)^+$ 329.2456, found 329.2452.

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