Synthetic Studies towards NG-121: Diastereoselective Synthesis of NG-121 Methyl Ether

Mandeep Singh, Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune 411 008, India
Fax +91(20)25902629; E-mail: np.argade@ncl.res.in

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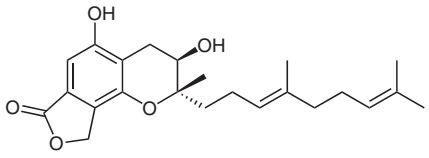
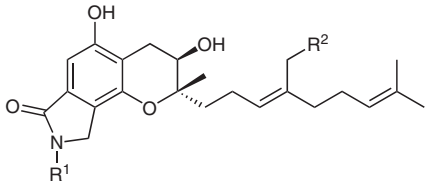
Abstract: Starting from unsymmetrically O-protected methyl 4-bromo-3,5-dihydroxybenzoate, a facile synthesis of the methyl ether of bioactive natural product NG-121 was accomplished in very good overall yield. The key steps were: Stille coupling reaction of the farnesyl unit with the electron-rich phenolic segment; hydroxy-directed selective epoxidation of the farnesyl chain along with concomitant phenol-driven intramolecular regio- and diastereoselective ring closure to the corresponding hydroxybenzopyran; and regioselective formylation followed by in situ reductive lactonization.

Key words: 4-bromo-3,5-dihydroxybenzoate, Stille coupling, intramolecular cyclization, formylation, lactonization, NG-121 methyl ether

A large number of structurally interesting and biologically important natural and unnatural benzopyrans are known in the literature.[1] Naturally occurring, novel multifunctional NG-121 and stachybotrin C were isolated from the culture broth of *Stachybotrys parvispora* F-4708[2] (Figure 1).

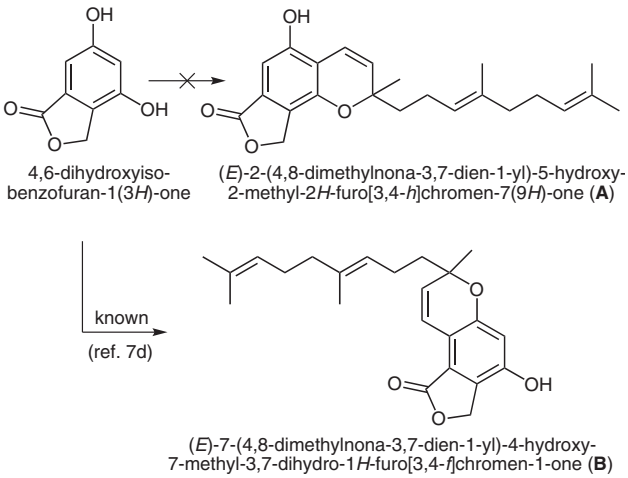




stachybotrin A (R^1 = H, R^2 = OH)
stachybotrin B (R^1 = R^2 = H)
stachybotrin C (R^1 = $C_2H_4C_6H_4OH$, R_2 = H)
SMTP congeners (R^1 = alkyl/aryl/amino acid moieties, R^2 = H)

Figure 1 Naturally occurring multifunctional bioactive chromanols[2–4]

NG-121 has been effective against Alzheimer's disease, while stachybotrin C prevents hypoxic neuronal injury caused by ischemia.[2] Stachybotrin A and B were isolated from *Stachybotrys* (SC-710-1) and possess antibacterial and antifungal activity.[3] SMTP congeners were isolated from *Stachybotrys microspora* and are effective plasminogen modulators.[4] Retrobiogenetically, Nature may be utilizing 3,4-dihydroxyphthalide, farnesal, an appropriate amine/amino acid, and enzymes to design these novel multifunctional architectures. A synthesis of the NG-121 model skeleton and the stachybotrin A–C core structure have been reported by Inoue et al., respectively utilizing [2,3]-sigmatropic rearrangement of a sulfur ylide and the Mannich reaction/Claisen rearrangement as the key steps.[5,6] However, total syntheses of these target compounds have not yet been accomplished and this is imperative from the point of view of advanced biological screenings. The real challenges in the synthesis of these natural products are: (i) regioselective introduction of farnesyl unit, (ii) stereoselective creation of two adjacent asymmetric carbon centers in the chromane ring, (iii) lactonization with the regioselective introduction of a formyl group, and (iv) preservation of the C=C bonds throughout the sequence. In continuation of our studies on selective couplings of phenolic substrates with long-chain hydrocarbons and their application in the synthesis bioactive natural products,[7] we herein report the first synthesis of NG-121 methyl ether (Schemes 1–3).



Scheme 1 Reported regioselective coupling of 4,6-dihydroxyphthalide and farnesal

Retrosynthetically, regioselective condensation of 4,6-dihydroxyphthalide with farnesal to constitute benzopyran **A** (Scheme 1), followed by selective hydroxy-directed

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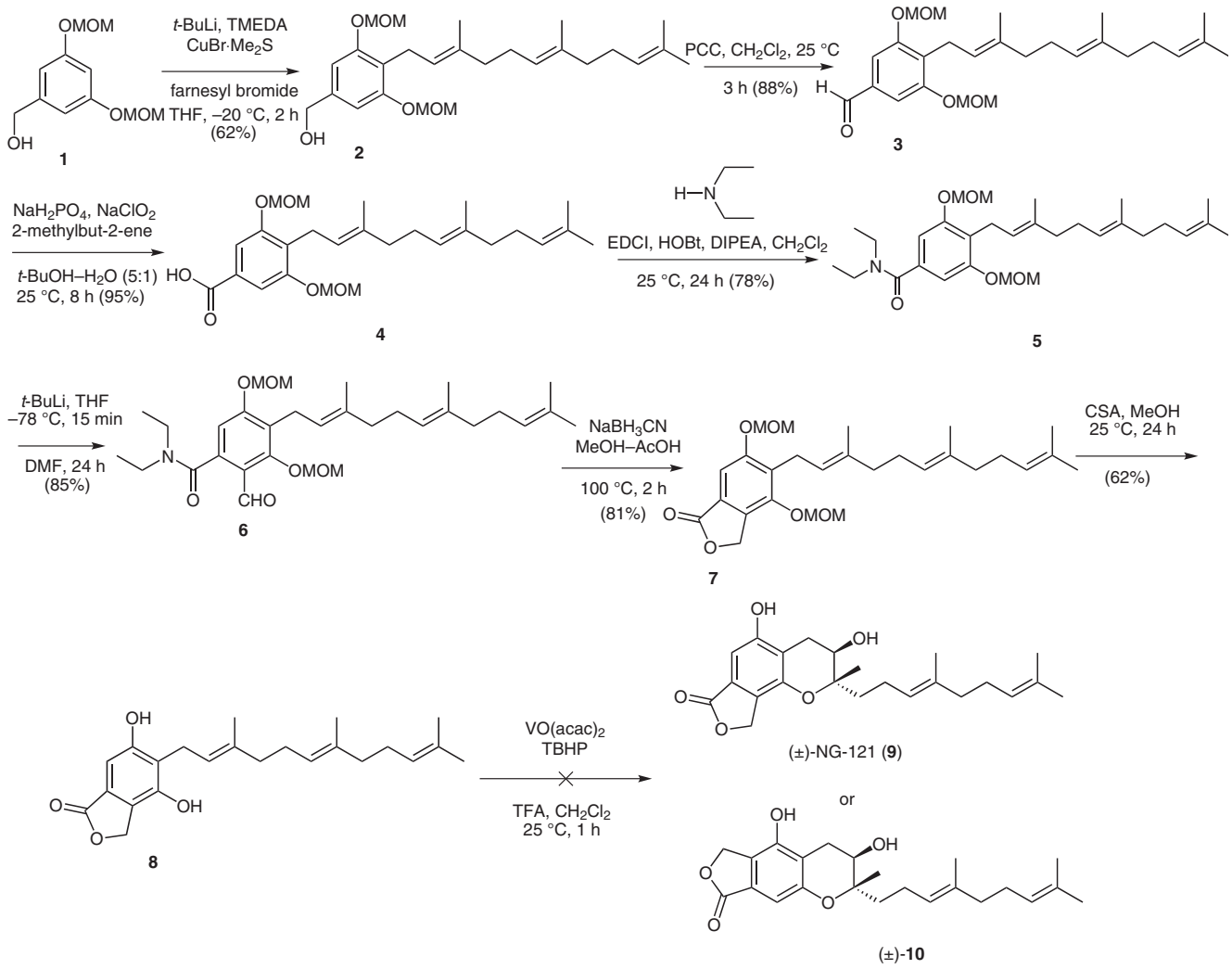
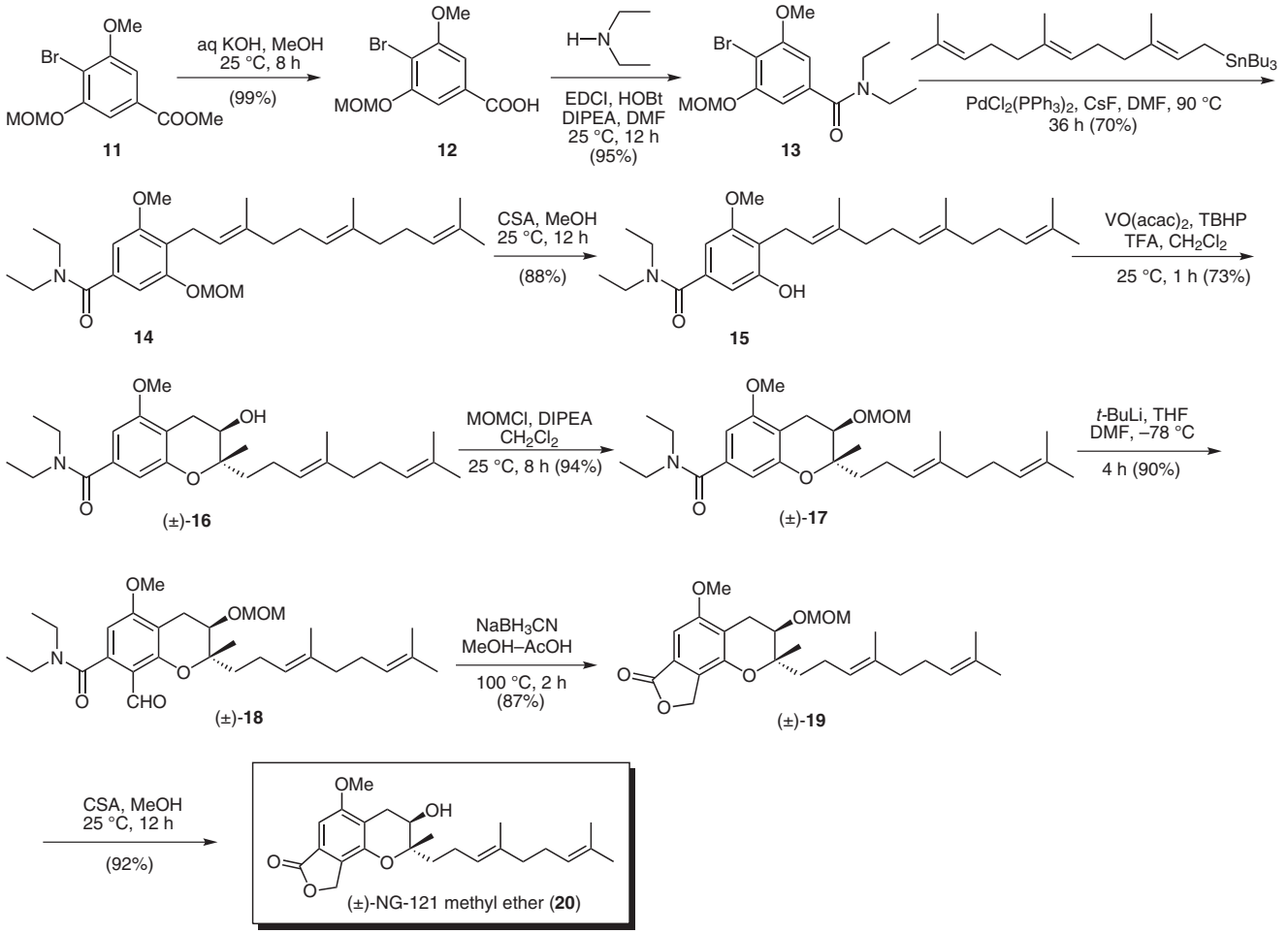
epoxidation and oxirane ring opening with metal hydride would formulate a concise approach to NG-121. However, as depicted in Scheme 1, the reaction of 4,6-dihydroxyphthalide with farnesal is known to produce the regioisomer **B**.[7d] Hence, we decided to initiate our synthesis with an appropriate resorcinol derivative, introducing the farnesyl unit first and then stepwise lactonization followed by chromanol generation (Scheme 2). The symmetrically double MOM-protected benzyl alcohol **1** on selective *o*-lithiation using *tert*-butyllithium as the base followed by reaction with farnesyl bromide gave the desired coupling product **2** in 62% yield. Pyridinium chlorochromate oxidation of benzyl alcohol **2** to the corresponding aldehyde **3** (88%) and subsequent Pinnick oxidation ($NaClO_2/NaH_2PO_4$)[8] provided the required carboxylic acid **4** in 95% yield. At this stage, for selectivity reasons it appeared appropriate to generate the lactone ring first by applying the *o*-formylation strategy. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) induced coupling of carboxylic acid **4** with diethylamine gave the appropriate amide **5** for the introduction of the formyl unit. The reaction of symmetrical amide **5** with *tert*-butyllithium and *N*,*N*-dimethylformamide selectively yielded the desired mono-formylated benzaldehyde derivative **6** in 85% yield. Sodium cyanoborohydride reduction of benzaldehyde derivative **6** to the corresponding intermediate benzyl alcohol and in situ lactonization furnished the required phthalide **7** in 81% yield. Selective mono-MOM deprotection of compound **7** was studied using known literature protocols (CSA/MeOH, 2 M HCl/MeOH, CBr_4/*i*-PrOH,[9a] I_2/MeOH[9b]). Unfortunately, all attempts were unsuccessful and resulted in double-MOM deprotection to yield the farnesylated dihydroxyphthalide **8** in 62% yield. Plausibly the mono-MOM deprotected intermediate under goes second deprotection at a rate faster than the starting material itself. Alas, mono-MOM protection of biphenolic compound **8** using different molar concentrations of MOMCl also resulted in di-MOM-protected compound **6** as the major product. The hydroxy-directed vanadyl acetylacetonate catalyzed selective epoxidation conditions developed by Lattanzi et al.[10] to obtain the chromanol were extended to biphenolic



Scheme 2 Attempted synthesis of chromanol (±)-NG-121

compound **8** in an attempt diastereoselectively synthesize either the (±)-NG-121 (**9**) or its regioisomer **10**; however, all attempts met with failure and the highly reactive biphenolic substrate **8** underwent instantaneous excessive decomposition.

To circumvent the above-mentioned difficulty involved in selective MOM-deprotection, we altered our plans and decided to commence the synthesis with the unsymmetrical methyl benzoate derivative **11** containing two different protecting groups, the methyl and MOM ethers (Scheme 3). The base-catalyzed hydrolysis of ester **11** to give corresponding carboxylic acid **12** (99%) followed by *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride induced coupling with diethylamine provided the appropriate amide **13** in 95% yield. Palladium-catalyzed Stille coupling reaction of electron-rich bromoresorcinol derivative **13** with tributyl(farnesyl)tin furnished the required coupling product **14**, but in 10–15% yield only.[11] However, as according to the literature report,[12] addition of cesium fluoride (2.0 equiv) as an accelerator improved the yield of the desired Stille coupling product **14** to 70%. As described in Scheme 2, *o*-formylation of ether **14** was planned for the generation of the requisite γ-lactone moiety. However, *tert*-butyllithium/*N*,*N*-dimethylformamide driven *o*-formylation of methyl and MOM ether protected unsymmetrical amide **14** was unselective and resulted in the formation of a mixture of the corresponding desired and undesired isomeric benzaldehyde derivatives utilizing both the available *o*-positions (3:2, by ^{1}H NMR). Hence deprotection of the MOM group was planned to generate the chromanol and then the formyl unit would be introduced. Camphorsulfonic acid driven selective MOM deprotection of compound **14** gave the desired phenol **15** in 88% yield. The hydroxy-directed vanadyl acetylacetonate/*tert*-butyl hydroperoxide (TBHP) mediated regioselective epoxidation of the C2=C3 bond in the farnesyl chain followed by concomitant regio- and diastereoselective intramolecular oxirane ring opening exclusively formed the pair of chromanol enantiomers (±)-**16** in 73% yield.



Scheme 3 Diastereoselective synthesis of NG-121 methyl ether

A pseudo-S_N2 epoxide opening resulted in the *cis* orientation of the secondary hydroxy group and the tertiary methyl group in compound (±)-**16**, which was established on the basis of NOESY studies; we propose that the present outcome is on the basis of thermodynamic stability (Figure 2).[13] The formed free secondary hydroxy group in compound (±)-**16** was MOM protected to obtain product (±)-**17** in 94% yield. Fortunately, the *tert*-butyllithium/*N*,*N*-dimethylformamide *o*-formylation of (±)-**17** was completely regioselective and exclusively furnished the requisite benzaldehyde derivative (±)-**18** in 90% yield. The presence of a formyl group at the 8-position in compound (±)-**18** was confirmed on the basis of NOESY studies. NOESY data revealed the interaction of the OMe group with an adjacent aromatic proton through space. Herein exclusive formylation at the 8-position in the starting material (±)-**17** could be due to the effective participation of the locked ring oxygen atom of the chromane system in the *o*-lithiation step. Sodium cyanoborohydride reduction of aldehyde (±)-**18** to the corresponding alcohol and in situ lactonization gave phthalide (±)-**19** in 87% yield. MOM deprotection of (±)-**19** provided NG-121 methyl ether (±)-**20** in 92% yield. The obtained spectral data for NG-121 methyl ether (±)-**20** was in concurrence with the data reported for the model compound.[5] We also prepared the 3,5-dinitrobenzoyl derivative of compound (±)-**20** with the prospect of establishing the structure by X-ray crystallography, but unfortunately the product was also a thick oil. We carefully studied the demethylation of compound (±)-**19**/**20** to get the actual natural product NG-121 (BCl_3, BBr_3, TMSI/DCM,[14a] LiCl/DMF,[14b] EtSNa/HMPA,[14c] BuSLi/HMPA,[14d] $B(C_6F_5)_3/Et_3SiH$[14e]) however, the result was always recovery of starting material and/or decomposition. Hence, we have accomplished the diastereoselective synthesis of the methyl ether of natural product NG-121.

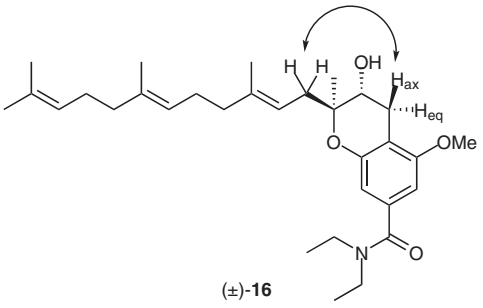


Figure 2 NOESY interaction between H_{ax} and methylene protons

In summary, the diastereoselective first synthesis of methyl ether of natural product NG-121 has been achieved in nine steps with 29% overall yield (an average of 88% yield each step) using an appropriate reactions sequence and essential protecting groups. Stille coupling to introduce the farnesyl chain on the electron-rich phenolic system, regio- and diastereoselective ring closure with the generation of two adjacent chiral centers, and selective *o*-formylation were the key steps involved. We feel that our present approach to NG-121 methyl ether is general in nature and would be useful to access the NG-121 and stachybotrin analogues, and SMTP congeners for SAR studies.

^{1}H NMR: 200, 400, and 500 NMR spectrometers (TMS internal standard); ^{13}C NMR: 200 (50 MHz), 400 (100 MHz), and 500 NMR spectrometers (125 MHz); MS: MS-TOF mass spectrometer; HRMS (ESI): TOF mass analyzer; IR: FT-IR spectrophotometer. Column chromatographic separations were carried out on silica gel (100–200 mesh); PE = petroleum ether. Commercially available *t*-BuLi, farnesyl bromide, TMEDA, CuBr·Me_2S, PCC, 2-methylbut-2-ene, Et_2NH·HCl, EDCI, HOBt, CsF, $PdCl_2(PPh_3)_2$, CSA, $VO(acac)_2$, MOMCl, TBHP, $NaBH_3CN$, $B(C_6F_5)_3$, and Et_3SiH were used. [3,5-Bis(methoxymethoxy)phenyl]methanol (**1**), methyl 4-bromo-3-methoxy-5-(methoxymethoxy)benzoate (**11**), and tributyl(farnesyl)tin were prepared by known procedures.[15]

{3,5-Bis(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]phenyl}methanol (2)

A 1.60 M *t*-BuLi in pentane soln (30.15 mL, 48.24 mmol) was added dropwise to a soln of alcohol **1** (5.00 g, 21.92 mmol) and TMEDA (6.86 mL, 46.05 mmol) in THF (60 mL) at –20 °C under argon; the mixture was stirred at –20 °C for 1 h. CuBr·Me_2S (9.44 g, 46.05 mmol) was added and the mixture was stirred at –20 °C for a further 1 h. A soln of farnesyl bromide (6.87 g, 24.12 mmol) in THF (20 mL) was added dropwise to this mixture, which was stirred at –20 °C for 2 h. The reaction was quenched with sat. aq NH_4Cl soln (10 mL) and then concentrated in vacuo. EtOAc (80 mL) was added to the residue and the organic soln was washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 1:1) afforded pure **2** as a thick oil; yield: 5.87 g (62%).

IR (neat): 3427, 1611, 1589 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.78 (s, 3 H), 1.80–2.14 (m, 8 H), 3.39 (d, *J* = 8 Hz, 2 H), 3.47 (s, 6 H), 4.61 (s, 2 H), 5.01–5.14 (m, 2 H), 5.14–5.25 (m, 1 H), 5.19 (s, 4 H), 6.78 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.0, 16.1, 17.6, 22.5, 25.7, 26.6, 26.7, 39.7, 39.8, 56.0, 65.5, 94.4, 106.5, 119.5, 122.6, 124.2, 124.4, 131.3, 134.7, 134.9, 140.0, 155.7.

MS (ESI): *m*/*z* = 455 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{40}O_5Na$: 455.2773; found: 455.2776.

3,5-Bis(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzaldehyde (3)

To a stirred suspension of PCC (3.74 g, 17.36 mmol) and 4 Å molecular sieves in CH_2Cl_2 (60 mL) at 0 °C was added a soln of alcohol **2** (5.00 g, 11.57 mmol) in CH_2Cl_2 (20 mL) under argon. The mixture was stirred at 25 °C for 3 h, and then diluted with Et_2O (20 mL). The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) afforded pure aldehyde **3** as a thick oil; yield: 4.37 g (88%).

IR ($CHCl_3$): 2723, 1699, 1586 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 1.85–2.10 (m, 8 H), 3.46 (d, *J* = 8 Hz, 2 H), 3.48 (s, 6 H), 5.06 (t, *J* = 8 Hz, 2 H), 5.15–5.28 (m, 1 H), 5.26 (s, 4 H), 7.29 (s, 2 H), 9.87 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.0, 16.1, 17.6, 23.2, 25.7, 26.5, 26.7, 39.7, 39.8, 56.1, 94.4, 108.9, 121.2, 124.0, 124.3, 127.5, 131.3, 135.0, 135.5, 135.7, 156.0, 191.6.

MS (ESI): *m*/*z* = 453 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{38}O_5Na$: 453.2617; found: 453.2611.

3,5-Bis(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzoic Acid (4)

To a stirred soln of aldehyde **3** (4.00 g, 9.30 mmol) in *t*-BuOH–H_2O (5:1, 40 mL) was added 2-methylbut-2-ene (5.91 mL, 55.81 mmol) at 25 °C, the mixture was stirred for 15 min, and then NaH_2PO_4 (1.67 g, 13.95 mmol) was added. After stirring at 25 °C for 10 min, $NaClO_2$ (3.36 g, 37.20 mmol) was added and stirring was continued for 8 h. The mixture was concentrated in vacuo, the EtOAc (60 mL) was added to the residue, and the organic soln was washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 2:3) afforded pure **4** as white solid; yield: 3.94 g (95%); mp 78–80 °C.

IR ($CHCl_3$): 1726, 1693, 1586 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.79 (s, 3 H), 1.90–2.10 (m, 8 H), 3.46 (d, *J* = 5 Hz, 2 H), 3.48 (s, 6 H), 5.07 (t, *J* = 10 Hz, 2 H), 5.19 (t, *J* = 10 Hz, 1 H), 5.25 (s, 4 H), 7.49 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.1, 17.6, 23.1, 25.7, 26.6, 26.7, 39.7, 39.8, 56.1, 94.5, 109.5, 121.5, 124.1, 124.3, 126.7, 127.9, 131.3, 135.0, 135.6, 155.4, 170.9.

MS (ESI): *m*/*z* = 447 $[M + H]^+$, 469 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{38}O_6Na$: 469.2566; found: 469.2578.

***N*,*N*-Diethyl-3,5-bis(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzamide (5)**

A soln of EDCI (1.64 g, 8.63 mmol) and HOBt (1.32 g, 8.63 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred suspension of acid **4** (3.50 g, 7.84 mmol) and Et_2NH·HCl (946 mg, 8.63 mmol) in CH_2Cl_2 (40 mL) at 0 °C under argon atmosphere. DIPEA (2.95 mL, 17.26 mmol) was added dropwise to the mixture, which was then stirred at 25 °C for 24 h. To the mixture was added EtOAc (60 mL) and the organic soln was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc. 3:1) afforded pure **5** as a thick oil; yield: 3.06 g (78%).

IR ($CHCl_3$): 1732, 1619, 1581 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05–1.33 (m, 6 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.78 (s, 3 H), 1.90–2.15 (m, 8 H), 3.15–3.60 (m, 4 H), 3.40 (d, *J* = 8 Hz, 2 H), 3.46 (s, 6 H), 5.00–5.28 (m, 3 H), 5.18 (s, 4 H), 6.79 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.9, 14.0, 15.9, 16.1, 17.6, 22.6, 25.6, 26.6, 26.7, 39.3, 39.7, 39.8, 43.3, 55.9, 94.5, 106.1, 121.1, 122.1, 124.2, 124.3, 131.2, 134.87, 134.93, 135.7, 155.5, 171.0.

MS (ESI): *m*/*z* = 524 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{48}NO_5$: 502.3532; found: 502.3529.

***N*,*N*-Diethyl-2-formyl-3,5-bis(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzamide (6)**

A 1.60 M *t*-BuLi in pentane soln (5.23 mL, 8.38 mmol) was added to a stirred soln of **5** (3.00 g, 5.98 mmol) in THF (30 mL) at –78 °C under argon, stirring was continued for a further 15 min, and then DMF (2.31 mL, 29.94 mmol) was added. The mixture was allowed to warm up to 25 °C and stirred for 24 h. The reaction was quenched with sat. aq NH_4Cl soln (10 mL) and concentrated in vacuo. EtOAc (50 mL) was added to the residue and the organic soln was washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 3:2) afforded pure **6** as a thick oil; yield: 2.69 g (85%).

IR ($CHCl_3$): 2857, 1740, 1684, 1634, 1594 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 10 Hz, 3 H), 1.33 (t, *J* = 10 Hz, 3 H), 1.58 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.79 (s, 3 H), 1.93–2.11 (m, 8 H), 3.09 (q, *J* = 10 Hz, 2 H), 3.42 (d, *J* = 5 Hz, 2 H), 3.45 (s, 3 H), 3.53–3.64 (m, 2 H), 3.59 (s, 3 H), 5.06 (s, 2 H), 5.08 (t, *J* = 5 Hz, 1 H), 5.09 (t, *J* = 5 Hz, 1 H), 5.16 (t, *J* = 10 Hz, 1 H), 5.25 (s, 2 H), 6.83 (s, 1 H), 10.21 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 13.5, 16.0, 16.3, 17.7, 23.2, 25.7, 26.6, 26.7, 38.8, 39.7 (2 C), 42.5, 56.2, 58.0, 94.1, 101.6, 108.7, 120.8, 121.5, 124.0, 124.3, 125.1, 131.3, 135.2, 136.1, 138.6, 159.9, 160.5, 169.5, 189.0.

MS (ESI): *m*/*z* = 530 $[M + H]^+$, 552 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{48}NO_6$: 530.3482; found: 530.3484.

4,6-Bis(methoxymethoxy)-5-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]isobenzofuran-1(3*H*)-one (7)

To a stirred soln of **6** (2.00 g, 3.78 mmol) in AcOH–MeOH (1:1, 20 mL) was added $NaBH_3CN$ (356 mg, 5.67 mmol) and the mixture was heated at 100 °C for 2 h. The reaction was allowed to attain 25 °C and concentrated in vacuo. EtOAc (40 mL) was added to the residue and the organic soln was washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 9:1) afforded pure **7** as a thick oil; yield: 1.40 g (81%).

IR ($CHCl_3$): 1768, 1619 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 3 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 1.90–2.12 (m, 8 H), 3.47 (s, 3 H), 3.48 (d, *J* = 8 Hz, 2 H), 3.54 (s, 3 H), 5.07 (s, 2 H), 5.07 (t, *J* = 8 Hz, 2 H), 5.14 (t, *J* = 8 Hz, 1 H), 5.26 (s, 2 H), 5.37 (s, 2 H), 7.38 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 16.2, 17.6, 23.8, 25.6, 26.4, 26.7, 39.6, 39.7, 56.1, 56.7, 69.0, 94.4, 97.1, 105.2, 121.2, 123.9, 124.2, 125.4, 129.5, 131.3, 135.1, 136.0, 150.3, 156.9, 171.0.

MS (ESI): *m*/*z* = 481 $[M + Na]^+$, 513 $[M + Na + MeOH]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{38}O_6Na$: 481.2566; found: 481.2566.

4,6-Dihydroxy-5-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]isobenzofuran-1(3*H*)-one (8)

To a stirred soln of **7** (1.00 g, 2.18 mmol) in MeOH (30 mL) was added camphorsulfonic acid (cat., 50 mg) and the mixture was stirred at 25 °C under argon for 24 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ (1 mL) and concentrated in vacuo. EtOAc (30 mL) was added to the residue and the organic soln was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) afforded pure **8** as a thick oil; yield: 500 mg (62%).

IR ($CHCl_3$): 3380, 1735, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.84 (s, 3 H), 1.90–2.20 (m, 8 H), 3.55 (d, *J* = 8 Hz, 2 H), 5.06 (t, *J* = 8 Hz, 1 H), 5.07 (t, *J* = 8 Hz, 1 H), 5.24 (s, 2 H), 5.30 (t, *J* = 8 Hz, 1 H), 6.48 (br s, 1 H), 7.07 (s, 1 H), 7.33 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 16.3, 17.6, 23.1, 25.6, 26.1, 26.6, 39.6 (2 C), 68.8, 103.3, 120.3, 120.8, 123.3, 124.2, 124.4, 126.1, 131.4, 135.9, 140.7, 150.4, 156.4, 173.0.

MS (ESI): *m*/*z* = 393 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_4Na$: 393.2042; found: 393.2041.

4-Bromo-3-methoxy-5-(methoxymethoxy)benzoic Acid (12)
Ester **11** (5.00 g, 16.44 mmol) was added to a mixture of 10% aq KOH soln (40 mL) and MeOH (40 mL) and the mixture was stirred at 25 °C for 8 h. The mixture was concentrated in vacuo and the residue was diluted with EtOAc (50 mL), acidified with 2 M HCl (100 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 2:3) afforded pure **12** as a white solid; yield: 4.72 g (99%); mp 160–162 °C.

IR (nujol): 2700–2500, 1687, 1588 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 3.41 (s, 3 H), 3.90 (s, 3 H), 5.33 (s, 2 H), 7.24 (s, 1 H), 7.37 (s, 1 H), 13.26 (br s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 56.1, 56.5, 94.8, 106.0, 106.6, 108.8, 131.3, 154.3, 156.6, 166.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}BrO_5Na$: 312.9688; found: 312.9695.

4-Bromo-*N*,*N*-diethyl-3-methoxy-5-(methoxymethoxy)benzamide (13)
A soln of EDCI (3.26 g, 17.06 mmol) and HOBt (2.61 g, 17.06 mmol) in DMF (15 mL) was added dropwise to a stirred suspension of acid **12** (4.50 g, 15.51 mmol) and Et_2NH·HCl (1.87 g, 17.06 mmol) in DMF (30 mL) at 0 °C under argon. DIPEA (5.84 mL, 34.13 mmol) was added dropwise to the mixture, which was stirred at 25 °C for 12 h. EtOAc (80 mL) was added and the organic layer was washed with brine (4 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 3:2) afforded pure **13** as a thick oil; yield: 5.08 g (95%).

IR (neat): 1634, 1581 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.05–1.35 (m, 6 H), 3.15–3.35 (m, 2 H), 3.40–3.60 (m, 2 H), 3.49 (s, 3 H), 3.91 (s, 3 H), 5.25 (s, 2 H), 6.62 (d, *J* = 2 Hz, 1 H), 6.82 (d, *J* = 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 14.1, 39.4, 43.3, 56.3, 56.5, 95.1, 103.0, 103.7, 106.3, 137.3, 154.8, 157.1, 170.1.

MS (ESI): *m*/*z* = 368 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}BrNO_4Na$: 368.0473; found: 368.0471.

***N*,*N*-Diethyl-3-methoxy-5-(methoxymethoxy)-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzamide (14)**
$Pd(PPh_3)_2Cl_2$ (200 mg, 10 mol%) was added to a stirred soln of aryl bromide **13** (1.00 g, 2.89 mmol) and tributyl(farnesyl)tin (2.86 g, 5.79 mmol) in DMF (14.5 mL) at 25 °C under argon. CsF (880 mg, 5.79 mmol) was added to the mixture, which was heated at 90 °C for 36 h. EtOAc (60 mL) was added to the mixture and the insoluble residue was removed by filtration. The organic layer was washed with brine (4 × 20 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 7:3) afforded pure **14** as a thick oil; yield: 955 mg (70%).

IR (neat): 1636, 1581 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.05–1.35 (m, 6 H), 1.56 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.76 (s, 3 H), 1.85–2.12 (m, 8 H), 3.15–3.60 (m, 4 H), 3.36 (d, *J* = 6 Hz, 2 H), 3.44 (s, 3 H), 3.81 (s, 3 H), 5.00–5.22 (m, 3 H), 5.16 (s, 2 H), 6.58 (s, 1 H), 6.73 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 14.1, 15.9, 16.0, 17.6, 22.3, 25.6, 26.6, 26.7, 39.2, 39.6, 39.7, 43.3, 55.7, 55.8, 94.5, 102.9, 105.2, 120.3, 122.2, 124.2, 124.3, 131.1, 134.75, 134.83, 135.6, 155.3, 158.1, 171.2.

MS (ESI): *m*/*z* = 494 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{46}NO_4$: 472.3427; found: 472.3424.

***N*,*N*-Diethyl-3-hydroxy-5-methoxy-4-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]benzamide (15)**
To a stirred soln of **14** (2.00 g, 4.24 mmol) in MeOH (50 mL) was added camphorsulfonic acid (100 mg) and the mixture was stirred at 25 °C under argon for 12 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ soln (1 mL) and concentrated in vacuo. EtOAc (50 mL) was added to the residue and the organic soln was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 2:1) afforded pure **15** as a thick oil; yield: 1.59 g (88%).

IR ($CHCl_3$): 3272, 1615, 1586 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.00–1.35 (m, 6 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.76 (s, 3 H), 1.35–2.15 (m, 8 H), 3.20–3.40 (m, 2 H), 3.40–3.60 (m, 2 H), 3.33 (d, *J* = 8 Hz, 2 H), 3.77 (s, 3 H), 5.00 (t, *J* = 6 Hz, 1 H), 5.08 (t, *J* = 6 Hz, 1 H), 5.19 (t, *J* = 6 Hz, 1 H), 6.37 (d, *J* = 2 Hz, 1 H), 6.55 (d, *J* = 2 Hz, 1 H), 7.35 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.8, 14.2, 15.9, 16.1, 17.6, 22.2, 25.6, 26.6, 26.7, 39.3, 39.7, 39.8, 43.3, 55.7, 100.5, 107.5, 117.4, 122.0, 124.1, 124.4, 131.2, 134.9, 135.0, 136.3, 155.6, 158.0, 171.9.

MS (ESI): *m*/*z* = 450 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}NO_3$: 428.3165; found: 428.3154.

(±)-2-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-*N*,*N*-diethyl-3-hydroxy-5-methoxy-2-methyl-3,4-dihydro-2*H*-chromene-7-carboxamide (16)
$VO(acac)_2$ (14 mg, 1.50 mol%) was added to a stirred soln of phenol **15** (1.50 g, 3.51 mmol) in CH_2Cl_2 (20 mL) at 25 °C under argon. After 15 min, a ~5.50 M TBHP in decane soln (0.83 mL, 4.56 mmol) was added to mixture followed by the dropwise addition of TFA (0.05 mL, 20 mol%) and the mixture was further stirred at 25 °C for 1 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, PE–EtOAc, 13:7) to afford pure **16** as a thick oil; yield: 1.13 g (73%).

IR ($CHCl_3$): 3393, 1612, 1579 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.00–1.30 (m, 6 H), 1.27 (s, 3 H), 1.50–1.65 (m, 2 H), 1.58 (s, 6 H), 1.66 (s, 3 H), 1.90–2.15 (m, 6 H), 2.20–2.45 (br s, 1 H), 2.61 (dd, *J* = 16, 4 Hz, 1 H), 2.81 (dd, *J* = 16, 4 Hz, 1 H), 3.20–3.40 (m, 2 H), 3.40–3.60 (m, 2 H), 3.73 (t, *J* = 8 Hz, 1 H), 3.81 (s, 3 H), 5.02–5.12 (m, 2 H), 6.41 (s, 1 H), 6.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 14.3, 15.9, 17.6, 19.0, 21.5, 25.6, 26.2, 26.6, 36.9, 39.1, 39.6, 43.2, 55.5, 67.5, 78.7, 100.2, 107.8, 109.2, 123.8, 124.2, 131.4, 135.5, 136.5, 153.3, 158.2, 171.1.

MS (ESI): *m*/*z* = 466 [M + Na]$^+$, 482 [M + K]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}NO_4$: 444.3114; found: 444.3109.

(±)-2-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-*N*,*N*-diethyl-5-methoxy-3-(methoxymethoxy)-2-methyl-3,4-dihydro-2*H*-chromene-7-carboxamide (17)
MOMCl (0.25 mL, 3.38 mmol) was added to a stirred soln of **16** (1.00 g, 2.25 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon and the mixture was stirred for 30 min. DIPEA (0.77 mL, 4.51 mmol) was added dropwise and the mixture was further stirred at 25 °C for 8 h and then quenched with H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 7:3) afforded pure **17** as a thick oil; yield: 1.03 g (94%).

IR ($CHCl_3$): 1637, 1581 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.30 (m, 6 H), 1.28 (s, 3 H), 1.58 (s, 6 H), 1.60–1.70 (m, 2 H), 1.66 (s, 3 H), 1.92–2.00 (m, 2 H), 2.00–2.08 (m, 2 H), 2.13 (q, *J* = 8 Hz, 2 H), 2.65 (dd, *J* = 16, 8 Hz, 1 H), 2.93 (dd, *J* = 16, 8 Hz, 1 H), 3.20–3.40 (m, 2 H), 3.40–3.60 (m, 2 H), 3.40 (s, 3 H), 3.81 (s, 3 H), 3.81 (t, *J* = 8 Hz, 1 H), 4.66 (d, *J* = 8 Hz, 1 H), 4.82 (d, *J* = 8 Hz, 1 H), 5.07 (t, *J* = 8 Hz, 1 H), 5.09 (t, *J* = 8 Hz, 1 H), 6.41 (s, 1 H), 6.46 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 14.3, 15.9, 17.6, 19.0, 21.4, 23.2, 25.6, 26.6, 37.4, 39.0, 39.6, 43.2, 55.5, 55.8, 72.5, 77.9, 95.3, 100.0, 107.8, 109.4, 123.9, 124.2, 131.2, 135.3, 136.3, 153.3, 157.9, 171.1.

MS (ESI): *m*/*z* = 510 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{46}NO_5$: 488.3376; found: 488.3380.

(±)-2-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl]-*N*,*N*-diethyl-8-formyl-5-methoxy-3-(methoxymethoxy)-2-methyl-3,4-dihydro-2*H*-chromene-7-carboxamide (18)

A 1.60 M *t*-BuLi in pentane soln (0.89 mL, 1.43 mmol) was added to a stirred soln of **17** (500 mg, 1.02 mmol) in THF (10 mL) at –78 °C and the mixture was stirred for 15 min. DMF (0.39 mL, 5.13 mmol) was added and the mixture was allowed to attain 25 °C and stirred for a further 4 h. The reaction was quenched with sat. aq NH_4Cl soln (5 mL) and then concentrated in vacuo. EtOAc (20 mL) was added to the residue and the organic soln was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 3:2) afforded pure **18** as a thick oil; yield: 475 mg (90%).

IR (neat): 1682, 1639, 1599 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 8 Hz, 3 H), 1.25–1.42 (m, 6 H), 1.59 (s, 6 H), 1.67 (s, 3 H), 1.65–1.80 (m, 2 H), 1.90–2.25 (m, 6 H), 2.55–2.75 (m, 1 H), 2.85–3.05 (m, 1 H), 3.08 (q, *J* = 6 Hz, 2 H), 3.43 (s, 3 H), 3.45–3.75 (m, 2 H), 3.86 (t, *J* = 6 Hz, 1 H), 3.88 (s, 3 H), 4.69 (d, *J* = 8 Hz, 1 H), 4.84 (d, *J* = 8 Hz, 1 H), 5.00–5.20 (m, 2 H), 6.31 (s, 1 H), 10.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 13.6, 16.0, 17.6, 21.5, 23.1, 25.6, 26.6, 37.6, 38.5, 39.6, 42.3, 55.87, 55.94, 72.1, 79.4, 95.5, 101.3, 115.0, 123.4, 124.2, 131.4, 135.8, 138.9, 157.0, 162.3, 170.1, 187.9.

MS (ESI): *m*/*z* = 538 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{45}NO_6Na$: 538.3145; found: 538.3135.

(±)-2-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-5-methoxy-3-(methoxymethoxy)-2-methyl-3,4-dihydro-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (19)

To a stirred soln of aldehyde **18** (400 mg, 0.77 mmol) in AcOH–MeOH (1:1, 10 mL) was added $NaBH_3CN$ (73 mg, 1.16 mmol) and the mixture was heated at 100 °C for 2 h. The reaction was allowed to warm up to 25 °C and concentrated in vacuo. EtOAc (25 mL) was added to the residue and the organic soln was washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 2:1) afforded pure **19** as a thick oil; yield: 300 mg (87%).

IR ($CHCl_3$): 1770, 1619 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.58 (s, 6 H), 1.55–1.75 (m, 2 H), 1.66 (s, 3 H), 1.90–2.22 (m, 6 H), 2.78 (dd, *J* = 18, 6 Hz, 1 H), 2.99 (dd, *J* = 18, 4 Hz, 1 H), 3.42 (s, 3 H), 3.88 (t, *J* = 8 Hz, 1 H), 3.88 (s, 3 H), 4.68 (d, *J* = 8 Hz, 1 H), 4.84 (d, *J* = 8 Hz, 1 H), 5.00–5.16 (m, 2 H), 5.16 (d, *J* = 14 Hz, 1 H), 5.25 (d, *J* = 14 Hz, 1 H), 6.90 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.9, 17.6, 19.4, 21.5, 23.8, 25.6, 26.6, 37.3, 39.6, 55.93, 55.96, 68.0, 72.1, 78.9, 95.5, 97.1, 114.8, 123.4, 124.1, 125.3, 127.8, 131.4, 135.7, 148.0, 159.4, 171.7.

MS (ESI): *m*/*z* = 483 $[M + K]^+$, 499 $[M + Na + MeOH]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{37}O_6$: 445.2590; found: 445.2585.

(±)-2-[(*E*)-4,8-Dimethylnona-3,7-dien-1-yl)-3-hydroxy-5-methoxy-2-methyl-3,4-dihydro-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (NG-121 Methyl Ether, 20)

To a stirred soln of **19** (250 mg, 0.56 mmol) in MeOH (10 mL) was added camphorsulfonic acid (cat., 20 mg) and the mixture was stirred at 25 °C for 12 h under argon. The reaction was quenched by the addition of sat. $NaHCO_3$ (1 mL) and concentrated in vacuo. EtOAc (20 mL) was added to the residue and the organic soln was washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) afforded pure **20** as a thick oil; yield: 207 mg (92%).

IR (neat): 3460, 1770, 1621 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.57 (s, 6 H), 1.59–1.65 (m, 2 H), 1.66 (s, 3 H), 1.89 (br s, 1 H), 1.92–2.18 (m, 4 H), 2.13 (q, *J* = 8 Hz, 2 H), 2.77 (dd, *J* = 18 and 4 Hz, 1 H), 2.98 (dd, *J* = 18 and 4 Hz, 1 H), 3.88 (s, 3 H), 3.95 (s, 1 H), 5.06 (t, *J* = 8 Hz, 1 H), 5.08 (t, *J* = 8 Hz, 1 H), 5.17 (d, *J* = 16 Hz, 1 H), 5.22 (d, *J* = 16 Hz, 1 H), 6.90 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 17.6, 19.1, 21.5, 25.7, 26.6, 26.9, 36.9, 39.6, 55.9, 67.3, 68.0, 79.5, 97.2, 114.7, 123.4, 124.1, 125.4, 127.8, 131.5, 136.0, 147.9, 159.5, 171.7.

MS (ESI): *m*/*z* = 423 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{32}O_5Na$: 423.2147; found: 423.2141.

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