# Total Synthesis of Manoalide

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**Abstract:** $Me_3Al/AlCl_3$-mediated hetero-Diels–Alder (HDA) additions of 2-silyloxy-1,3-dienes to formylated butenolide **6** containing a protected hydroxy function afford, in one step, a variety of pyranofuranones including manoalide precursor **16**, which is a stable monoprotected seco-manoalide.

**Key words:** hetero-Diels–Alder reaction, NSAIDs, γ-hydroxybutenolides, $Me_3Al/AlCl_3$, marine natural products, manoalide

Manoalide is a sesterterpene ($C_{25}$), which has attracted interest as an irreversible $PLA_2$ inhibitor and functions as an NSAID (nonsteroidal anti-inflammatory drug). The hydrophilic core of manoalide can be considered bioisosteric with the tetracyclic steroidal skeleton (Figure).

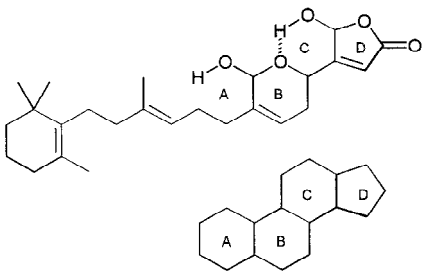
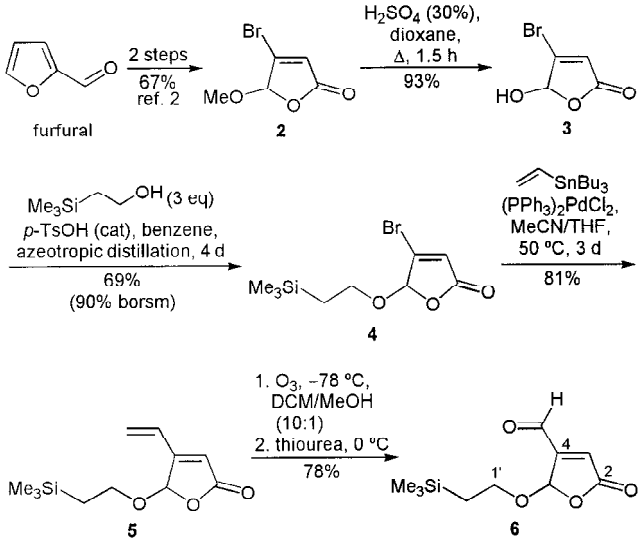



**Figure.** Manoalide, Bioactive Sesterpene ($C_{25}$) of Marine Origin and Bio-Isosteric NSAID

Manoalide has been synthesized several times, namely by Katsumura and Isoe,[1a,c] Garst,[1b] Kocienski[1d,e] and their respective coworkers. The reported approaches have in common that the sensitive γ-hydroxybutenolide moiety was generated in the last step, by a Diels–Alder addition of singlet oxygen to a 2-trialkylsilylfuran derivative. We report here a new approach using a 3-formylated butenolide, which was submitted to a Lewis acid mediated hetero-Diels–Alder (HDA) reaction. Several silyloxydienes were used in the key cycloaddition.

Specifically, furfural furnishes 4-bromo-5-methoxyfuran-2(5*H*)-one **(2)** in two reliable steps.[2a,b,3] Transacetalization of **2** was carried out via hemiacetal **3**, which was submitted to azeotropic distillation with 2-trimethylsilylethanol, giving protected γ-hydroxybutenolide **4**. Cross-coupling[4] with vinylstannane provided vinylated butenolide **5**, which on careful ozonolysis and anhydrous workup furnished the desired 4-formyl-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5H)-one **6** as key intermediate (Scheme 1).

HDA model reactions between aldehyde **6** and Danishefsky's diene or 2-trimethylsilyloxybuta-1,3-diene gave peri- and regioselectively the cycloaddition products

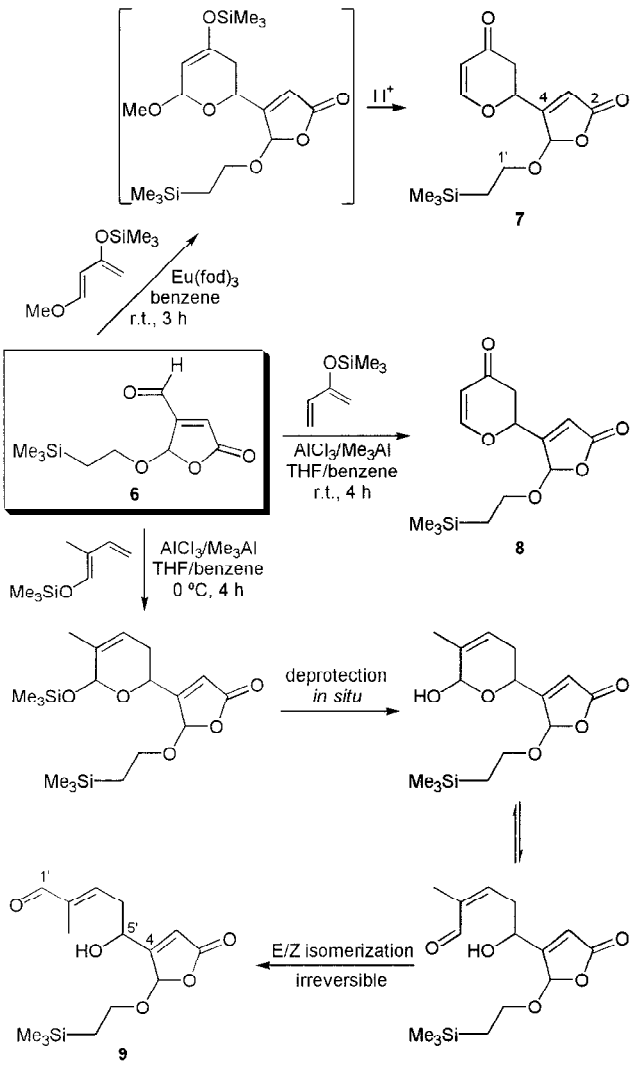



**Scheme 1**

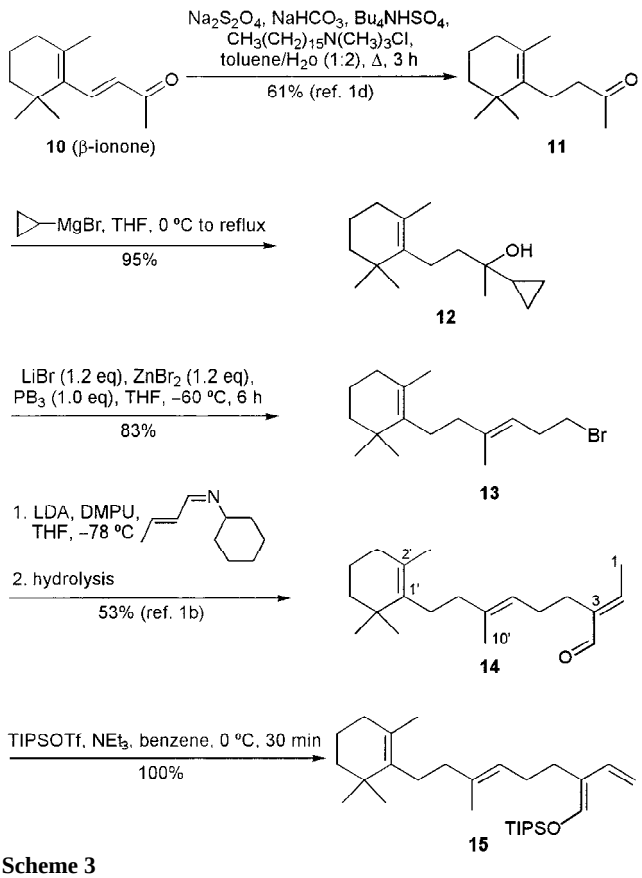
**7** and **8**. In these reactions, catalyst tuning ($AlCl_3/Me_3Al$) was decisive for success. 2-Methyl-1-trimethylsilyloxybuta-1,3-diene, which is readily available from tiglic aldehyde, combined with aldehyde **6** to the protected 10 carbon *eastern* segment **9** of *seco*-manoalide (Scheme 2).

The required 20 carbon *western* silyloxydiene **15** was prepared in 5 steps from inexpensive β-ionone. Following the Kocienski procedure[1d] site-specific hydrogenation under phase-transfer conditions provided ketone **11**,[1d] which was converted into cyclopropylcarbinyl alcohol **12**. It was important to carry out the Julia–Johnson reaction[5,6] by addition of salt (LiBr, $ZnBr_2$) and at low temperature (–60 °C). Under optimized conditions, the preparation of homoallylic bromide **13** proceeded (*E*)-selectively, and only two steps were required to convert methyl ketone **11** into **13** in good overall yield (Scheme 3).

Combination of silyloxydiene **15** and aldehyde **6** under the conditions of the model study (Scheme 2), afforded the HDA cycloadduct which was desilylated in situ (silica gel, $H_2O$) at carbon C-24 giving monoprotected *seco*-manoalide **(16)**. Deprotection with trifluoroacetic acid furnished manoalide **(1b)** (Scheme 4). As an alternative to the usual photoisomerization[1a–e,7] of **1b** into **1a** we cyclized **16** to monoprotected manoalide **17**. Unlike the natural product **1a**, the 2-(trimethylsilyl)ethyl derivative **17** gave a clean $^1H$ NMR spectrum and showed no tendency to generate its precursor, i.e. open-chain tautomer **16**. Deprotection led to the reported[1d] complex mixture of 8 diastereomers.




**Scheme 2**



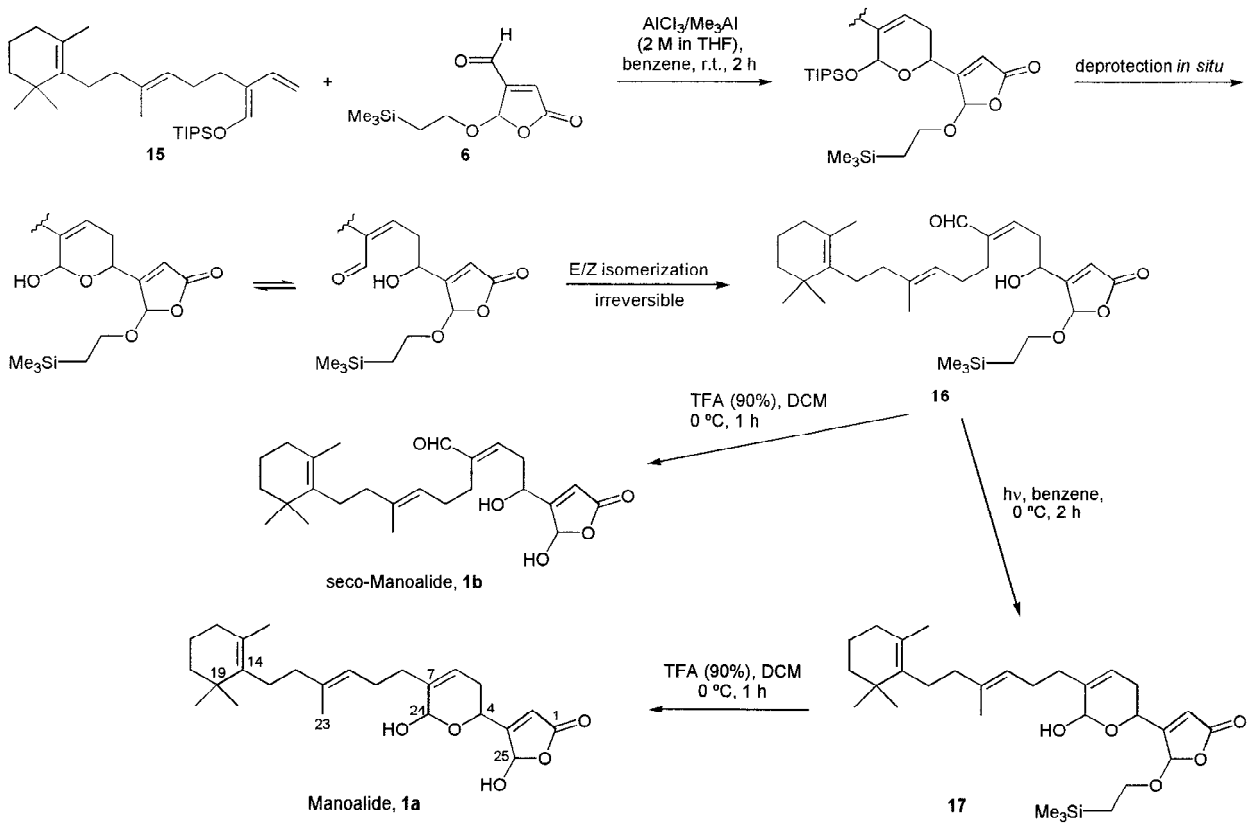

**Scheme 3**

In conclusion, we have described a synthesis of pyranofuranones and manoalide by a convergent route, which is also amenable to a combinatorial approach. A variety of manoalide analogues are directly accessible, for the evaluation of biological activity. Aldehyde **6**, in addition to other 4-formyl- and 4-vinylfuran-2(5*H*)-ones prepared by us,[2a] is a useful building block in the synthesis of bioregulatory natural products including heteroprostanoids.[8a,b]

Melting points: Büchi apparatus. Infrared spectra: Perkin-Elmer 1710 spectrometer. $^1$H NMR spectra: Bruker WP 200 SY or AM 400 spectrometer. Chemical shifts are reported in $\delta$ values relative to TMS as internal standard. $^{13}$C NMR spectra: Bruker WP 200 SY or a Bruker AM 400 spectrometer. Chemical shifts are reported in $\delta$ values relative to TMS. APT (*a*ttached *p*roton *t*est): spin-echo-based selection of multiplicities of $^{13}$C NMR signals. Quaternary C and $CH_2$ carbon atoms give positive signals (+), while CH and $CH_3$ give negative signals (–). Low- and high-resolution EI-MS: Finnigan MAT 312 spectrometer with an ionization potential of 70 eV at r.t., unless otherwise stated. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30 60 μm). Analytical TLC was carried out on aluminium-backed 0.2 mm silica gel 60 $F_{254}$ plates (E. Merck). E ($Et_2O$) and PE (light petroleum, bp 40–60 °C).

**4-Bromo-5-hydroxyfuran-2(5*H*)-one (3):**
A suspension of compound **2** (1.9 g, 10 mmol), $H_2SO_4$ (30%, 130 mL) and dioxane (180 mL) was heated to reflux for 1.5 h under vigorous stirring. The mixture was cooled to r.t. and then poured onto ice. The aqueous phase was extracted with $Et_2O$ (250 mL portions) and the combined organic layer dried ($MgSO_4$). After evaporation of the solvent the crude product was purified by chromatography (E/PE, 1 : 1) to afford **3** (1.7 g, 9.3 mmol, 93%) as colourless crystals; mp 73 °C.
$^1$H NMR (200 MHz, $CDCl_3$/TMS), *J*(Hz): $\delta$ = 6.42 (s, 1 H, H-3), 6.09 (s, 1 H, H-5), 5.83 (br s, 1 H, OH).
$^{13}$C NMR (50.32 MHz, APT, $CDCl_3$/TMS): $\delta$ = 169.41 (+, C-2), 148.15 (+, C-4), 124.00 (–, C-3), 99.59 (–, C-5).
IR ($CHCl_3$): $\nu$ = 3300, 3112, 1800, 1712, 1608, 1448, 1332, 1296, 1256, 1184, 1136, 1036, 952, 856, 716, 668, 452 cm$^{-1}$.
MS (70 eV): *m*/*z* (%) = 180 (14), 178 ($M^+$,14), 152 (15), 150 (15), 134 (100), 132 (97), 107 (21), 106 (44), 105 (23), 104 (42), 99 (55), 71 (13).
HRMS: *m*/*z* Calcd. for $C_4H_3O_3Br$, 177.9266. Found 177.9263.

**4-Bromo-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5*H*)-one (4):**
To a solution of alcohol **3** (1.6 g, 9 mmol) and 2-(trimethylsilyl)ethan-1-ol (3.9 mL, 27 mmol) in benzene (20 mL) was added *p*-TsOH (cat). The mixture was distilled azeotropically (Dean–Stark separator) for 4 d. After cooling to r.t. the solvent was removed and the crude product purified by chromatography [PE/E, 8 : 1, then 1 : 1 to recover starting material (0.38 g, 2.1 mmol, 23%)] to yield **4** (1.7 g, 6.2 mmol, 69%, 90% based on recovered starting material); colourless solid; mp 44 °C.
$^1$H NMR (200 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 6.41 (d, *J* = 1, 1 H, H-3), 5.78 (d, *J* = 1, 1 H, H-5), 3.88 (m, 2 H, H-1'), 1.04 (m, 2 H, H-2'), 0.04 [s, 9 H, $OSi(CH_3)_3$].




**Scheme 4**

$^{13}$C NMR (50.32 MHz, APT, $CDCl_3$): $\delta$ =167.98 (+, C-2), 145.71 (+, C-4), 124.48 (–,C-3), 103.30 (–, C-5), 68.19 (+, C-1'), 17.97 (+, C-2'), –1.46 [–, $OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3040, 2956, 2856, 1792, 1764, 1612, 1408, 1340, 1128, 1068, 956, 852 cm$^{-1}$. MS (70 eV): *m/z* (%) = 278 ($M^+$, 0), 209 ($M^+$+2 –TMS, 48), 207 ($M^+$–TMS, 48), 199 (14), 171 (13), 163 (14), 161 (13), 139 (15), 137 (15), 103 (18), 81 (13), 75 (50), 73 (100).
Anal. Calcd. for $C_9H_{15}BrO_3Si$ (279.2): C, 38.72; H 5.42. Found: C, 38.64; H, 5.34.

**5-[2-(Trimethylsilyl)eth-1-oxy]-4-vinylfuran-2(5*H*)-one (5):**
To a suspension of **4** (558 mg, 2.00 mmol) and bis(triphenylphosphine)palladium dichloride (70 mg, 5 mol%) in MeCN (10 mL) and THF (2 mL) was added tributylvinyl stannane (0.61 mL, 2.1 mmol) at r.t. under $N_2$ and exclusion of moisture. The yellow suspension became clear within a few minutes. The solution was stirred for 3 d at 50 °C. The resulting black solution was cooled to r.t., evaporated and the residue was chromatographed (PE/E, 4 : 1) to give **5** (366 mg, 1.60 mmol, 81%) as colourless oil.
$^1$H NMR (200 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 6.61 (dd, *J* = 18, 11, 1 H, H-3'), 6.06 (d, *J* = 1, 1 H, H-3), 6.01 (d, *J* = 1, 1 H, H-5), 5.91 (d, *J* = 18, 1 H, H-4'), 5.70 (d, *J* = 11, 1 H, H-4'), 3.87 (m, 2 H, H-1'), 1.04 (m, 2 H, H-2'), 0.04 [s, 9 H, $OSi(CH_3)_3$].
$^{13}$C NMR (50.32 MHz, APT, $CDCl_3$): $\delta$ = 170.28 (+, C-2), 159.29 (+, C-4), 126.71 (–, C-3'), 125.41 (+, C-4'), 118.15 (–, C-3), 101.56 (–, C-5), 66.84 (+, C-1'), 17.93 (+, C-2'), –1.69 [–, $OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3040, 2956, 2896, 1784, 1760, 1644, 1364, 1308, 1252, 1228, 1164, 1128, 1128, 1028, 988, 960s, 940, 904, 864, 836 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 227 (1), 226 ($M^+$,1), 171 (11), 137 (20), 105 (12), 73 (100), 69 (12).

**4-Formyl-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5*H*)-one (6):**
A solution of **5** (1.1 g, 5.0 mmol) in $CH_2Cl_2$ (60 mL) and MeOH (1 mL) was ozonized at –78 °C until a light-blue colour was observed. When the mixture became cloudy during ozonolysis, MeOH was added dropwise. After complete reaction thiourea (0.38 g, 5.0 mmol) in MeOH (2 mL) was added. The mixture was allowed to reach 0 °C, silica gel was added and the solvent removed. Chromatography afforded **6** (866 mg, 3.80 mmol, 78%) as a colourless solid; mp 39 °C.
$^1$H NMR (200 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 10.04 (s, 1 H, CHO), 6.77 (d, 1 Hz, 1 H, H-3), 6.14 (d, 1 Hz, 1 H, H-5), 3.89 (m, 2 H, H-1'), 1.02 (m, 2 H, H-2'), 0.03 [s, 9 H, $OSi(CH_3)_3$].
$^{13}$C NMR (50.32 MHz, APT, $CDCl_3$): $\delta$ = 185.19 (–, CHO), 168.75 (+, C-2), 155.99 (+, C-4), 131.13 (–, C-3), 101.46 (–, C-5), 69.49 (+, C-1'), 18.04 (+, C-2'), -1.41 [–, $OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3040, 2956, 2900, 1796, 1768, 1704, 1412, 1356, 1252, 1128, 1064, 1040, 956, 908, 860, 840 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 228 ($M^+$, 0), 199 (8), 185 (29), 171 (4), 158 (6), 157 (47), 110 (12), 103 (79), 83 (6), 78 (5), 75 (31), 74 (9), 73 (100), 72 (4).
Anal. Calcd. for $C_{10}H_{16}O_4Si$ (228.3): C, 52.61; H, 7.06. Found C, 52.57; H, 7.10.

**4-[2,3-Dihydropyran-4-on-2-yl]-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5*H*)-one (7):**
To a solution of **6** (228 mg, 1.00 mmol) and $Eu(fod)_3$ (52 mg, 0.050 mmol) in benzene (4 mL) was added freshly distilled Danishefsky's diene (258 mg, 1.50 mmol) dropwise at 0 °C under $N_2$ and exclusion of moisture. The mixture was stirred for 3 h at r.t., then glacial AcOH (0.100 mL, 1.75 mmol) and silica gel (100 mg) were added. After complete reaction (TLC monitoring) the solvent was removed and the crude product chromatographed (PE/E, 5 : 1 to E) to afford **7** (88 mg, 0.33 mmol, 33%) as colourless oil (mixture of diastereomers).
$^1$H NMR (400 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 7.48 (d, *J* = 6, 1 H, H-6'), 6.24 (d, *J* = 0.5, 1 H, H-3), 5.85 (d, *J* = 0.5, 1 H, H-5), 5.54 (d, *J* = 6, 1 H, H-5'), 5.32 (m, 1 H, H-2'), 3.86 (m, 2 H, H-1''), 2.82 (m, 2 H, H-3'), 1.01 (m, 2 H, H-2''), 0.03 [s, 9 H, $OSi(CH_3)_3$].

$^{13}$C NMR (100.61 MHz, DEPT, $CDCl_3$): $\delta$ = 189.88 (C-4'), 168.90 (C-2), 163.48 (C-6'), 161.25 (C-4), 119.77 (C-3), 107.90 (C-5'), 101.89 (C-5), 74.40 (C-2'), 68.99 (C-1"), 39.48 (C-3'),18.24 (C-2"), –1.47 [$OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3000, 2956, 2932, 1796, 1768, 1680, 1600, 1456, 1400, 1264, 1124, 1040, 964, 860, 840 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 268 ($M^+$, 0), 243 (2), 198 (10), 111 (18), 105 (12), 74 (10), 73 (100), 69 (12).

**5-[2-(Trimethylsilyl)eth-1-oxy]-4-[4-trimethylsilyloxy-3,6-dihydro-2*H*-pyran-2-yl]furan-2(5*H*)-one (8):**
To a solution of **6** (114 mg, 0.500 mmol) in benzene (2 mL) was added a solution of the catalyst (1 mL) [prepared from anhyd $AlCl_3$ (133 mg, 1.00 mmol) in THF (1 mL) and $AlMe_3$ (2 mL, 1 M solution in toluene) at 0 °C] followed by 2-trimethylsilyloxybuta-1,3-diene (107 mg, 0.75 mmol) at 0 °C under $N_2$ and exclusion of moisture. The mixture was stirred for max. 4 h at r.t. (TLC monitoring). The mixture was cooled with an ice-bath and $H_2O$ was added carefully, until the yellowish suspension did not foam during addition. The layers were separated, the organic layer was dried, the solvent removed and the residue chromatographed (PE/E, 1 : 1 to E) to give **8** (50 mg, 0.14 mmol, 27%) as yellow oil (mixture of diastereomers).
$^1$H NMR (400 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 6.10 (dt, *J* = 2, 1, 1 H, H-3), 5.82 (d, *J* = 1, 1 H, H-5), 4.92 (m, 1 H, H-5'), 4.52 (ddd, *J* = 11, 3, 1.75, 1 H, H-2'), 4.28 (m, 2 H, H-6'), 3.88 (m, 2 H, H-1"), 2.10 (m, 2 H, H-2'), 1.02 (m, 2 H, H-2"), 0.21 [m, 9 H, $OSi(CH_3)_3$/pyran ring], 0.03 [s, 9 H, $OSi(CH_3)_3$/furan ring].
$^{13}$C NMR (50.32 MHz, APT, $CDCl_3$/TMS): $\delta$ = 170.18 (C-2), 161.24 (C-4), 146.13 (C-4'), 119.53 (C-3), 101.86 (C-5), 100.31 (C-5'), 70.73 (C-2'), 68.89 (C-1"), 64.81 (C-6'), 34.75 (C-3'), 18.24 (C-2"), 0.21 [$OSi(CH_3)_3$/pyran ring], –1.46 [$OSi(CH_3)_3$/ furan ring].
IR ($CHCl_3$): $\nu$ = 3120, 3000, 2956, 2896, 1796, 1764, 1656, 1344, 1252, 1124, 1040, 948, 860 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 379 ($M^+$, 0), 298 (17), 210 (39), 159 (43), 131 (25), 103 (18), 73 (100), 69 (7).

**4-[(2*E*)-5-Hydroxy-2-methylpent-2-enon-5-yl]-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5*H*)-one (9):**
Compound **6** (114 mg, 0.500 mmol) and 2-methyl-1-trimethylsilyloxybuta-1,3-diene (117 mg, 0.750 mmol) were allowed to react at 0 °C as described for **8**. After chromatography **9** was obtained as yellowish oil (80 mg, 0.26 mmol, 51%).
$^1$H NMR (400 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 9.38 (s, 1 H, CHO), 6.54 (t, *J* = 7, 1 H, H-3'), 6.10 (s, 1 H, H-3), 5.95 (s, 1 H, H-5), 4.78 (t, *J* = 7, 1 H, H-5'), 3.87 (m, 2 H, H-1"), 2.75 (m, 2 H, H-4'), 1.78 (s, 3 H, $CH_3$), 1.60 (br, 1 H, OH), 1.02 (m, 2 H, H-2"), 0.03 [s, 9 H, $OSi(CH_3)_3$].
$^{13}$C NMR (100.61 MHz, DEPT, $CDCl_3$): δ = 195.10 (CHO), 172.90 (C-2), 169.05 (C-4), 148.32 (C-2), 145.87 (C-3'), 118.77 (C-3), 102.89 (C-5), 69.00 (C-1"), 66.87 (C-5'), 28.09 (C-4'), 19.21 ($CH_3$), 18.24 (C-2"), –1.46 [$OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3604, 3464, 3432, 3368, 3120, 3000, 2956, 2928, 2900, 1796, 1764, 1688, 1648, 1604, 1404, 1380, 1344, 1304, 1252, 1228, 1124, 960, 900, 860, 840, 616 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 312 ($M^+$, 0), 251 (2), 223 (4), 201 (13), 156 (15), 111 (18), 84 (19), 75 (40), 74 (9), 73 (100), 69 (8), 55 (18), 45 (9).

**(3*E*)-1-Bromo-4-methyl-6-(2,6,6-trimethylcyclohex-1-en-1-yl)hex-3-ene (13):**
A mixture of $\beta$-ionone (**10**; 10 mL, 50 mmol), $Bu_4NHSO_4$ (2.6 g, 7.5 mmol), hexadecyltrimethylammonium chloride (2.8 g, 7.5 mmol) and $NaHCO_3$ (21 g, 75 mmol) in toluene (100 mL) and $H_2O$ (200 mL) was stirred vigorously under $N_2$. Sodium dithionite (11 g, 65 mmol) was added in one portion at r.t., then the mixture was heated to reflux for 30 min. The mixture was cooled to r.t and a second portion of sodium dithionite (11 g, 65 mmol) was added. The mixture was heated to reflux for further 2 h and then cooled to r.t. The layers were separated and the aqueous phase was extracted with $Et_2O$ (6 × 100 mL). The combined organic layers were washed with $H_2O$ (50 mL), dried ($MgSO_4$). Twofold chromatography (PE/E, 35 : 1) afforded dihydro-$\beta$-ionone **11** (5.9 g, 31 mmol, 61%) as light-yellow liquid.

To a mixture of Mg turnings (1.1 g, 43 mmol) and $I_2$ (catalytic amounts) in THF (25 mL) was added cyclopropyl bromide (a few drops, to start the reaction). Then the residual cyclopropyl bromide (2.1 mL, 26 mmol) was added in such manner that the solution refluxed gently. After complete addition the mixture was stirred for 30 min at 50 °C, then cooled to r.t. A solution of dihydro-$\beta$-ionone **11** (3.8 g, 20 mmol) in THF (10 mL) was added. The resulting mixture was stirred for 2 h at r.t. and 1.5 h at reflux temperature. After cooling to 0 °C, the reaction mixture was treated with satd aq $NH_4Cl$ solution, until the precipitate of $Mg(OH)_2$ had dissolved. The layers were separated and the aqueous layer was extracted with $Et_2O$ (5 × 50 mL). The combined organic phase was dried ($MgSO_4$), silica gel was added and the solvent evaporated. The residue was purified by chromatography (PE/E, 30 : 1) to give the tertiary alcohol **12** (4.4 g, 19 mmol, 95%) as colourless oil. To a suspension of anhyd LiBr (1.0 g, 12 mmol) and anhyd $ZnBr_2$ (2.7 g, 12 mol) in THF (50 mL) was added a solution of alcohol **12** (2.4 g, 10 mmol) in THF (80 mL) at –60 °C. After 1 h $PBr_3$ was added dropwise and the mixture was stirred for 5 h at –60 °C. Then PE (50 mL) and NaCl solution (50%, 50 mL) were added. The mixture was allowed to reach r.t., the layers were separated and aqueous layer was extracted with PE (5 × 50 mL). The combined organic phase was dried ($MgSO_4$), evaporated and chromatographed (PE/E, 30 : 1) to afford bromide **13** (2.5 g, 8.3 mmol, 83%) (*E*/*Z*, 9 : 1) as colourless oil. The spectroscopic data were in agreement with the literature.[1d]

**(2*E*,6*E*)-7-Methyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,6-dien-3-carbaldehyde (14).**
To a solution of LDA (16 mmol) were added DMPU (1.9 mL, 16 mmol) and freshly prepared imine (2.8 mL, 16 mmol) [preparation: to a mixture of freshly distilled cyclohexyl amine (18 mL, 160 mmol) and $CaCl_2$ (2.5 g, 23 mmol) in $Et_2O$ (75 mL) was added crotonaldehyde (6.1 mL, 75 mmol) at –15 °C; the mixture was stirred for 1 h at 0 °C, then for 16 h at r.t.; workup and distillation at 90 °C afforded the imine]. The resulting yellow solution was stirred for 10 min at –78 °C, the bromide **13** (5.0 g, 17 mmol) in THF (6.5 mL) was added and the red solution was stirred for 5 h at –78 °C. At 0 °C satd aq $NH_4Cl$ solution was added, the layers were separated and the aqueous layer was extracted with $Et_2O$ (50 mL portions). The combined organic layer was dried ($MgSO_4$) and evaporated. The residue was mixed with $Et_2O$ (30 mL), $H_2O$ (15 mL), glacial AcOH (15 mL) and NaOAc (3.5 g) and stirred for 1 h. After separation the aqueous phase was extracted with $Et_2O$ (5 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent was removed. The crude product was chromatographed (PE/E, 50 : 1) to give the aldehyde **14** (2.4 g, 9.0 mmol, 53%) as light yellow oil.
$^1$H NMR (400 MHz, $CDCl_3$/TMS), *J*(Hz): $\delta$ = 9.38 (s, 1 H, CHO), 6.60 (br t, *J* = 7, 1 H, H-2), 5.15 (br t, *J* = 7, 1 H, H-6), 2.60 (m, 3 H, H-1), 2.32 (m, 2 H, H-4), 2.15–1.87 (m, 8 H, H-5, H-8, H-9, H-3'), 1.66 (s, 3 H, H-10'), 1.61 (s, 3 H, H-9'), 1.58 (m, 2 H, H-5'), 1.42 (m, 2 H, H-4'), 0.98 (s, 6 H, H-8', H-7').
$^{13}$C NMR (100.61 MHz, DEPT, $CDCl_3$/TMS), *J*(Hz): $\delta$ = 195.21 (CHO), 150.20 (C-3), 144.38 (C-2), 137.09 (C-7), 137.00 (C-1'), 126.96 (C-2'), 122.70 (C-6), 40.23 (C-8), 39.86 (C-5'), 34.99 (C-4), 34.72 (C-6'), 32.76 (C-3'), 28.63 (C-8', C-7'), 27.79 (C-1), 26.91 (C-5), 24.46 (C-9), 21.97 (C-9'), 19.80 (C-4'), 15.99 (C-10').
IR ($CHCl_3$): $\nu$ = 2956, 2932, 2864, 1684, 1644, 1600, 1456, 1400, 1380, 1360, 1228, 1116, 1052, 972 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 288 ($M^+$, 2), 287 (3), 151 (6), 137 (100), 136 (31), 121 (11), 95 (39), 81 (35), 79 (8), 69 (17), 67 (11).
Anal. Calcd. for $C_{20}H_{32}O$ (288.5): C, 83.27; H, 11.18. Found C, 83.35; H, 11.21.

**Monoprotected *seco*-Manoalide, {4-[[(3*E*,7*E*)-10-(2,6,6-Trimethylcyclohex-1-en-1-yl]-8-methyl-4-formyl-1-hydroxydeca-3,7-dien-1-yl]-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5*H*)-one} (16):**
To a solution of aldehyde **14** (430 mg, 1.5 mmol) in benzene (2 mL) was added TIPSOTf (0.44 mL, 1.7 mmol) and $Et_3N$ (0.30 mL, 2.2 mmol) at 0°C. The mixture was stirred for 30 min and was then neutralized with dil HCl (pH control). The aqueous phase was extracted with $Et_2O$ (5 × 10 mL), the combined organic layer was dried ($MgSO_4$) and the solvent removed. Diene **15** was obtained in quantitative yield (670 mg, 1.50 mmol, ca. 100%). Furanone **6** (230 mg, 1.0 mmol) and diene **15** (670 mg, 1.5 mmol) were allowed to react at r.t as described for compound **8**. The crude product was purified by chromatography (PE/E, 3 : 1) to afford **16** (130 mg, 0.4 mmol, 27%).
$^1$H NMR (400 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 9.38 (s, 1 H, CHO), 6.53 (br t, *J* = 6.5, 1 H, H-6), 6.08 (br, 1 H, H-25), 5.92 (s, 1 H, H-2), 5.11 (br t, *J* = 6.5, 1 H, H-10), 4.72 (br, 1 H, H-4), 3.81 (m, 2 H, H-26), 2.80 (m, 2 H, H-5), 2.28 (m, 2 H, H-8), 2.14–1.85 (m, 8 H, H-16, H-13, H-12, H-9), 1.61 (s, 3 H, H-23), 1.56 (s, 3 H, H-22), 1.55–1.51 (m, 2 H, H-18), 1.45–1.30 (m, 3 H, OH, H-17), 1.00 (m, 2 H, H-27), 0.97 (s, 6 H, H-21, H-20), 0.03 [s, 9 H, $OSi(CH_3)_3$].
$^{13}$C NMR (100.61 MHz, DEPT, $CDCl_3$), *J*(Hz): $\delta$ = 194.50 (CHO), 169.88 (C-1), 167.49 (C-3), 147.51 (C-7), 145.85 (C-6), 137.48 (C-11), 136.92 (C-14), 127.01 (C-15), 122.26 (C-10), 118.78 (C-2), 101.79 (C-25), 68.93 (C-26), 67.01 (C-4), 40.19 (C-12), 39.79 (C-18), 34.94 (C-8), 34.73 (C-19), 32.70 (C-16), 28.59 (C-21, C-20), 27.75 (C-5), 26.87 (C-9), 24.51 (C-13), 21.63 (C-22), 19.77 (C-17), 18.24 (C-27), 16.03 (C-23), –1.48 [$OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3600, 3512, 3428 br, 2956, 2928, 2868, 1796, 1764, 1684, 1640, 1600, 1444, 1380, 1252, 1172, 1124, 1076, 960, 908, 860, 840 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 516 ($M^+$, 1), 470 (1), 415 (1), 397 (1), 311 (1), 267 (1), 216 (4), 184 (4), 137 (100), 121 (11), 95 (44), 81 (33), 79 (12), 75 (15), 73 (45), 69 (12), 67 (11).
HRMS: *m*/z Calcd. for $C_{30}H_{48}O_5Si$, 516.3195. Found 516.3171.

***seco*-Manoalide, {5-Hydroxy-4-[[(3*E*,7*E*)-10-(2,6,6-trimethylcyclohex-1-en-1-yl]-8-methyl-4-formyl-1-hydroxydeca-3,7-dien-1-yl]furan-2(5*H*)-one} (1b):**
To a solution of the monoprotected *seco*-manoalide **16** (52 mg, 0.1 mmol) in $CH_2Cl_2$ (0.5 mL) was added trifluoro acetic acid (90%) at 0°C. The mixture was stirred for 1 h at 0°C, then EtOAc (3 mL) and toluene (6 mL) were added. After drying ($MgSO_4$) the solvent was evaporated and the residue was chromatographed (PE/E, 3 : 1 to 1 : 1) to afford *seco*-manoalide **1b** (14 mg, 0.03 mmol, 34%) as violet oil (mixture of diastereomers). The spectroscopic data were in agreement with the literature.[1d]

**Monoprotected Manoalide, {4-[2,3-Dihydro-6-hydroxy-5-[(3*E*)-4-methyl-6-(2,6,6-trimethylcyclohex-1-en-1-yl)hex-3-en-1-yl]-(5*H*)-pyran-2-yl]-5-[2-(trimethylsilyl)eth-1-oxy]furan-(5*H*)-one} (17):**
Aldehyde **16** (22 mg, 0.04 mmol) was dissolved in benzene (15 mL) and irradiated with a Philips HPK 125 W lamp at 0°C. After evaporation of the solvent the crude product was chromatographed (PE/E, 1:1) to give **17** (12 mg, 0.02 mmol, 55%) as colourless oil (mixture of diastereomers).
$^1$H NMR (400 MHz, $CDCl_3$), *J*(Hz): $\delta$ = 6.07 (s, 1 H, H-25), 5.92 (s, 1 H, H-2), 5.72 (m, 1 H, H-6), 5.32 (s, 1 H, H-24), 5.14 (t, *J* = 7.8, 1 H, H-10), 4.76 (dd, *J* = 11, 3.5, 1 H, H-4), 3.98, 3.80 (m, 2 H, H-26), 2.39–2.25 (m, 2 H, H-5), 2.24–1.98 (m, 8 H, H-16, H-13, H-12, H-8), 1.91 (t, *J* = 5.8, 2 H, H-12), 1.64 (s, 3 H, H-23), 1.59 (s, 3 H, H-22), 1.57–1.52 (m, 2 H, H-18), 1.44–1.35 (m, 3 H, OH, H-17), 1.02 (m, 2 H, H-27), 0.98 (s, 6 H, H-21, H-20), 0.03 [s, 9 H, $OSi(CH_3)_3$].
$^{13}$C NMR (100.61 MHz, DEPT, $CDCl_3$), *J*(Hz): $\delta$ = 170.56 (C-1), 169.09 (C-3), 137.91 (C-7), 137.40 (C-11), 136.91 (C-14), 127.01 (C-15), 122.71 (C-10), 121.12 (C-6), 118.05 (C-2), 101.87 (C-25), 91.7 (C-24), 68.90 (C-26), 63.27 (C-4), 40.96 (C-8), 40.09 (C-12), 39.98 (C-18), 34.85 (C-19), 33.02 (C-5), 32.78 (C-16), 28.61 (C-21, C-20), 26.97 (C-9), 25.61 (C-13), 20.98 (C-22), 19.87 (C-17), 18.09 (C-27), 16.10 (C-23), –1.46 [$OSi(CH_3)_3$].
IR ($CHCl_3$): $\nu$ = 3600, 3528, 3376, 2956, 2928, 2856, 1796, 1764, 1652, 1600, 1456, 1380, 1252, 1228, 1128, 1016, 956, 836 cm$^{-1}$.
MS (70 eV): *m/z* (%) = 516 ($M^+$, 1), 470 (1), 415 (1), 397 (1), 380 (1), 267 (1), 244 (1), 215 (2), 202 (3), 185 (3), 185 (3), 184 (4), 177 (3), 157 (5), 137 (100), 136 (26), 135 (8), 123 (12), 121 (13), 111 (11), 109 (14), 107 (11), 95 (55), 93 (13), 81 (42), 75 (20), 73 (51), 69 (23).
HRMS: *m* /z Calcd. for $C_{30}H_{48}O_5Si$: 516.3195. Found 516.3172.

**Manaolide (1a):**
Monoprotected manoalide **17** was allowed to react with trifluoroacetic acid as described for *seco*-manoalide (**1b**) to afford manoalide (**1a**) as the reported[1d] complex mixture of diastereomers and ring-chain tautomers.

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