65. A Concise Synthesis of (*E*)- and (*Z*)-Neomanoalides

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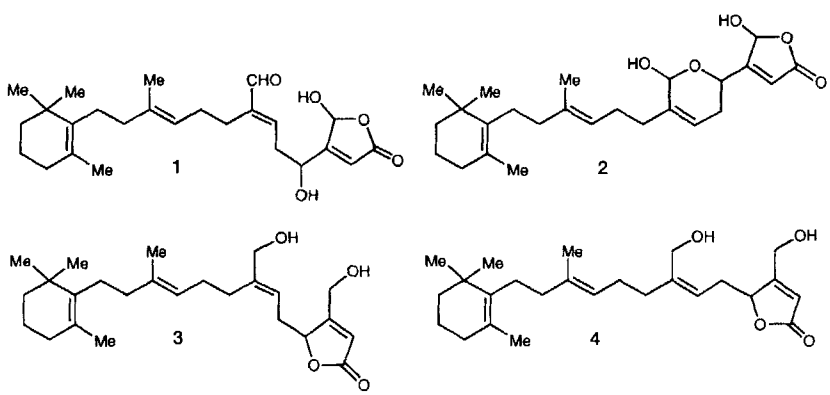
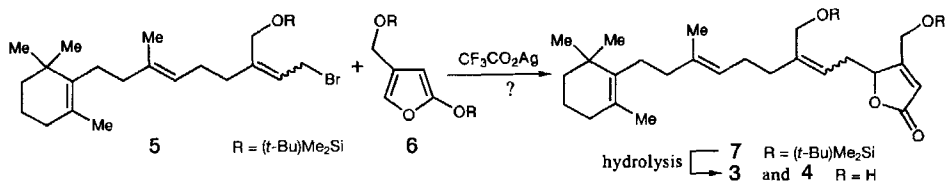
The first synthesis of (*Z*)-neomanoalide (**4**) and an improved synthesis of its (*E*)-isomer **3** was accomplished in a concise, regiocontrolled manner by exploiting 2-[(*tert*-butyl)dimethylsiloxy]-4{[(*tert*-butyl)dimethylsiloxy]-methyl}furan (**6**) as the key reagent. Lithiation of **6** and subsequent reaction with the (2*Z*)- or (2*E*)-isomer of (6*E*)-3-{[(*tert*-butyl)dimethylsiloxy]methyl}-7-methyl-9-(2′,6′,6′-trimethylcyclohex-1′-enyl)nona-2,6-dienyl bromide (**5**), followed by hydrolysis, afforded the corresponding neomanoalide.

Introduction. – The sesterterpenes secomanoalide (**1**), manoalide (**2**), and (*E*)- and (*Z*)-neomanoalides (**3** and **4**, resp.) were isolated from the marine sponge *Luffariella variabilis* [1] [2]. All four displayed *in vitro* activity against *Gram*-positive bacteria, but more importantly, **1** inhibited aldose reductase [3], whereas **2** inhibited phospholipase A2 and showed promise as a topical inflammatory agent [4]. Consequently, their syntheses have attracted attention. So far, **1**–**3** have been prepared [5] [6]. It occurred to us that the (*E*)- and (*Z*)-neomanoalides (**3** and **4**, resp.) should be accessible by an appropriate application of our furanolate technology which already worked well for synthesizing γ-lactones and furans [7] [8]. Logically, the (2*E*)- and (2*Z*)-allyl bromides **5** and 2-[(*tert*-butyl)dimethylsiloxy]-4-{[(*tert*-butyl)dimethylsiloxy]methyl}furan (**6**) would be the reagents of choice, since their coupling should give the (*E*)- and (*Z*)-neomanoalides (**3** and **4**, resp.) directly after deprotection of the intermediate butenolides **7** (*Scheme 1*).



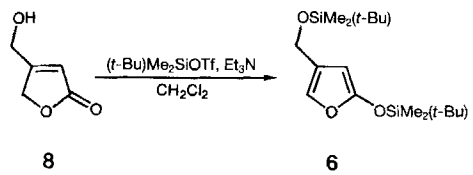
We now describe the first synthesis of **4**, and another shorter synthesis of **3**, which were achieved by exploiting **6** as a new furanolate reagent.

Scheme 1



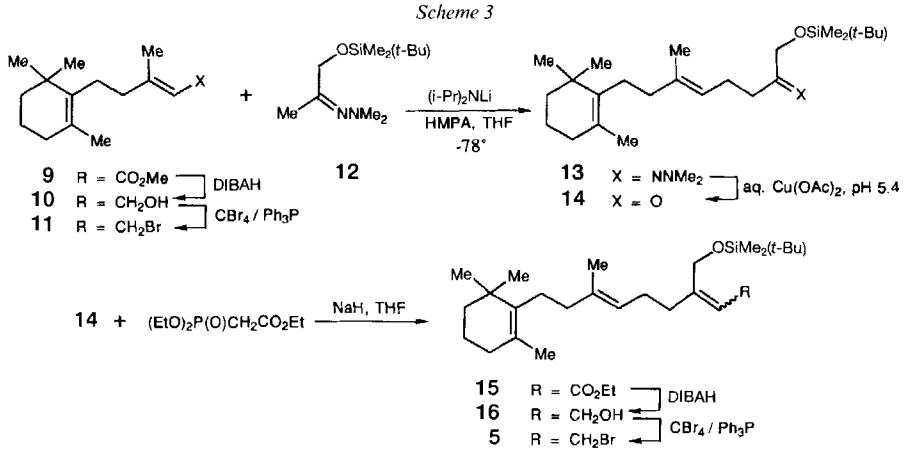
Results and Discussion. – The key reagent, 2-[(*tert*-butyl)dimethylsiloxy]-4-{[(*tert*-butyl)dimethyl-siloxy]methyl}furan (**6**), was prepared from 4-(hydroxymethyl)furan-2(5*H*)-one (**8**) [9] by treatment with (*tert*-butyl)dimethylsilyl trifluoromethanesulfonate in the presence of Et_3N (yield 89%; *Scheme 2*).

Scheme 2



Preparation of the other reagent, the allyl bromide **5**, was readily achieved by modifying and extending the side chain of (*E*)-methyl monocyclofarnesate (**9**) [19] (*Scheme 3*). Reduction of **9** with diisobutylaluminium hydride (DIBAH) afforded alcohol **10** (83%) which, on reaction with CBr_4 and Ph_3P, gave bromide **11** in 98% yield. Next, the hydroxyacetone element was attached by employing 1-[(*tert*-butyl)dimethylsiloxy]propan-2-one dimethylhydrazone (**12**) [11]. The least substituted anion of **12** was generated *in situ* by the action of $(i\text{-}Pr)_2NLi$ in hexamethylphosphoramide (HMPA) at −78° and alkylated with **11**. After quenching with H_2O and extraction with Et_2O, the hydrazone **13**

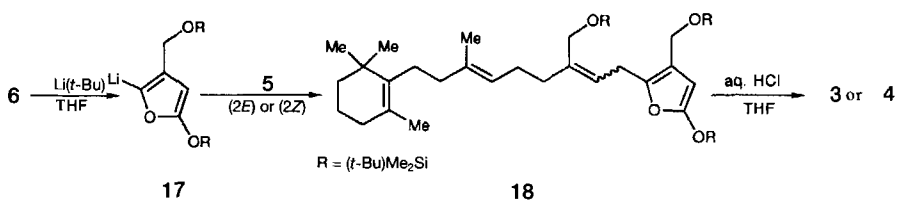
Scheme 3



so obtained was dissolved in THF and selectively hydrolyzed with $Cu(OAc)_2 \cdot H_2O$ in H_2O at pH 5.4 to avoid damaging the siloxy group [12]. The resulting ketone **14**, obtained in 52% yield, was then submitted to *Wittig* reaction with ethyl (diethoxyphosphoryl)acetate and NaH in THF at 25°. Fortuitously, both the resulting (2*E*)- and (2*Z*)-isomers of ethyl ester **15** were formed in a 1:1 ratio and in 95% yield. Separation was easily achieved by column chromatography (silica gel). Thereafter, each isomer was converted to the (2*E*)- and (2*Z*)-alcohols **16** and bromides **5** in 73% overall yield by repeating the previous procedures of reduction and bromination.

Having assembled the two reaction partners, all that remains is their union. Disappointingly, activation of allyl bromide **5** with silver trifluoroacetate, despite several attempts, failed to bring about alkylation of the furanolate reagent **6** (*Scheme 1*). When the (2*Z*)-isomer of **5** was used, the partially hydrolyzed furanolate reagent was recovered in substantial amounts together with by-products of unknown structure. None of the expected product **7** was obtained. Clearly, the silver salt did not render **5** sufficiently electrophilic for reaction. An alternative solution was to turn the furanolate partner **6** into a nucleophile. Treatment of **6** with *t*-BuLi in anhydrous THF under Ar −50° generated the 5-lithio derivative **17**, an unequivocal nucleophile [13] [14] (*Scheme 4*). When the (2*Z*)-isomer of allyl bromide **5** was added, coupling occurred giving the penultimate product, the furan **18**. Finally, hydrolysis with 2M aqueous HCl in THF delivered (*Z*)-neomanoalide (**4**) in 50% yield. The same sequence was applied to the (2*E*)-isomer of **5** and furnished (*E*)-neomanoalide (**3**) also in 50% yield. Both synthetic products were spectrally identical to the natural materials [1] [2].

Scheme 4



Conclusion. – The present synthesis of **3** and **4** offers certain advantages. The furanolate reagent **6** is easy to prepare and use. Once coupling is accomplished, the required O-substituent at C(2) is already in place. Simple deprotection not only exposes the two OH groups but unmasks the but-2-enolide entity, thereby producing the neomanoalides in just a few steps.

We are indebted to the *Swiss National Science Foundation* (grant No. 20-32'166.91) for financial support.

Experimental Part

General. All solvents were distilled prior to use. THF and Et_2O were dried over Na-K alloy/benzophenone and freshly distilled before use. CH_2Cl_2 was dried over $NaHCO_3$, distilled, and stored over molecular sieves (*Union Carbide*, type 4 Å). HMPA was distilled from CaH_2 and stored over molecular sieves (*Union Carbide*, type 4 Å). Anh. EtOH was distilled from Mg turnings and a small amount of I_2. TLC: plastic pre-coated silica gel *60* F_{254} plates (*Merck*, layer thickness 0.20 mm). Flash column chromatography (FC) [15]: *Merck* silica gel *60* (230–400

mesh). M.p.: *Reichert* hot-stage microscope; uncorrected. IR Spectra: *Perkin-Elmer-681* spectrometer or *FT-M Polaris*: solns. in KBr cell; in cm^{-1}. ^{1}H-NMR: *Varian T-60* (60 MHz), *XL-200* (200 MHz), and *Bruker-AMX-400* (400 MHz) spectrometers; chemical shifts δ in ppm rel. to internal $SiMe_4$ (= 0 ppm), coupling constants J in Hz; commercial $CDCl_3$ was used without further purification, unless otherwise noted. ^{13}C-NMR: *Varian XL-200* (50 MHz) or *Bruker AMX-400* (100 MHz) spectrometers; the spectra are assigned as o (odd) for C-atoms bearing 1 or 3 H-atoms and e (even) for C-atoms without or with 2 attached H-atoms. MS: *m/z* (intensities in % rel. to base peak); *Finnigan GC/MS-4023* instrument using the INCOS data system; electron impact 70 eV. High-resolution (HR) MS: *VG-7070E*.

*2-[(*tert*-Butyl)dimethylsiloxy]-4-{[(*tert*-butyl)dimethylsiloxy]methyl}furan* (**6**). To a stirred soln. of 4-(hydroxymethyl)furan-2(5*H*)-one [9] (**8**; 600 mg, 5.26 mmol) and Et_3N (1.78 ml, 12.9 mmol) in anh. CH_2Cl_2 (10 ml) was added dropwise (*tert*-butyl)dimethylsilyl triflate (2.78 ml, 12.1 mmol), under Ar, at −5 to 0°. The mixture was warmed to r.t. and then stirred for 4 h. The solvent was evaporated and the residue extracted with pentane (3 × 5 ml). The pentane extracts were cooled to −78° overnight when a colorless solid precipitated. The supernatant liquid phase containing the by-product $[(t\text{-Bu})Me_2Si]_2O$ was removed by syringe and the solid washed with pre-cooled pentane (3 ml, −78°). After evaporation of excess pentane from the solid, **6** (1.60 g, 89%) was obtained as a pale yellow oil at 20°. IR ($CDCl_3$): 3020*w*, 2970*s*, 2930*s*, 2860*s*, 1630*s*, 1570*s*, 1470*m*, 1390*w*, 1290*m*, 1250*s*, 1200*m*, 1070*s* (br.). ^{1}H-NMR ($CDCl_3$): 0.07 (*s*, 6 H); 0.22 (*s*, 6 H); 0.90 (*s*, 9 H); 0.96 (*s*, 9 H); 4.48 (*d*, J = 1.1, 2 H); 5.11 (*d*, J = 1.4, 1 H); 6.73 (*m*, 1 H).

*(*E*)-3-Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)pent-2-en-1-ol* (**10**). To a stirred soln. of methyl (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)pent-2-enoate (= (*E*)-methyl monocyclofarnesate [10]; **9**; 5.37 g, 24.4 mmol) in THF (70 ml) was added 1M DIBAH in THF (66.6 ml, 66.6 mmol) [16] at −78°. The mixture was stirred at −78° for 2 h and then gradually allowed to warm to −10° over 4 h. The mixture was again cooled to −50°, 1M aq. HCl (120 ml) added, and the mixture allowed to warm to r.t. The resulting mixture was extracted with Et_2O (4 × 60 ml). The extracts were washed with H_2O (2 × 30 ml), sat. aq. $NaHCO_3$ soln. (50 ml), and brine (50 ml), dried ($MgSO_4$), and evaporated. Purification of the residue by FC (SiO_2, hexane/AcOEt 5:1) afforded **10** (4.0 g, 83.4%). Colorless oil. IR: 3620*m*, 2930*s*, 2860*s*, 1670*w*, 1470*m*, 1460*m*, 1440*m*, 1380*m*, 1360*m*, 1210*w*, 1110*w*, 980*m*. ^{1}H-NMR ($CDCl_3$): 0.98 (*s*, 6 H); 1.32–1.46 (*m*, 2 H); 1.48–1.62 (*m*, 2 H); 1.59 (*s*, 3 H); 1.71 (*s*, 3 H); 1.90 (*t*, J = 6, 2 H); 2.06 (*s*, 4 H); 4.14 (*d*, J = 7, 2 H); 5.43 (*t*, J = 7, 1 H). MS: 222 (2.4, M^+), 204 (3.7, $[M-18]^+$), 189 (4.4), 137 (100), 121 (16.8), 107 (11.2), 95 (70.4), 81 (48.8), 69 (20.8), 55 (21.6).

*(*E*)-3-Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)pent-2-enyl Bromide* (**11**). To a mixture of **10** (1.44 g, 6.49 mmol) and CBr_4 (3.0 g, 9.1 mmol) in dry CH_2Cl_2 (40 ml) was added dropwise a soln. of Ph_3P (2.2 g, 8.44 mmol) in CH_2Cl_2 (5 ml) at −60°. The mixture was stirred at −60° for 2 h [17], the solvent then evaporated, and the residue passed quickly through a short column (SiO_2, pentane/Et_2O 6:1) to give a mixture (3.14 g) of $CHBr_3$ and **11**. Evaporation of $CHBr_3$ at r.t./0.6 Torr gave pure **11** (1.81 g, 97.8%). Pale yellow oil. ^{1}H-NMR ($CDCl_3$): 0.98 (*s*, 6 H); 1.35–1.47 (*m*, 2 H); 1.50–1.63 (*m*, 2 H); 1.59 (*s*, 3 H); 1.76 (*d*, J = 1, 3 H); 1.90 (*t*, J = 6, 2 H); 2.07 (*s*, 4 H); 4.03 (*d*, J = 8, 2 H); 5.55 (*t*, J = 8, 1 H). MS: 287 (0.1, $[M+2]^+$), 286 (0.58, $[M+1]^+$), 285 (0.1, M^+), 284 (0.2, $[M-1]^+$), 218 (2.62), 216 (2.77), 205 (1.77), 137 (96.59), 95 (100), 81 (81.26), 79 (31.43), 69 (29.91), 67 (51.65), 55 (45.55), 53 (41.33).

*(*E*)-1-[(*tert*-Butyl)dimethylsiloxy]-6-methyl-8-(2′,6′,6′-trimethylcyclohex-1′-enyl)oct-5-en-2-one* (**14**). BuLi (1.6M in hexane) was added dropwise at −20 to −10° under Ar to a stirred soln. of $(i\text{-Pr})_2NH$ (1.11 g, 11 mmol) and HMPA (2 ml) in anh. THF (10 ml) containing 2,2′-dipyridyl as the indicator, until the orange color persisted for a few s. More BuLi (6.9 ml, 11 mmol) was added dropwise to achieve complete deprotonation. The resulting soln. was stirred for 30 min and then cooled to −78°. A soln. of 1-[(*tert*-butyl)dimethylsiloxy]propan-2-one dimethylhydrazone (**12**; 2.50 g, 11 mmol) in THF (3 ml) was slowly added and stirring continued for 1 h at −65 to −50° [10]. The mixture was again cooled to −70° and a soln. of **11** (2.85 g, 10 mmol) in THF (3 ml) added dropwise. Then the mixture was gradually allowed to warm to r.t. over 5 h. The mixture was quenched with H_2O (10 ml) and extracted with Et_2O (3 × 20 ml). The Et_2O extracts were washed with H_2O (2 × 10 ml) and evaporated. The crude hydrazone **13** (dark red oil) was dissolved in THF (60 ml) and added to a soln. of $Cu(OAc)_2 \cdot H_2O$ (4 g, 20 mmol) in H_2O (60 ml; pH *ca.* 5.5) [12]. After stirring at r.t. for 2 h, NH_4OH/NH_4Cl (30 ml; pH *ca.* 10) was added and the mixture extracted with Et_2O (4 × 30 ml). The org. extracts were washed with H_2O (30 ml) and brine (30 ml), dried ($NaSO_4$), and evaporated. Purification of the residue by FC (SiO_2, R_f 0.28, pentane/Et_2O 100:5) afforded **14** (2.04 g, 52.0%). Colorless oil. IR ($CHCl_3$): 3060*w*, 2930*s*, 2870*s*, 1730*s*, 1670*w*, 1650*w*, 1480*m*, 1440*m*, 1320*m*, 1260*s*, 1160*m*, 1110*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 0.08 (*s*, 6 H); 0.91 (*s*, 9 H); 0.97 (*s*, 6 H); 1.40 (*m*, 2 H); 1.55 (*m*, 2 H); 1.58 (*s*, 3 H); 1.62 (*s*, 3 H); 1.85 (*t*, J = 6.5, 2 H); 2.00 (*s*, 4 H); 2.24 (*m*, 2 H); 2.51 (*t*, J = 7, 2 H); 4.16 (*s*, 2 H); 5.09 (*t*, J = 7, 1 H). ^{13}C-NMR ($CDCl_3$): −5.5 (o); 16.02 (o); 18.32 (e); 19.54 (e); 19.80 (o); 21.94 (e); 25.78 (o); 27.80 (e); 28.61 (o); 32.75 (e); 34.96 (e); 38.46 (e); 39.86 (e); 40.21 (e); 69.44 (e); 121.99 (o); 126.98 (e); 137.06 (e); 137.43 (e); 210.65 (e). MS:

393 (0.9, $[M+1]^+$), 392 (2.6, M^+), 336 (6.9), 335 (26.2, $[M-(t\text{-Bu})]^+$), 255 (3.0), 199 (10.0), 137 (100), 121 (6.4), 107 (10.0), 95 (31.8), 81 (24.5), 73 (18.2), 69 (11.3), 67 (7.3), 57 (8.0), 55 (9.1).

Ethyl (6E)-3-{[(tert-Butyl)dimethylsiloxy]methyl}-7-methyl-9-(2′,6′,6′-trimethylcyclohex-1′-enyl)nona-2,6-dienoates (**15**). To a stirred suspension of NaH (153 mg, 80% in mineral oil, 5.10 mmol) in THF (15 ml) was added dropwise a soln. of ethyl (diethylphosphoryl)acetate (1.14 g, 5.1 mmol) in THF (3 ml), under Ar at r.t. The mixture was stirred for 1 h, and then a soln. of **14** (1.0 g, 2.55 mmol) in THF (3 ml) was added. After stirring for 20 h and ensuring that all starting material had disappeared, the mixture was quenched with cold H_2O and extracted with Et_2O (4 × 20 ml). The Et_2O extracts were washed with H_2O (30 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (SiO_2, pentane/Et_2O 100:1.5): (2*E*,6*E*)/(2*Z*,6*E*)-**15** 0.93:1 (95%), *i.e.* 540 mg of (2*E*,6*E*)-**15** (R_f 0.1) and 580 mg of (2*Z*,6*E*)-**15** (R_f 0.14).

(2E,6E)-**15**: IR ($CDCl_3$): 3050*w*, 2930*s*, 2860*s*, 1700*s*, 1650*m*, 1250*s*, 1160*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 0.09 (*s*, 6 H); 0.94 (*s*, 9 H); 0.99 (*s*, 6 H); 1.29 (*t*, *J* = 7.2, 3 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.60 (*s*, 3 H); 1.65 (*s*, 3 H); 1.91 (*t*, *J* = 6.2, 2 H); 2.03 (*m*, 4 H); 2.18 (*d*, *J* = 7.4, 1 H); 2.21 (*d*, *J* = 7.4, 1 H); 2.51 (*d*, *J* = 8.1, 1 H); 2.53 (*d*, *J* = 7.4, 1 H); 4.17 (*s*, 2 H); 4.18 (*q*, *J* = 7.2, 2 H); 5.18 (*t*, *J* = 7.0, 1 H); 5.97 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): −5.45 (o); 14.33 (o); 16.04 (o); 18.37 (e); 19.55 (e); 19.80 (o); 25.88 (o); 27.43 (e); 27.82 (e); 28.60 (o); 29.58 (e); 32.75 (e); 34.97 (e); 39.85 (e); 40.20 (e); 59.55 (e); 66.05 (e); 113.31 (o); 122.87 (o); 126.92 (e); 136.92 (e); 137.10 (e); 161.30 (e); 166.70 (e). MS: 464 (1.4, $[M+2]^+$), 463 (2.5, $[M+1]^+$), 462 (6.4, M^+), 417 (5.1, $[M-OEt]^+$), 406 (16.1), 405 (50.6, $[M-(t\text{-Bu})]^+$), 389 (3.2), 325 (4.6), 311 (4.6), 279 (9.2), 269 (15.8), 257 (55.5), 223 (7.3), 193 (6.4), 165 (8.2), 137 (100), 136 (71.8), 121 (23.6), 95 (52.7), 73 (40.9), 69 (18.2), 67 (13.6), 57 (13.6), 55 (17.3).

(2Z,6E)-**15**: IR ($CDCl_3$): 3050*w*, 2930*s*, 2860*s*, 1700*s*, 1650*m*, 1250*s*, 1160*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 0.09 (*s*, 6 H); 0.93 (*s*, 9 H); 1.00 (*s*, 6 H); 1.28 (*t*, *J* = 7.2, 3 H); 1.42 (*m*, 2 H); 1.53 (*m*, 2 H); 1.61 (*s*, 3 H); 1.65 (*s*, 3 H); 1.91 (*t*, *J* = 6.2, 2 H); 2.03 (*m*, 4 H); 2.18 (*d*, *J* = 7.4, 1 H); 2.22 (*d*, *J* = 7.4, 1 H); 2.36 (*d*, *J* = 8.1, 1 H); 2.37 (*d*, *J* = 7.0, 1 H); 4.13 (*q*, *J* = 7.0, 2 H); 4.82 (*d*, *J* = 1.3, 2 H); 5.13 (*t*, *J* = 7.0, 1 H); 5.64 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): −5.47 (o); 14.29 (o); 16.05 (o); 18.25 (e); 19.56 (e); 19.80 (o); 25.88 (o); 26.51 (e); 27.93 (e); 28.61 (o); 32.76 (e); 34.54 (e); 34.97 (e); 39.86 (e); 40.28 (e); 59.68 (e); 61.74 (e); 114.54 (o); 122.68 (o); 126.93 (e); 136.98 (e); 137.15 (e); 163.71 (e); 166.25 (e). MS: 464 (1.3, $[M+2]^+$), 463 (2.4, $[M+1]^+$), 462 (4.9, M^+), 417 (4.9, $[M-OEt]^+$), 406 (31.8), 405 (100), 375 (4.9), 279 (6.2), 269 (5.7), 257 (16.7), 223 (2.3), 200 (7.1), 193 (3.4), 172 (5.7), 165 (3.3), 137 (52.4), 136 (7.6), 121 (10.0), 107 (7.1), 95 (33.3), 75 (28.1), 69 (11.4), 69 (11.4), 67 (7.6), 57 (7.1), 55 (10.0).

(6E)-3-{[(tert-Butyl)dimethylsiloxy]methyl}-7-methyl-9-(2′,6′,6′-trimethylcyclohex-1′-enyl)nona-2,6-dien-1-ols (**16**). To a stirred soln. of (2*E*,6*E*)-**15** (425 mg, 0.92 mmol) in THF (10 ml) was added a soln. of 1M DIBAH in THF (2.3 ml, 2.3 mmol), under Ar at −78°. The mixture was stirred at −78° for 2 h, warmed to −10° over 4 h, then quenched with sat. aq. potassium sodium tartrate (5 ml), and extracted with Et_2O (4 × 10 ml). The Et_2O extracts were washed with H_2O (10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated. The residue was purified by FC (SiO_2, R_f 0.35, pentane/Et_2O 2:1): (2*E*,6*E*)-**16** (309 mg, 80.0%).

Similar treatment of (2*Z*,6*E*)-**15** gave (2*Z*,6*E*)-**16** in comparable yield.

(2E,6E)-**16**: IR ($CDCl_3$): 3610*m*, 3030*w*, 2930*s*, 2860*s*, 1670*w*, 1470*s*, 1260*s*, 1110*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 0.09 (*s*, 6 H); 0.93 (*s*, 9 H); 1.00 (*s*, 6 H); 1.41 (*m*, 2 H); 1.57 (*m*, 2 H); 1.61 (*s*, 3 H); 1.64 (*s*, 3 H); 1.91 (*t*, *J* = 6.3, 2 H); 2.03 (*m*, 4 H); 2.11 (*m*, 4 H); 4.10 (*s*, 2 H); 4.21 (*d*, *J* = 7.0, 2 H); 5.15 (br., 1 H); 5.71 (*t*, *J* = 7.0, 1 H). ^{13}C-NMR ($CDCl_3$): −5.35 (o); 16.05 (o); 18.40 (e); 19.54 (e); 19.80 (o); 25.94 (o); 27.21 (e); 27.77 (e); 28.12 (e); 28.61 (o); 32.75 (e); 34.97 (e); 39.85 (e); 40.21 (e); 58.94 (e); 66.12 (e); 122.93 (o); 123.23 (o); 127.00 (e); 137.01 (e); 137.04 (e); 142.14 (e). MS: 421 (3.8, $[M+1]^+$), 420 (9.5, M^+), 402 (3.8, $[M-H_2O]^+$), 390 (10.4), 389 (29.7), 363 (6.0), 345 (1.4), 251 (14.5), 215 (36.4), 137 (100), 121 (10.9), 107 (10.0), 95 (54.5), 81 (38.2), 75 (47.0), 69 (19.8), 67 (14.5), 57 (13.5), 55 (17.3).

(2Z,6E)-**16**: IR ($CDCl_3$): 3610*m*, 3030*w*, 2930*s*, 2860*s*, 1670*w*, 1470*s*, 1260*s*, 1110*s*, 840*s*. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.92 (*s*, 9 H); 1.00 (*s*, 6 H); 1.41 (*m*, 2 H); 1.57 (*m*, 2 H); 1.61 (*s*, 3 H); 1.65 (*s*, 3 H); 1.91 (*t*, *J* = 6.3, 2 H); 2.03 (*m*, 4 H); 2.13 (*d*, *J* = 3.2, 4 H); 4.17 (*d*, *J* = 7.0, 2 H); 4.20 (*s*, 2 H); 5.14 (br., 1 H); 5.58 (*t*, *J* = 7.0, 1 H). ^{13}C-NMR ($CDCl_3$): −5.39 (o); 16.04 (o); 18.26 (e); 19.54 (e); 19.80 (o); 25.88 (o); 26.62 (e); 27.91 (e); 28.61 (o); 32.75 (e); 34.97 (e); 35.37 (e); 39.85 (e); 40.27 (e); 58.72 (e); 61.40 (e); 123.13 (o); 125.88 (o); 126.91 (e); 136.47 (e); 137.13 (e); 142.61 (e). MS: 421 (1.2, $[M+1]^+$), 420 (2.7, M^+), 402 (1.9, $[M-H_2O]^+$), 390 (6.9), 389 (21.0), 363 (4.4), 345 (1.2), 271 (4.8), 258 (6.1), 251 (9.3), 238 (2.3), 215 (29.1), 137 (100), 121 (10.9), 109 (10.0), 95 (45.5), 81 (35.5), 75 (42.7), 69 (15.5), 67 (14.5), 57 (13.5), 55 (17.3).

(6E)-3-{[(tert-Butyl)dimethylsiloxy]methyl}-7-methyl-9-(2′,6′,6′-trimethylcyclohex-1′-enyl)nona-2,6-dien-1-yl Bromides (**5**). The (2*E*,6*E*)- and (2*Z*,6*E*)-**5** were individually prepared by using the same procedure as that described for **11**. Treatment of **16** (280 mg, 0.67 mmol), with CBr_4 (398 mg, 1.20 mmol) and Ph_3P (314 mg, 1.20 mmol) in CH_2Cl_2 (10 ml) gave **5** (296 mg, 91.4%). These products were handled with care as they are very sensitive to light and SiO_2.

(2E,6E)-**5**: IR ($CHCl_3$): 3020*w*, 2930*s*, 2860*s*, 1660*w*, 1470*s*, 1383*m*, 1257*s*, 1078*s*, 838*s*. ^{1}H-NMR ($CDCl_3$): 0.08 (*s*, 6 H); 0.93 (*s*, 9 H); 1.00 (*s*, 6 H); 1.42 (*m*, 2 H); 1.58 (*m*, 2 H); 1.61 (*s*, 3 H); 1.66 (*s*, 3 H); 1.91 (*t*, *J* = 6.2, 2 H); 2.04 (*m*, 4 H); 2.15 (*m*, 4 H); 4.07 (*d*, *J* = 8.4, 2 H); 4.13 (*s*, 2 H); 5.16 (br. *s*, 1 H); 5.82 (*t*, *J* = 8.4, 1 H). MS: 484 (0.6), 483 (0.3, M^+), 482 (0.5), 450 (0.4), 427 (1.8), 415 (1.0), 404 (1.8), 403 (5.0), 402 (6.3, $[M - Br]^+$), 387 (0.8), 370 (1.0), 353 (2.7), 345 (6.0), 271 (10.9), 177 (7.3), 137 (100), 123 (20.0), 107 (14.5), 95 (38.2), 81 (29.1), 69 (15.5), 67 (12.3), 57 (8.2), 55 (15.5).

(2Z,6E)-**5**: IR ($CHCl_3$): 3020*w*, 2930*s*, 2860*s*, 1660*w*, 1470*s*, 1383*m*, 1257*s*, 1078*s*, 838*s*. ^{1}H-NMR ($CDCl_3$): 0.10 (*s*, 6 H); 0.92 (*s*, 9 H); 1.00 (*s*, 6 H); 1.42 (*m*, 2 H); 1.58 (*m*, 2 H); 1.61 (*s*, 3 H); 1.65 (*s*, 3 H); 1.91 (*t*, *J* = 6.2, 2 H); 2.04 (*m*, 4 H); 2.16 (*m*, 4 H); 4.09 (*d*, *J* = 8.4, 2 H); 4.26 (*s*, 2 H); 5.14 (*m*, 1 H); 5.59 (*t*, *J* = 8.4, 1 H). MS: 484 (0.1, $[M + 1]^+$), 440 (0.5), 439 (0.5), 438 (1.2), 427 (0.3), 404 (1.1), 403 (3.4), 402 (7.3, $[M - Br]^+$), 389 (2.1), 345 (2.7), 233 (19.1), 197 (14.5), 137 (100), 121 (8.5), 107 (10.0), 95 (40.0), 81 (29.1), 69 (14.5), 67 (12.3), 57 (18.2), 55 (16.5).

*Attempted Synthesis of 4-{[(*tert*-Butyl)dimethylsiloxy]methyl}-5-{3′-{[(*tert*-butyl)dimethylsiloxy]methyl}-7′-methyl-9′-(2″,6″,6″-trimethylcyclohex-1″-yl)nona-2′,6′-dienyl}furan-2(5*H*)-one* (**7**). The reaction of (2*Z*,6*E*)-**5** (70 mg, 0.15 mmol), **6** (54.6 mg, 0.16 mmol), and $Ag(CF_3COO)$ (35.3 mg, 0.16 mmol) in CH_2Cl_2 (5 ml) gave *4-{[(*tert*-butyl)dimethylsiloxy]methyl}furan-2(5*H*)-one* (31 mg, 81%) and a mixture of unidentifiable by-products (33 mg). {[(*tert*-Butyl)dimethylsiloxy]methyl}furan-2(5*H*)-one: IR ($CHCl_3$): 3020*w*, 2950*s*, 2930*s*, 2860*s*, 1780*s*, 1750*s*, 1650*m*, 1470*m*, 1260*s*, 1180*m*, 1140*s*, 1110*s*, 1030*s*, 846*s*. ^{1}H-NMR ($CDCl_3$): 0.17 (*s*, 6 H); 0.98 (*s*, 9 H); 4.63 (*s*, 2 H); 4.85 (*s*, 2 H); 6.03 (br. *s*, 1 H).

*4-(Hydroxymethyl)-5-[(2′E,6′E)- and -(2′Z,6′E)-3′-(Hydroxymethyl)-7′-methyl-9′-(2″,6″,6″-trimethylcyclohex-1″-enyl)nona-2′,6′-dienyl]furan-2(5*H*)-one* (= (E)- *and* (Z)-*Neomanoalide, resp.*; **3** *and* **4**, *resp.*). To a stirred soln. of **6** (84.5 mg, 0.25 mmol) in anh. THF (2 ml) containing 2,2′-bipyridyl as indicator, 1M *t*-BuLi in hexane was added dropwise under Ar at −50° until a red color appeared, at which time a further amount of 1M *t*-BuLi (0.16 ml) was added. After stirring at −40° for 1.5 h, the mixture was again cooled to −60° and a soln. of **5** (50 mg, 0.106 mmol) in THF (0.5 ml) added dropwise. The mixture was allowed to warm to r.t. over 4 h, stirred for another h, then quenched with sat. aq. NH_4Cl soln. (2 ml) and extracted with Et_2O (2 × 4 ml). The Et_2O extracts were washed with H_2O (4 ml) and brine (4 ml), dried (Na_2SO_4), and evaporated: **18** as an oil. To a stirred soln. of **18** in THF (4 ml) was added dropwise 2M aq. HCl (2 ml), under Ar at 0°. After stirring for 2.5 h, the mixture was extracted with Et_2O (3 × 10 ml), washed with H_2O (5 ml) and brine, (5 ml), dried ($MgSO_4$), and evaporated. Purification of the residue by FC (SiO_2, AcOEt/Et_2O 1:3) gave **3** (21.0 mg, 50%) and **4** (21.0 mg, 50%, R_f 0.15) as oils.

3: IR ($CHCl_3$): 3610*m* (sharp), 3430*m* (br.), 3020*w*, 2930*s*, 2860*s*, 1750*s*, 1650*w*, 1475*m*, 1460*m*, 1440*m*, 1380*m*, 1360*m*, 1340*w*, 1260*w*, 1210*w*, 1170*m*, 1140*m*, 1060*m*, 990*m*, 930*m*, 860*m*. ^{1}H-NMR ($CDCl_3$): 0.99 (*s*, 6 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.60 (*s*, 3 H); 1.64 (*s*, 3 H); 1.90 (*t*, *J* = 6.2, 2 H); 2.01 (*m*, 4 H); 2.12 (*m*, 4 H); 2.47 (*m*, 1 H); 2.74 (*m*, 1 H); 2.93 (br., 1 H); 4.05 (*s*, 2 H); 4.47 (*AB*, 2 H); 5.09 (*t*, *J* = 5, 1 H); 5.15 (*t*, *J* = 6.4, 1 H); 5.38 (*t*, *J* = 7.4, 1 H); 6.05 (*d*, *J* = 1.6, 1 H). ^{13}C-NMR ($CDCl_3$): 16.07 (o); 19.52 (e); 19.80 (o); 26.66 (e); 27.89 (e); 28.47 (e); 28.61 (o); 30.32 (e); 32.73 (e); 34.97 (e); 39.81 (e); 40.21 (e); 58.66 (e); 66.28 (e); 81.61 (o); 115.12 (o); 117.43 (o); 122.67 (o); 127.03 (e); 136.98 (e); 137.11 (e); 143.43 (e); 171.57 (e); 172.62 (e). MS: (20 eV): 403 (8.1, $[M + 1]^+$), 402 (29.8, M^+), 400 (0.9, $[M - 2]^+$), 384 (9.0, $[M - 18]^+$), 369 (3.0), 353 (1.4), 341 (1.3), 318 (1.3), 316 (1.7), 288 (1.5), 271 (3.0), 265 (3.0), 260 (2.2), 249 (3.0), 233 (3.0), 217 (5.5), 197 (3.6), 179 (4.5), 167 (10.9), 137 (100), 121 (12.7), 95 (14.6), 81 (10.9), 69 (4.5), 57 (4.5).

4: IR ($CHCl_3$): 3610*m* (sharp), 3430*m* (br.), 3020*w*, 2930*s*, 2860*s*, 1750*s*, 1650*w*, 1475*m*, 1460*m*, 1440*m*, 1380*m*, 1360*m*, 1340*w*, 1260*w*, 1210*w*, 1170*m*, 1140*m*, 1060*m*, 990*m*, 930*m*, 860*m*. ^{1}H-NMR ($CDCl_3$): 0.99 (*s*, 6 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.60 (*s*, 3 H); 1.63 (*s*, 3 H); 1.90 (*t*, *J* = 6.2, 2 H); 2.01 (*m*, 4 H); 2.13 (*m*, 4 H); 2.54 (*m*, 1 H); 2.79 (*m*, 1 H); 3.25 (br., 1 H); 4.12 (*AB*, 2 H); 4.51 (*AB*, 2 H); 5.10 (br. *m*, 2 H); 5.24 (*t*, *J* = 7.7, 1 H); 6.01 (*d*, *J* = 1.8, 1 H). ^{13}C-NMR ($CDCl_3$): 16.11 (o); 19.56 (e); 19.84 (o); 26.79 (e); 27.92 (e); 28.64 (o); 30.31 (e); 32.77 (e); 34.99 (e); 35.63 (e); 39.85 (e); 40.29 (e); 58.60 (e); 60.23 (e); 81.87 (o); 115.97 (o); 119.90 (o); 122.95 (o); 127.01 (e); 136.92 (e); 137.08 (e); 143.42 (e); 171.75 (e); 172.82 (e). MS: (20 eV): 403 (3.5, $[M + 1]^+$), 402 (11.9, M^+), 400 (0.9, $[M - 2]^+$), 384 (9.1, $[M - 18]^+$), 369 (3.0), 341 (1.3), 353 (1.2), 318 (1.3), 316 (1.7), 288 (1.5), 272 (3.0), 267 (9.5), 260 (2.4), 249 (0.6), 233 (3.5), 217 (9.1), 197 (6.4), 179 (11.8), 167 (12.7), 137 (100), 121 (15.5), 107 (6.4), 95 (16.4), 81 (13.6), 69 (6.4), 57 (4.5).

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