# 53. Synthetic Studies Directed toward the Pseurotins

Part II[1])

## Synthesis of Related Highly Functionalized Furan-3(2*H*)-ones

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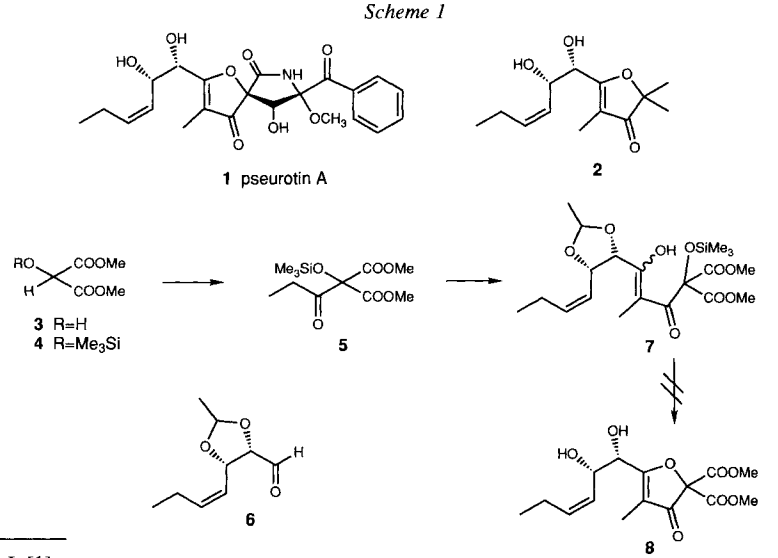
The synthesis of 2,2-bis(hydroxymethyl)-4-methyl-5-phenylfuran-3(2*H*)-one (**9**), 5-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-2,2-bis(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**24**), and 5-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**28**), which represent more advanced, suitably functionalized intermediates for the synthesis of pseurotin A (**1**), a secondary metabolite of *Pseudeurotium ovalis* STOLK, is described.

**Introduction.** – In a previous communication [1], a strategy directed to the total synthesis of pseurotin A (**1**) has been outlined, and as a first result, the synthesis of 5-[(1*S*,2*S*,*Z*)-1,2-dihydroxyhex-3-enyl]-2,2,4-trimetylfuran-3(2*H*)-one (**2**) was described. In this paper, we report the synthesis of compounds **9**, **24**, and **28**, which represent more advanced, suitably functionalized intermediates for the construction of pseurotin A (**1**). In addition, ring closure of an $\alpha$-hydroxy $\beta$-diketone leading to a furan-3(2*H*)-one under basic conditions has been observed as demonstrated by the successful synthesis of compound **23**. This reaction may prove to be useful in analogous cases.

*Scheme 1*

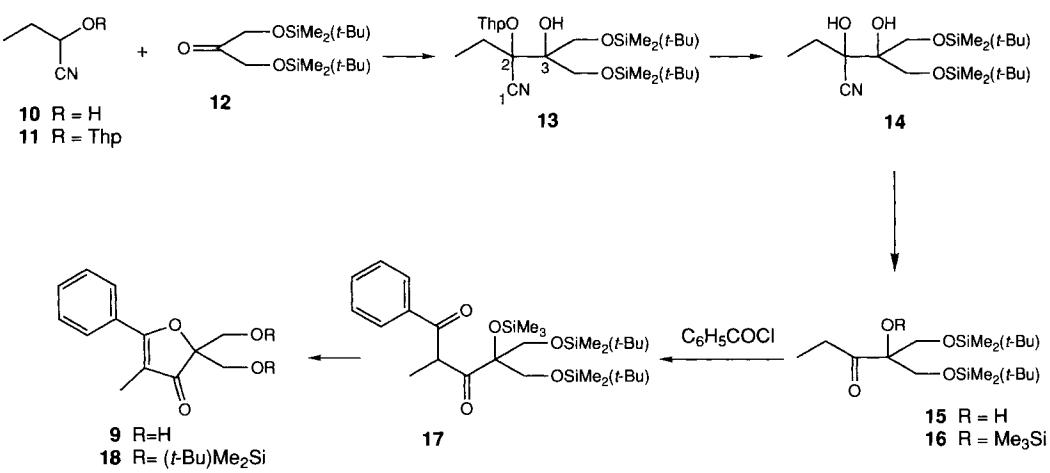



[1]) Part I: [1].

**Results.** – Having successfully completed the synthesis of furan-3(2*H*)-one **2**, the preparation of the corresponding derivative **8**, which contains a 2,2-bis(methoxycarbonyl) moiety in place of the geminal dimethyl group, was attempted in an analogous manner (*Scheme 1*). Dimethyl tartronate (**3**) served as starting material [2]. The OH group was protected by the $Me_3Si$ group [3]. Deprotonation of diester **4** with BuLi proceeded without elimination of the protecting group. Subsequent treatment with propionyl chloride [4] yielded adduct **5**. Aldol condensation of **5** with aldehyde **6**, which has been prepared from D-glucose [1], was not successful. The desired product **7** was obtained only once. We were not able to reproduce the result. An explanation for this failure is the rapid decomposition of the lithium enolate of **5** into the more stable anion of **4** before condensation takes place, because **4** was isolated as the main product.

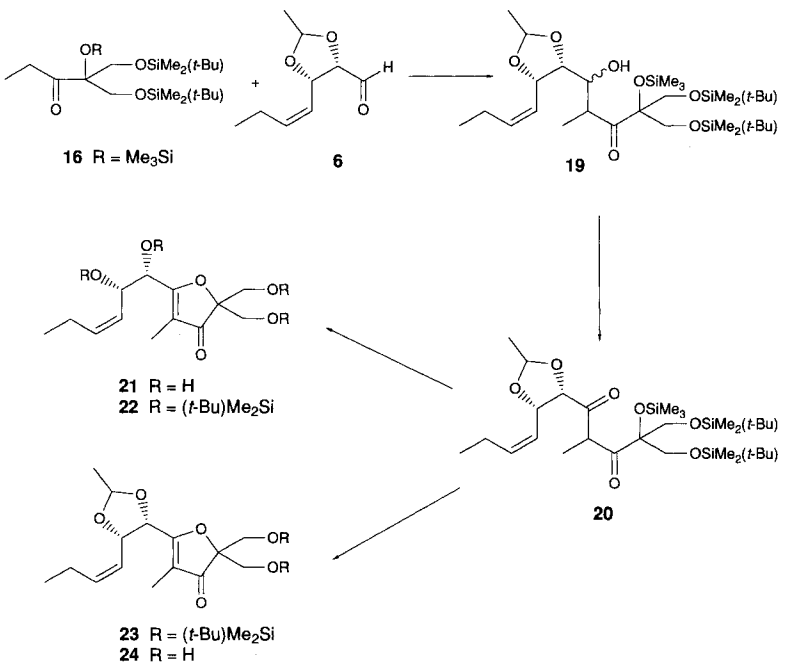
After it had not been possible to obtain diester **8**, it was decided to synthesize the corresponding 2,2-bis(hydroxymethyl) derivatives of furan-3(2*H*)-one using essentially the same approach. For the synthesis of 2,2-bis(hydroxymethyl)-4-methyl-5-phenylfuran-3(2*H*)-one (**9**), which was anticipated to serve as a test compound, the cyanohydrin **10** of propionaldehyde was transformed into the tetrahydropyranyl (Thp) derivative **11** (*Scheme 2*). Subsequent deprotonation of **11** with lithium diisopropylamide (LDA) and reaction with the silyl derivative **12** of dihydroxyacetone (from dihydroacetone dimer and (*t*-Bu)$Me_2SiCl$) gave compound **13**. Selective removal of the Thp group in **13** was achieved with pyridinium 4-toluenesulfonate (Py·TsOH) in MeOH. A retrocyanohydrin reaction of **14** with NaOH and subsequent treatment of hydroxyketone **15** with hexamethyldisilazane (HMDS) and $Me_3SiCl$ [5] yielded ketone **16**. Condensation of **16** with benzoyl chloride gave β-diketone **17**. After selective removal of the $Me_3Si$ group and treatment with Py·TsOH, not the desired compound **18** but 2,2-bis(hydroxymethyl)-4-methyl-5-phenylfuran-3(2*H*)-one (**9**) was obtained. The loss of both protecting groups was not expected. Thus, the (*t*-Bu)$Me_2Si$ groups were re-introduced by treating **9** with (*t*-Bu)$Me_2SiCl$ in the presence of imidazole (→ **18**).

*Scheme 2*



Having prepared the Ph-substituted furan-3(2*H*)-ones **9** and **18**, the synthesis of 5-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-2,2-bis(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**24**) was accomplished in the same way, *i.e.* by condensing ketone **16** with aldehyde **6** (*Scheme 3*). The hydroxyketone **19** obtained was oxidized to the diketone **20** using the *Swern* method (oxalyl chloride, DMSO, and $Et_3N$) [7]. Cyclization of ketone **20** with TsOH and then with Py·TsOH gave furan-3(2*H*)-one **21** in which all protecting groups had been removed. Therefore, we attempted a selective protection of the primary OH groups in **21** by treatment with (*t*-Bu)$Me_2SiCl$, but, unfortunately, all four OH groups reacted (→ **22**). The problem was finally solved by carrying out the cyclization under basic conditions: treatment of β-diketone **20** with $K_2CO_3$ in MeOH at room temperature for 16 h gave the desired **23** in 86% yield. Subsequent removal of the (*t*-Bu)$Me_2Si$ protecting groups with $Bu_4NF$ [6] afforded diol **24** in nearly quantitative yield. The spectral data of **24** were in full agreement with those of the dimethyl analogue **2** and the left-hand part of pseurotin A (**1**).

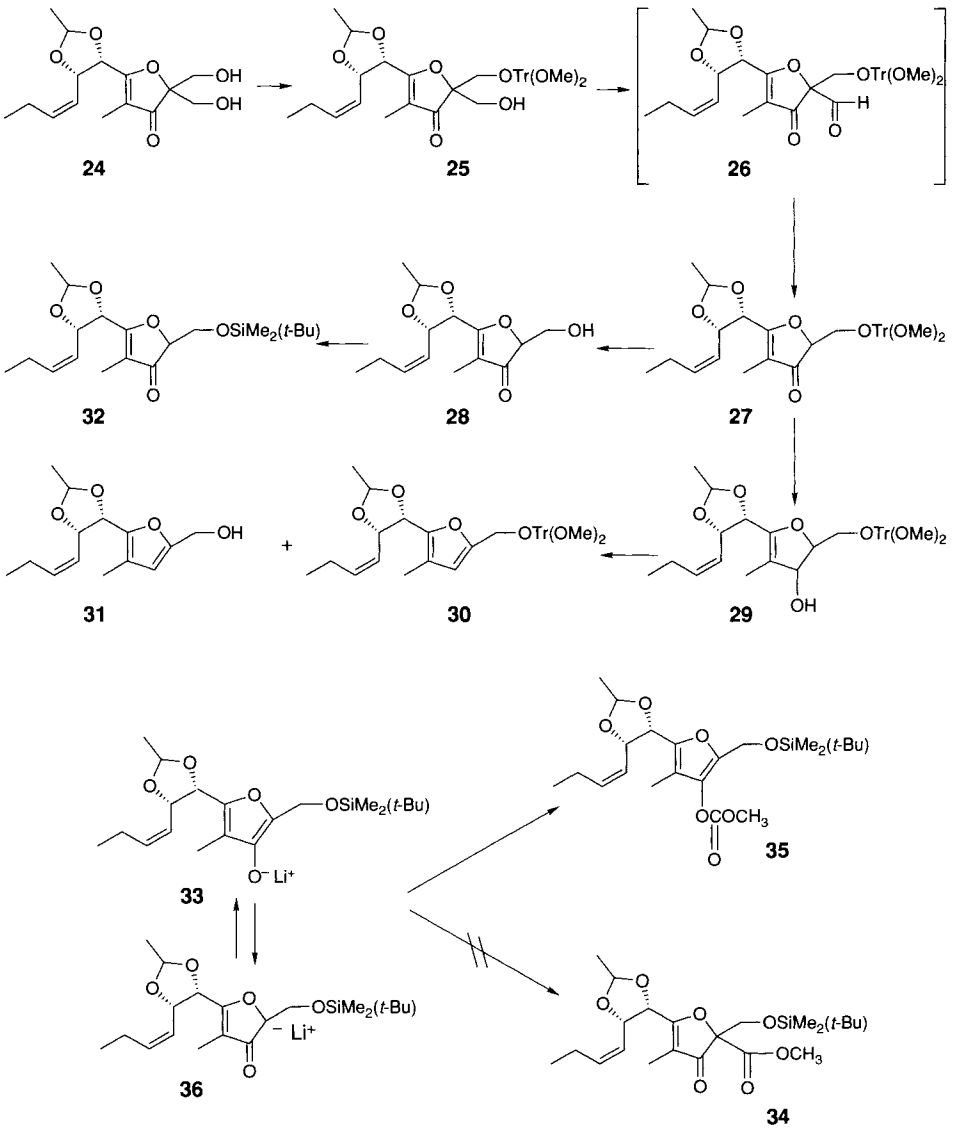
*Scheme 3*




For the planned attachment of the right-hand moiety of **1** to **24**, *i.e.* the spirocyclization (see [1]), differentiation of the two $CH_2OH$ groups was required. After several unsuccessful attempts, selective protection was achieved by treatment of **24** with 4,4'-dimethoxytrityl chloride according to *Chaudhary* and *Hernandez* [8] (*Scheme 4*): **25** was obtained in 40% yield. The remaining $CH_2OH$ group was oxidized (*Swern* reagent) to the unstable aldehyde **26** which was decarbonylated to **27** within 12 h in 92% yield. Deprotection of **27** was

successfully achieved by treatment with 3% $CHCl_2COOH$ in $CH_2Cl_2$, yielding **28** (72%). The subsequent conversion of the $CH_2OH$ group into an aldehyde or carboxyl group proved to be extremely difficult. Neither *Swern*'s [7] nor *Corey* and *Schmidt*'s [9] nor *Griffith*'s method [10] were successful. Moreover, **28** decomposed completely under the condition used.

*Scheme 4*




$(MeO)_2Tr$ = 4,4'-dimethoxytriphenylmethyl

Obviously, the unsuccessful oxidation of the primary OH group of **28** is due to the presence of a β-keto group, β-oxocarbonyl systems being known to decompose in both acidic and basic medium. Therefore, we tried to protect the carbonyl group in **27** first. With ethylene glycol and a catalytic amount of TsOH in benzene [11] or by ethylene glycol and *Dowex* [12], no reaction of **27** was observed. Therefore, the carbonyl group was reduced to a OH group with diisobutylaluminium hydride (DIBAH) at 5° [13] (→ **29** in 76% yield). Hovever, protection of the newly formed OH group by treatment with $Me_3SiCl$ or (*t*-Bu)$Me_2SiCl$ was also unsuccessful: according to the NMR data, only *ca.* 10% of the desired products were formed. Reaction of **29** with (2-methoxyethoxy)methyl chloride [14] led to elimination, and the two furane derivatives **30** and **31** were formed, the driving force being obviously aromatization of the heterocycle.

Next, we attempted to introduce a methoxycarbonyl group at C(2) of **28**, after protection of the $CH_2OH$ group as (*t*-Bu)$Me_2Si$ ether (→ **32** in 55% yield; *Scheme 4*). For the acylation of **32** with methyl chloroformate in THF at –78° in the presence of hexamethyldisilylamine (HMDS), 2 equiv. of BuLi were required [15], the first one producing the Li salt of HMDS which reacted with **32** and produced the Li salt **33** and HMDS. The latter was captured by the second equiv. of BuLi, thus allowing a better reaction of the nucleophile **33** with methyl chloroformate. Surprisingly, according to IR and NMR data, the product was not the expected **34** but **35** (similar NMR data were found for 3-methylfuran and furan-2-methanol [16]). Apparently, *O*-acylation had occurred in place of *C*-acylation.

The preferred *O*-acylation could be explained by the stability of the intermediates **33** and **36**, and of the products. Normally, the enolate form is less stable than its tautomer, and as a result, only *C*-acylation is observed. Hovever, enolate **33** is a furan derivative, *i.e.* an aromatic intermediate, and hence its stability is increased. Moreover, the aromatic *O*-acylation product **35** is more stable than the non-aromatic *C*-acylated compound **34**.

The conversion of the $CH_2OH$ group of **28** into an aldehyde or carboxy group has not yet been achieved. Decarbonylation of aldehyde **26** and the stability of **33** leading to preferred *O*-acylation proved to be the main problems. Our present work is focused on the construction of the right-hand moiety of pseurotin A (**1**).

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## Experimental Part

*General.* See [1].

*Dimethyl 2-(Trimethylsilyloxy)propanedioate* (**4**). To a soln. of 9.56 g (88 mmol) of $Me_3SiCl$ and 9.61 g (95 mmol) of $Et_3N$ in 100 ml of abs. THF, 10.0 g (67.5 mmol) of **3** were added. After 15 min, the mixture was poured into 250 ml of $Et_2O$, washed with brine, evaporated, and purified by CC ($CH_2Cl_2$): 12.78 g (98%) of **4**. IR (film): 2960, 1750 (C=O), 1440, 1250, 1200, 1160, 1040, 880, 850, 760. $^1$H-NMR (60 MHz): 0.0 (*s*, $Me_3Si$); 3.6 (*s*, 2 MeO); 4.5 (*s*, H–C(2)).

*Dimethyl 2-Propanoyl-2-(trimethylsilyloxy)propanedioate* (**5**). To a soln. of 8.24 g (37 mmol) of **4** and indicator (a few mg of 2,2'-bipyridine) in 50 ml of abs. THF at –70°, a soln. of BuLi/hexane (1.5M, 24.7 ml) was added dropwise, until the yellow colour changed to red. Then, 5.27 g (57 mmol) of propionyl chloride in 5 ml of abs. THF were added, and the mixture was stirred at –70° for 15 min. After addition of 20 ml of sat. aq. $NH_4Cl$ soln., the mixture was poured into 300 ml of $Et_2O$ and washed with sat. aq. $Na_2CO_3$ soln. After CC, 9.20 g (90%) of **5** were obtained as colourless oil. IR (film): 2960, 1750 (C=O), 1440, 1250, 1200, 1180, 1080,

1030, 870, 840, 760. $^1$H-NMR (60 MHz): 0.0 (*s*, $Me_3Si$); 0.8 (*t*, *J* = 7, $CH_3CH_2CO$); 2.4 (*q*, *J* = 7, $CH_3CH_2CO$); 3.5 (*s*, 2 MeO).

*2-[(Tetrahydro-2H-pyran-2-yl)oxy]butanenitril* (**11**). To a soln. of 14.40 g (171 mmol) of **10** in 30 ml of abs. benzene, 28.77 g (340 mmol) of 3,4-dihydro-2*H*-pyrane and a few drops of $SOCl_2$ were added. The mixture was stirred under Ar and cooled with a $H_2O$-bath for 2 h. Then, 150 ml of $Et_2O$ were added, and the mixture was washed with 1M $KHCO_3$. Destillation (115°/0.35 Torr) gave 24.08 g (83%) of **11**. IR (film): 2940, 2880, 1460, 1390, 1260, 1200, 1120, 1040, 1000, 960, 910, 870. $^1$H-NMR (60 MHz): 1.1 (*t*, *J* = 6, $CH_3$(4)); 1.3–2.2 (*m*, 6 H of Thp, $CH_2$(3)); 3.5–3.9 (*m*, 2 H of Thp); 4.2 , 4.4 (2 *t*, *J* = 6, H–C(1)); 4.8 (*m*, acetal H of Thp).

*1,3-Bis[(*tert*-butyl)dimethylsilyloxy]propan-2-one* (**12**). A soln. of 4.00 g (21.6 mmol) of dihydroxyacetone dimer, 15.92 g (105.6 mmol) of (*t*-Bu)$Me_2SiCl$ and 14.96 g (220.0 mmol) of imidazole in 50 ml of abs. DMF was stirred at r.t. overnight. After addition of 300 ml of $Et_2O$, the mixture was washed with ice/$H_2O$ and evaporated, and the residue filtered over silica gel ($CH_2Cl_2$): 13.76 g (100%) of **12** as colourless oil. IR (film): 2960, 2930, 2890, 2860, 1740 (C=O), 1460, 1360, 1260, 1190, 1140, 1100, 840, 780. $^1$H-NMR (60 MHz): 0.0 (*s*, 2 $Me_2Si$); 0.8 (*s*, 2 *t*-BuSi); 4.3 (*s*, 2 H–C(1), 2 H–C(3)).

*4-[(*tert*-Butyl)dimethylsilyloxy]-3-[[(*tert*-butyl)dimethylsilyloxy]methyl]-2-ethyl-3-hydroxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]butanenitrile* (**13**). To a cooled (–78°) soln. of 1.2 mol-equiv. of LDA (2.24 g (22 mmol) of $(i\text{-}Pr)_2NH$, 12.5 ml (18.8 mmol) of BuLi (1.5M)) in 50 ml of abs. THF, a soln. of 2.66 g (15.7 mmol) of **11** in 20 ml of hexamethylphosphoramide was added dropwise. After 5 min, 5.00 g (15.7 mmol) of **12** in a little amount of abs. THF was added within 1.5 h. This mixture was stirred for additional 1.5 h, after removal of the cooling bath. Then, the mixture was added to 300 ml of $Et_2O$, washed with ice/$H_2O$, and evaporated. Filtration over silica gel ($Et_2O$) gave 6.41 g (13.1 mmol) of crude **13** as ochre-coloured oil. A sample was purified by CC ($CH_2Cl_2$) for characterization. IR (film): 3450 (OH), 2960, 2860, 1470, 1260, 1080, 1030, 840, 780. $^1$H-NMR (60 MHz): 0.0 (*s*, $Me_2Si$); 0.8 (*s*, 2 *t*-BuSi); 1.1 (*t*, *J* = 6, $CH_3CH_2$); 1.3–2.0 (*m*, 6 H of Thp, $CH_3CH_2$); 3.4–3.8 (*m*, 2 H of Thp, 2 $CH_2OSi$); 5.1 (*s*, acetal H of Thp).

*4-[(*tert*-Butyl)dimethylsilyloxy]-3-{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-ethyl-2,3-dihydroxybutanenitrile* (**14**). Overnight, 6.41 g (13.1 mmol) of **13** were treated with 0.33 g (1.3 mmol) of Py·TsOH in 50 ml of abs. MeOH at 40°. The mixture was poured into 200 ml of $Et_2O$, washed with brine, and evaporated. CC (petroleum ether/$Et_2O$ 1:1) gave 3.86 g (61% referring to **11**) of **14**. $^1$H-NMR (60 MHz): 0.0 (*s*, 2 $Me_2Si$); 0.8 (*s*, 2 *t*-BuSi); 1.0 (*t*, *J* = 7, $CH_3CH_2$); 1.5–2.0 (*m*, $CH_3CH_2$); 2.9 (*s*, OH); 3.6 (*AB*, *J* = 10, 2 $CH_2OSi$); 4.4 (*s*, OH).

*1-[(*tert*-Butyl)dimethylsilyloxy]-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-hydroxypentan-3-one* (**15**). At r.t., 1.08 g (2.5 mmol) of **14** in 20 ml of THF and 10 ml of 1M NaOH were stirred for 5 h. The mixture was extracted with $Et_2O$, washed with brine, and evaporated. Purification on silica gel ($CH_2Cl_2$) gave 0.77 g (81%) of **15** as colourless oil. IR (film): 3470 (OH), 2960, 2860, 1710 (C=O), 1460, 1260, 1100, 840, 780. $^1$H-NMR (60 MHz): 0.0 (*s*, 2 $Me_2Si$); 0.8 (*s*, 2 *t*-BuSi); 1.0 (*t*, *J* = 7, $CH_3$(5)); 2.6 (*q*, *J* = 7, $CH_2$(4)); 3.6 (*AB*, *J* = 10, 2, $CH_2OSi$); 4.6 (*s*, OH).

*1-[(*tert*-Butyl)dimethylsilyloxy]-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-(trimethylsilyloxy)pentan-3-one* (**16**). To a soln. of 0.35 g (2.2 mmol) of HMDS and 0.18 g (1.6 mmol) of $Me_3SiCl$ in 10 ml of dry pyridine, 0.43 g (1.1 mmol) of **15** was added. After 24 h, the mixture was poured into $Et_2O$, washed with ice/$H_2O$, and evaporated. Filtration over silica gel ($CH_2Cl_2$) gave 0.49 g (100%) of **16** as colourless oil. IR (film): 2960, 2940, 2860, 1720 (C=O), 1460, 1250, 1200, 1100, 1040, 1000, 840, 780. $^1$H-NMR (60 MHz): 0.0 (*s*, 2 $Me_2Si$); 0.1 (*s*, $Me_3Si$); 0.8 (*s*, 2 *t*-BuSi); 1.1 (*t*, *J* = 7, $CH_3$(5)); 2.6 (*q*, *J* = 7, $CH_2$(4)); 3.6 (*s*, 2 $CH_2OSi$); 4.6 (*s*, OH). $^{13}$C-NMR (22.63 MHz): –5.4 (*q*, $Me_2Si$); 2.4 (*q*, $Me_3Si$); 7.3 (*q*, C(5)); 18.4 (*s*, $(CH_3)_3CSi$); 26.0 (*q*, $(CH_3)_3CSi$); 32.7 (*t*, C(4)); 66.5 (*t*, $CH_2OSi$); 86.8 (*s*, C(2)); 214.4 (*s*, C=O).

*5-[(*tert*-Butyl)dimethylsilyloxy]-4-{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-methyl-1-phenyl-4-(trimethylsilyloxy)pentane-1,3-dione* (**17**). As for **13**, 0.77 g (1.7 mmol) of **16** was deprotonated with 1.2 mol-equiv. of LDA in THF at –78° for 30 min. Then, 0.25 g (1.8 mmol) of PhCOCl in a little amount of THF was added. After stirring for 1 h at –78°, the mixture was poured into 150 ml of $Et_2O$, washed with cooled $H_2O$, and evaporated. CC (petroleum ether/$Et_2O$) yielded 0.58 g (62%) of **17**. IR (film): 2960, 2940, 2860, 1730 (C=O), 1680 (C=O), 1470, 1260, 1190, 1110, 1030, 980, 840, 780. $^1$H-NMR (60 MHz): 0.0 (*s*, $Me_3Si$); 0.1 (*s*, $Me_2Si$); 1.0 (*s*, 2 *t*-BuSi); 1.4 (*d*, *J* = 7, $CH_3$–C(2)); 3.9 (*m*, 2 $CH_2OSi$); 5.0 (*q*, *J* = 7, H–C(2)); 7.3–8.3 (*m*, 5 arom. H).

*2,2-Bis{[(*tert*-butyl)dimethylsilyloxy]methyl}-4-methyl-5-phenylfuran-3(2H)-one* (**18**). At 40°, 200 mg (0.36 mmol) of **17** in 5 ml of abs. MeOH were stirred with a few mg of TsOH for 2 days. The mixture was poured into 100 ml of $Et_2O$, washed with brine, and evaporated. The colourless powder (**9**) obtained was then immediately reacted with 0.15 g (1 mmol) of (*t*-Bu)$Me_2SiCl$ and 0.14 g (2 mmol) of imidazole in 5 ml of abs. DMF at 40° under Ar for 6 h. The mixture was poured into $Et_2O$ and washed with cooled $H_2O$. After CC

($CH_2Cl_2$), 93 mg (56% based on **17**) of **18** were obtained. IR (film): 2960, 2920, 2860, 1700 (C=O), 1620 (C=C), 1460, 1410, 1370, 1260, 1130, 1100, 1070,1020, 840, 780, 700. $^1$H-NMR (60 MHz): 0.0 (*s*, 2 $Me_2Si$); 0.8 (*s*, 2 *t*-BuSi); 1.9 (*s*, $CH_3$–C(4)); 3.9 (*AB*, *J* = 10, 2 $CH_2OSi$); 7.4-8.0 (*m*, 5 arom. H). $^{13}$C-NMR (22.63 MHz): –5.4 (*q*, $Me_2Si$); 7.2 (*q*, $CH_3$–C(4)); 18.2 (*s*, $(CH_3)_3CSi$); 25.8 (*q*, $(CH_3)_3CSi$); 64.0 (*t*, $CH_2OSi$); 92.1 (*s*, C(2)); 111.5 (*s*, C(4)); 127.9–131.2 (arom. C); 180.0 (*s*, C(5)); 203.9 (*s*, C(3)).

*(6S,7S,Z)-1-[(*tert*-Butyl)dimethylsilyloxy]-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}-6,7-(ethylidenedioxy)-5-hydroxy-4-methyl-2-(trimethylsilyloxy)undec-8-en-3-one* (**19**). As for **13**, the aldol condensation of 335 mg (1.9 mmol) of **6** and of 807 mg (1.8 mmol) of **16** yielded, after CC (petroleum ether/$Et_2O$), 1.03 g of **19/16** 7:3 as colourless oil. IR (film): 3500 (OH), 2960, 2940, 2860, 1710 (C=O), 1470, 1410, 1260, 1200, 1110, 840, 780. $^1$H-NMR (90 MHz): 0.0–0.2 (2 *s*, 2 $Me_2Si$, $Me_3Si$); 0.8 (*s*, 2 *t*-BuSi); 1.0–1.3 (*m*, $CH_3$(11), $CH_3CHO_2$, $CH_3$–C(4)); 1.8–2.2 (*m*, $CH_2$(10)); 2.7–2.8 (br., OH); 3.4–4.2 (*m*, H–C(4), H–C(5), H–C(6), 2 $CH_2OSi$); 4.7–5.0 (*m*, $CH_3CHO_2$, H–C(7)); 5.3–5.7 (*m*, H–C(8), H–C(9)).

*(6S,7S,Z)-1-[(*tert*-Butyl)dimethylsilyloxy]-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}-6,7-(ethylidenedioxy)-4-methyl-2-(trimethylsilyloxy)undec-8-ene-3,5-dione* (**20**). The oxidation of **19** to **20** was performed according to [7]. As for **27** (see below), 325 mg (47%) of **20** were obtained as colourless oil after CC (petroleum ether/$Et_2O$ 1:1) from 689 mg (1.1 mmol) of **19**. IR (film): 2960, 2940, 2880, 2860, 1740 (C=O), 1700 (C=O), 1470, 1420, 1260, 1100, 1030, 840, 780, 740. $^1$H-NMR (90 MHz): 0.0 (2 *s*, 2 $Me_2Si$); 0.2 (*s*, $Me_3Si$); 0.9, (2 *s*, 2 diastereoisotopic *t*-BuSi); 1.0–1.2 (*m*, $CH_3$(11), $CH_3CHO_2$); 1.45 (*d*, *J* = 4, $CH_3$–C(4)); 1.9–2.3 (*m*, $CH_2$(10)); 3.8 (*d*, *J* = 3, 2 $CH_2OSi$); 4.0 (2 *m*, *J* = 5, H–C(7)); 4.6 (*d*, *J* = 5, H–C(6)); 4.8–5.2 (2 *m*, $CH_3CHO_2$, H–C(4)); 5.5–5.9 (*m*, H–C(8), H–C(9)). $^{13}$C-NMR (22.63 MHz): –5.5 (2 *q*, $Me_2Si$); 2.1 (*q*, $Me_3Si$); 11.4 (*q*, $CH_3$–C(4)); 13.8 (*q*, C(11)); 18.2, 18.5 (2 *s*, $(CH_3)_3CSi$); 19.2 (*q*, $CH_3CHO_2$); 21.1 (*t*, C(10)); 25.9 (2 *q*, $(CH_3)_3CSi$); 55.2 (*d*, C(4)); 67.1, 67.5 (2 *t*, $CH_2OSi$); 74.9 (*d*, C(7)); 82.6 (*d*, C(6)); 88.4 (*s*, C(2)); 102.2 (*d*, $CH_3CHO_2$); 123.8 (*d*, C(8)); 137.4 (*d*, C(9)); 202.4 (*s*, C=O); 208.9 (*s*, C=O).

*2,2-Bis[[(*tert*-butyl)dimethylsilyloxy]methyl]-5-{(1S,2S,Z)-1,2-bis[(*tert*-butyl)dimethylsilyloxy]hex-3-enyl}-4-methylfuran-3(2H)-one* (**22**). At 40°, 325 mg (0.5 mmol) of **20** were stirred with 13 mg (0.05 mmol) of Py · TsOH in 5 ml of abs. MeOH. Additional 13 mg of Py·TsOH were added after 24 h. After another 24 h, 17 mg (0.1 mmol) of TsOH were added to complete the reaction, and 3 h later, the soln. was neutralized with $Et_3N$. The solvent was evaporated and the residue dried under high vacuum. To the crude **21**, 320 mg (2.2 mmol) of (*t*-Bu)$Me_2SiCl$ and 288 mg (4.4 mmol) of imidazole in 5 ml of abs. DMF were added, and the mixture was stirred at 40° for 24 h. Then, it was poured into $Et_2O$, washed with brine, and evaporated. After CC ($CH_2Cl_2$), 127 mg (33% based on **20**) of **22** were obtained. IR (film): 2960, 2940, 2900, 2860, 1700 and 1630 (C=O), 1470, 1380, 1260, 1100, 1010, 840, 780, 740. $^1$H-NMR (90 MHz): 0.00 (*s*, 4 $Me_2Si$); 0.90 (*m*, 4 *t*-BuSi, $CH_3$(6')); 1.70 (*s*, $CH_3$–C(4)); 1.8–2.1 (*m*, $CH_2$(5')); 3.70, 3.85 (2 *AB*, *J* = 8, 2 $CH_2OSi$); 4.4–4.7 (*m*, H–C(1'), H–C(2')); 5.3–5.6 (*m*, H–C(3'), H–C(4')). $^{13}$C-NMR (22.63 MHz): –4.0–5.0 (*m*, 4 $Me_2Si$); 6.1 (*q*, $CH_3$–C(4)); 14.0 (*q*, C(6')); 18.4, 18.5 (2 *s*, 4 $(CH_3)_3CSi$); 21.6 (*t*, C(5')); 26.0 (*s*, 4 $(CH_3)_3CSi$); 63.8, 64.0 (2 *t*, 2 $CH_2OSi$); 76.2 (*d*, C(1')); 71.8 (*d*, C(2')); 91.8 (*s*, C(2)); 113.2 (*s*, C(4)); 129.2 (*d*, C(3')); 133.5 (*d*, C(4')); 184.7 (*s*, C(5)); 203.8 (*s*, C(3)).

*2,2-Bis{[(*tert*-butyl)dimethylsilyloxy]methyl}-5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3(2H)-one* (**23**). At r.t., 1.038 g (1.68 mmol) of **20** were stirred with 136 mg of $K_2CO_3$ in 50 ml of MeOH. After 18 h, the mixture was poured into 50 ml of $Et_2O$, washed with ice/$H_2O$, evaporated, and purified by CC (petroleum ether/$Et_2O$ 20:3): 758 mg of **23** (85%) as mixture of diastereoisomers. UV (MeOH): 279 (3.881). IR ($CHCl_3$): 2960, 2940, 2860, 1700 and 1630 (C=C–C=O), 1470, 1260, 1100, 840. $^1$H-NMR (90 MHz): 0.0 (*s*, 4 $Me_2Si$), 0.8 (*s*, 2 *t*-BuSi), 0.95 (*t*, $CH_3$(6')); 1.45 (*d*, $CH_3CHO_2$); 1.7 (*s*, $CH_3$–C(4));1.85–2.4 (*m*, $CH_2$(5')); 3.85 (*q*, 2 *AB*, 2 $CH_2OSi$); 4.63 (*d*, H–C(1')); 4.95 (*t*, H–C(2')); 5.25 (*q*, $CH_3CHO_2$); 5.55 (*d*, H–C(3')); 5.75 (2 *td*, H–C(4')). $^{13}$C-NMR (22.63 MHz): –5.5, –5.6 (2 *q*, 2 $Me_2Si$); 5.1 (*q*, $CH_3$–C(4)); 14.1 (*q*, C(6')); 18.1, 18.2 (2 *s*, $(CH_3)_3CSi$); 19.6 (*q*, $CH_3CHO_2$); 21.2 (*t*, C(5')); 25.7 (*q*, 2 $(CH_3)_3CSi$); 63.6, 63.7 (2 *t*, 2 $CH_2OSi$); 76.6, 77.3 (2 *d*, C(1'), C(2')); 92.7 (*s*, C(2)); 103.0 (*d*, $CH_3CHO_2$); 112.9 (*s*, C(4)); 125.4 (*d*, C(3')); 138.1 (*d*, C(4')); 182.5 (*s*, C(5)); 203.4 (*s*, C(3)). CI-MS ($NH_3$): 527 ($[M + H]^+$), 483 ($[M - 44]^+$), 469 ($[M - HC(CH_3)_3]^+$), 425, 401, 385, 343, 301, 281, 197, 171, 132 ($[HOSi(CH_3)_2C(CH_3)_3]^+$), 106, 90, 72, 58, 44.

*5-[(1S,2S,Z)-1,2-(Ethylidenedioxy)hex-3-enyl]-2,2-bis(hydroxymethyl)-4-methylfuran-3(2H)-one* (**24**). To a soln. of 290 mg (0.55 mmol) of **23** in 1 ml of THF, 0.5 ml of $Bu_4NF$ soln. (1M in THF) was added. After 20 min, the mixture was filtered immediately over a silica-gel column ($Et_2O$/MeOH 18:1): 154.3 mg (94%) of **24** as colourless oil. IR ($CHCl_3$): 3490 (OH), 2980, 2940, 2880, 1700 and 1630 (C=C–C=O), 1450, 1400, 1380, 1150, 1090, 1050, 1020, 900, 845. $^1$H-NMR (90 MHz): 0.93 (*t*, *J* = 7.4, $CH_3$(6')); 1.47 (*d*, *J* = 4.7, $CH_3CHO_2$); 1.68 (*s*, $CH_3$–C(4)); 1.97–2.17 (*m*, $CH_2$(5')); 2.8–3.2 (br., 2 OH); 3.85 (br., 2 $CH_2OSi$); 4.62 (*d*, *J* = 7.5, H–C(1')); 4.93 (*t*, *J* = 7.8, H–C(2')); 5.37 (*q*, *J* = 4.8, $CH_3CHO_2$); 5.55 (*dd*, *J* = 10.9, 8.0, H–C(3')); 5.63–5.98 (*m*,

H–C(4')). $^{13}$C-NMR (22.63 MHz): 5.2 (*q*, *C*H$_3$–C(4)); 14.1 (*q*, C(6')); 19.7 (*q*, *C*H$_3$CHO$_2$); 21.3 (*t*, C(5')); 62.8 (2 *t*, 2 CH$_2$OSi); 76.2, 77.0 (2 *d*, C(1'), C(2')); 91.6 (*s*, C(2)); 103.6 (*d*, CH$_3$*C*HO$_2$); 113.6 (*s*, C(4)); 124.1 (*d*, C(3')); 139.3 (*d*, C(4')); 183.2 (*s*, C(5)); 204.9 (*s*, C(3)). CI-MS (NH$_3$): 299 ([*M* + H]$^+$), 281, 269, 251, 239, 206, 197, 166, 141, 112, 83, 44.

*2-[(4,4'-Dimethoxytrityloxy)methyl]-5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2H)-one* (**25**). *Method A*: A soln. of 128 mg (0.43 mmol) of **24**, 145 mg (0.43 mmol) of (MeO)$_2$TrCl, 81 µl (0.058 mmol) of Et$_3$N and 1 mg (0.008 mmol) of 4-(dimethylamino)pyridine in CH$_2$Cl$_2$ was stirred under Ar at r.t. for 30 min. The mixture was poured into H$_2$O and extrated with CH$_2$Cl$_2$. The org. layer was washed with a 4M aq. NH$_4$Cl soln. and H$_2$O. CC (petroleum ether/Et$_2$O 1:1) yielded 175 mg (68%) of **25** as yellow oil.

*Method B*: To a soln. of 200 mg (0.67 mmol) of **24** in 7.2 ml of dry pyridine, 280 mg (0.83 mmol) of (MeO)$_2$TrCl were added and stirred for 24 h. The mixture was concentrated to *ca.* 2 ml and added to 15 ml of 5% aq. NaHCO$_3$ soln. It was then washed with H$_2$O and evaporated. After CC, 289 mg (72%) of **25** were obtained. IR (film): 3500 (OH), 3100–3050 (arom. CH), 1700 and 1630 (C=C–C=O), 1610, 1510, 1250, 700. $^1$H-NMR (90 MHz): 0.85 (*t*, *J* = 7.4, CH$_3$(6')); 1.51 (*d*, *J* = 4.7, C*H*$_3$CHO$_2$); 1.73 (*s*, CH$_3$–C(4)); 1.85–2.4 (*m*, CH$_2$(5')); 2.52 (br., OH); 3.35 (*AB*, CH$_2$O); 3.75 (*s*, 2 CH$_3$O); 3.84 (*s*, CH$_2$O); 4.71 (*d*, H–C(1')); 5.22 (*t*, H–C(2')); 5.45 (*q*, *J* = 4.8, CH$_3$C*H*O$_2$); 5.5–5.9 (*m*, H–C(3'), H–C(4')); 6.74–7.41 (*m*, 13 arom. H). $^{13}$C-NMR (22.63 MHz): 5.3 (*q*, *C*H$_3$–C(4)); 14.1 (*q*, C(6')); 19.8 (*q*, *C*H$_3$CHO$_2$); 21.2 (*t*, C(5')); 55.2 (*q*, CH$_3$O); 63.2, 64.3 (2 *t*, CH$_2$OH, CH$_2$O); 76.4, 76.5 (2 *d*, C(1'), C(2')); 86.4 (*s*, C(2)); 91.0 (*s*, arom. C); 103.5 (*d*, CH$_3$*C*HO$_2$); 113.3 (*d*, arom. C); 113.6 (*s*, C(4)); 124.9 (*d*, C(3')); 126.9 (arom. C); 127.8 (*s*, arom. C); 128.3 (arom. C); 130.2 (*s*, arom. C); 135.6, 135.6 (2 *s*, arom. C); 138.7 (*d*, C(4')); 144.6 (*s*, arom. C); 158.8 (*s*, arom. C); 182.8 (*s*, C(5)); 204.2 (*s*, C(3)).

*2-[(4,4'-Dimethoxytrityloxy)methyl]-5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3(2H)-one* (**27**). The reaction of 110 mg (0.18 mmol) of **25** with 30 µl (0.34 mmol) of oxalyl chloride, 50 µl (0.70 mmol) of DMSO, and 137 µl (0.9 mmol) of Et$_3$N gave 116 mg of crude **26/27**. CC (petroleum ether/Et$_2$O 1:1.2) yielded 95 mg (92%) of **27** as a yellow oil. IR (film): 3100–3000 (arom. CH), 1710 and 1640 (C=C–C=O), 1610, 700. $^1$H-NMR (90 MHz): 0.73, 0.89 (2 *t*, *J* = 7.5, CH$_3$(6')); 1.51 (*d*, *J* = 4.8, C*H*$_3$CHO$_2$); 1.69, 1.73 (2 *s*, CH$_3$–C(4)); 1.80–2.21 (*m*, CH$_2$(5')); 3.38, 3.47 (*AB*, CH$_2$O); 3.78 (*s*, 2 CH$_3$O); 4.56, 4.70 (*m*, H–C(2), H–C(1')); 4.90, 5.02 (*dd*, *J* = 8.0, 8.0, H–C(2')); 5.32–5.86 (*m*, CH$_3$C*H*O$_2$, H–C(3'), H–C(4')); 6.76–7.50 (*m*, 13 arom. H). EI-MS: 570 (*M*$^+$), 320, 303.

*5-[(1S,2S,Z)-1,2-(Ethylidenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2H)-one* (**28**). *Method A*: A soln. of **27** (35.4 mg, 0.062 mmol) in 1 ml of CHCl$_3$/MeOH 7:3 was stirred with 2% of TsOH for 1 h at 0°. The mixture was then washed with 5% aq. Na$_2$CO$_3$ soln. and H$_2$O. After evaporation and CC (petroleum ether/Et$_2$O 1:1), **28** was obtained in 72.3% (12 mg) yield.

*Method B*: At –10°, 32 mg (0.056 mmol) of **27** were mixed together with 4 ml of 3% CHCl$_2$COOH in CH$_2$Cl$_2$. After 1 h, the mixture was poured into 5% aq. NaHCO$_3$ soln. and extrated with CH$_2$Cl$_2$. The org. soln. was washed with H$_2$O. CC gave 0.9 mg (72.5%) of **28**. IR (film): 3450 (OH), 1700 and 1630 (C=C–C=O), 1450, 1420, 1380, 1315, 1145, 1080, 1025, 900, 850. $^1$H-NMR (90 MHz): 0.97 (*t*, *J* = 7.5, CH$_3$(6')); 1.50 (*d*, *J* = 4.5, C*H*$_3$CHO$_2$); 1.72 (*s*, CH$_3$–C(4)); 1.82–2.4 (*m*, CH$_2$(5'), OH); 3.95 (*d*, *J* = 5, CH$_2$O); 4.53–4.58 (*m*, H–C(2), H–C(1')); 4.90 (*m*, H–C(2')); 5.20–5.85 (*m*, H–C(3'), H–C(4'), CH$_3$C*H*O$_2$). $^{13}$C-NMR (101 MHz): 5.4 (*C*H$_3$–C(4)); 14.1 (C(6')); 19.7 (*C*H$_3$CHO$_2$); 21.3 (C(5')); 61.7 (CH$_2$OH); 74.7, 75.0 (C(1'), C(2')); 84.0 (C(2)); 102.6 (CH$_3$*C*HO$_2$); 113.9 (C(4)); 123.8 (C(4')); 138.2 (C(3')); 181.9 (C(5)); 203.6 (C(3)). CI-MS (NH$_3$): 269 ([*M* + H]$^+$), 251, 239, 225, 209, 195, 179, 44.

*2-[(4,4'-Dimethoxytrityloxy)methyl]-5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-2,3-dihydro-4-methylfuran-3-ol* (**29**). To a soln. of 78 µl (0.078 mmol) of DIBAH in 1.3 ml of abs. benzene, 34.7 mg (0.129 mmol) of **27** were added. After 30 min, 5 ml of MeOH were added, and the mixture was immediately filtered over *Celite* and the solvent removed. The crude product was purified by CC (petroleum ether/Et$_2$O 1:1): 26.5 mg (76%) of **29**. IR (film): 3450 (OH), 1600, 1500, 1250, 1170. $^1$H-NMR (400 MHz): 0.78, 0.94 (2 *t*, *J* = 7.0, CH$_3$(6')); 1.44 (*d*, *J* = 4.5, C*H*$_3$CHO$_2$); 1.73, 1.75 (2 *s*, CH$_3$–C(4)); 1.80–2.20 (*m*, CH$_2$(5')); 3.36–3.70 (*m*, CH$_2$O); 3.79 (*s*, 2 CH$_3$O); 4.36 (*m*, H–C(3)); 4.39–4.56 (*m*, H–C(2)); 4.64–4.92 (*m*, H–C(1'), H–C(2')); 5.32–5.92 (*m*, H–C(3'), H–C(4'), CH$_3$C*H*O$_2$); 6.8–7.5 (*m*, 13 arom. H).

*2-[(4,4'-Dimethoxytrityloxy)methyl]-5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran* (**30**) *and 5-[(1S,2S,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-2-methanol* (**31**). According to [14], 6.4 mg (0.011 mmol) of **29** reacted with 2.1 mg (0.017 mmol) of (2-methoxyethoxy)methyl chloride and 2.1 mg (0.017 mmol) of (i-Pr)$_2$NEt in 0.2 ml of CH$_2$Cl$_2$ at r.t. for 14 h. The mixture was poured into 10 ml of CH$_2$Cl$_2$, washed with 4M aq. NH$_4$Cl and H$_2$O, and evaporated. CC (petroleum ether/Et$_2$O 1:1) gave 1.5 mg (54%) of **31** and

2.0 mg (36%) of **30**. $^1$H-NMR for **30** (400 MHz): 0.79 (*t*, *J* = 7.5, $CH_3$(6')); 1.45 (*d*, *J* = 4.8, $CH_3CHO_2$); 1.80–2.10 (*m*, $CH_2$(5')); 2.00 (*s*, $CH_3$–C(4)); 3.81 (*s*, 2 $CH_3O$); 4.56 (*s*, $CH_2O$); 4.57 (*d*, *J* = 7.7, H–C(1')); 5.05 (*m*, H–C(2')); 5.42–5.47 (*m*, H–C(3'), $CH_3CHO_2$); 5.63–5.69 (*m*, H–C(4')); 6.12 (*s*, H–C(3)); 6.83–7.33 (*m*, 13 arom. H). $^1$H-NMR for **31** (400 MHz): 0.79 (*t*, *J* = 7.5, $CH_3$(6')); 1.45 (*d*, *J* = 4.9, $CH_3CHO_2$); 1.80–2.10 (*m*, $CH_2$(5')); 2.00 (*s*, $CH_3$–C(4)); 4.56 (*s*, $CH_2O$); 4.59 (*d*, *J* = 8.1, H–C(1')); 5.00 (*t*, *J* = 7.7, H–C(2')); 5.42–5.48 (*m*, H–C(3'), $CH_3CHO_2$); 5.63–5.70 (2 *m*, H–C(4')); 6.12 (*s*, H–C(3)).

*2-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-5-[(1*S*,2*S*,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3(2*H*)-one* (**32**). As for **25**, with 46 mg (0.172 mmol) of **28,** 39.4 mg (0.262 mmol) of (*t*-Bu)$Me_2SiCl$, 45 µl of $Et_3N$, 1.5 mg of 4-(dimethylamino)pyridine, and 1 ml of $CH_2Cl_2$. CC (petroleum ether/$Et_2O$ 7:3) yielded 33 mg (50%) of **32**. IR (film): 2980, 2950, 2880, 1710 and 1640 (C=C–C=O), 1420, 1140, 1100, 850, 790. $^1$H-NMR (90 MHz): 0.0, 0.05 (2 *s*, $Me_2Si$); 0.70–1.15 (*m*, $CH_3$(6'), *t*-BuSi); 1.45 (*d*, *J* = 4.5, $CH_3CHO_2$); 1.65 (*s*, $CH_3$–C(4)); 1.85–2.30 (*m*, $CH_2$(5')); 3.75–4.15 (*m*, $CH_2O$); 4.42 (*m*, H–C(2)); 4.55 (*d*, *J* = 7, H–C(1')); 4.95 (*m*, H–C(2')); 5.22–5.90 (*m*, H–C(3'), H–C(4'), $CH_3CHO_2$). CI-MS ($NH_3$): 383 ([*M* + H]$^+$), 339, 251, 207, 91, 44.

*2-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-5-[(1*S*,2*S*,Z)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3-yl Methyl Carbonate* (**35**). To a soln. of 0.3 ml (0.045 mmol) of HMDS in 10 ml of abs. THF, 28 µl (0.0445 mmol) of BuLi were added at –78°. After 5 min, a soln. of **32** in 0.25 ml of THF was added and the mixture stirred for 50 min at –78°. Then, 26 µl of BuLi were added, and after 10 min, 14 µl (0.15 mmol) of methyl chloroformate. After 30 min at –78°, the mixture was warmed to r.t. CC (petroleum ether/$Et_2O$ 1:1) yielded 16.7 mg (66%) of **35**. IR (film): 2960, 2940, 2860, 1780 (–O–C=O),1440, 1250, 1090, 840, 780. $^1$H-NMR (90 MHz): 0.0 (*s*, $Me_2Si$); 0.8 (*m*, $CH_3$(6'), *t*-BuSi); 1.35 (*d*, *J* = 4.5, $CH_3CHO_2$); 1.80 (*s*, $CH_3$–C(4)); 1.70–2.30 (*m*, $CH_2$(5')); 3.80 (*s*, $CH_3O$); 4.45–4.50 (*m*, H–C(1'), $CH_2OSi$); 4.98 (*t*, *J* = 7.5, H–C(2')); 5.25–5.72 (*m*, H–C(3'), H–C(4'), $CH_3CHO_2$). CI-MS ($NH_3$): 458 ([*M* + $NH_4$]$^+$), 441 ([*M* + H]$^+$), 383, 309, 265, 251, 225, 199, 112, 91, 83, 74, 44.

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