

53. Synthetic Studies Directed toward the Pseurotins

Part II¹⁾

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

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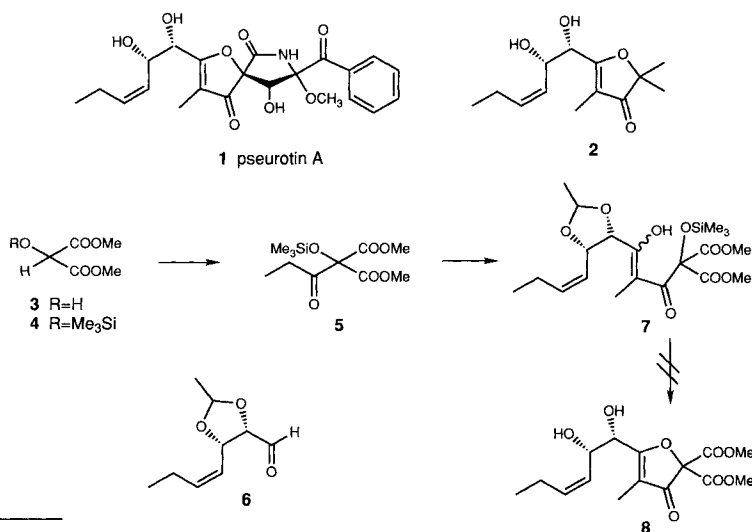
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The synthesis of 2,2-bis(hydroxymethyl)-4-methyl-5-phenylfuran-3(2*H*)-one (**9**), 5-[(1*S*,2*S*,*Z*)-1,2-(ethylenedioxy)hex-3-enyl]-2,2-bis(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**24**), and 5-[(1*S*,2*S*,*Z*)-1,2-(ethylenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**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-trimethylfuran-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 α -hydroxy β -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

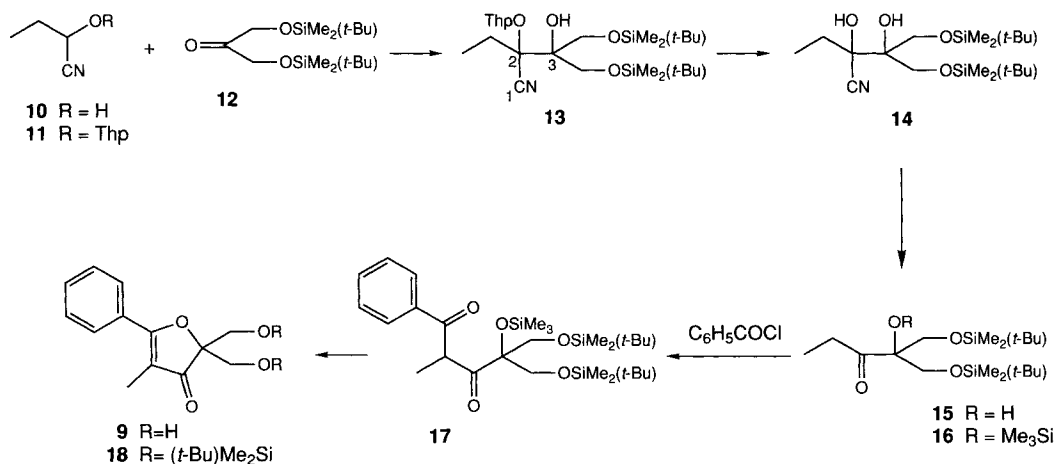


¹⁾ Part I: [1].

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 Me₃Si 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.

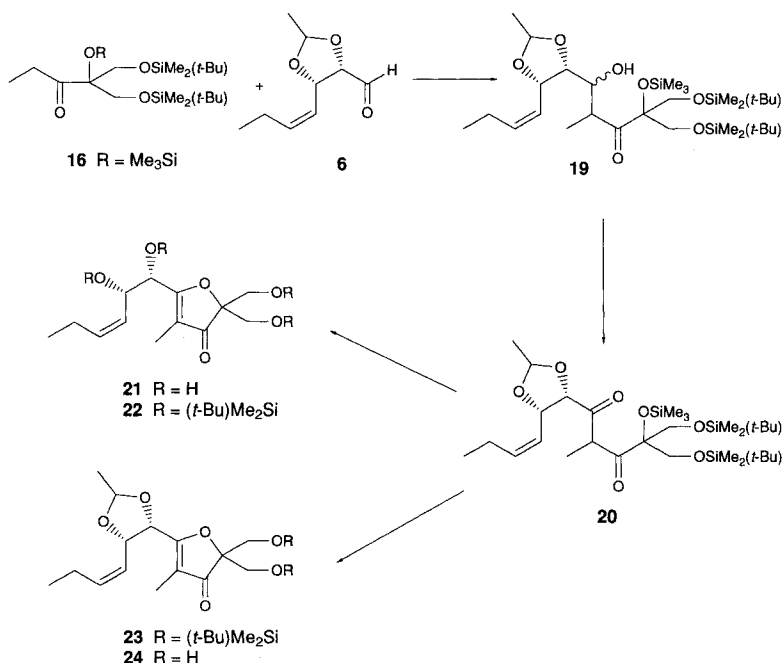
After it had not been possible to obtain diester **8**, it was decided to synthesize the corresponding 2,2-bis(hydroxymethyl) derivatives of furan-3(2*H*)-one using essentially the same approach. For the synthesis of 2,2-bis(hydroxymethyl)-4-methyl-5-phenylfuran-3(2*H*)-one (**9**), which was anticipated 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)Me₂SiCl) 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 Me₃SiCl [5] yielded ketone **16**. Condensation of **16** with benzoyl chloride gave β-diketone **17**. After selective removal of the Me₃Si 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)Me₂Si groups were re-introduced by treating **9** with (*t*-Bu)Me₂SiCl 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-(ethylenedioxy)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 Et₃N) [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)Me₂SiCl, but, unfortunately, all four OH groups reacted ($\rightarrow$ **22**). The problem was finally solved by carrying out the cyclization under basic conditions: treatment of β -diketone **20** with K₂CO₃ in MeOH at room temperature for 16 h gave the desired **23** in 86% yield. Subsequent removal of the (*t*-Bu)Me₂Si protecting groups with Bu₄NF [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**).

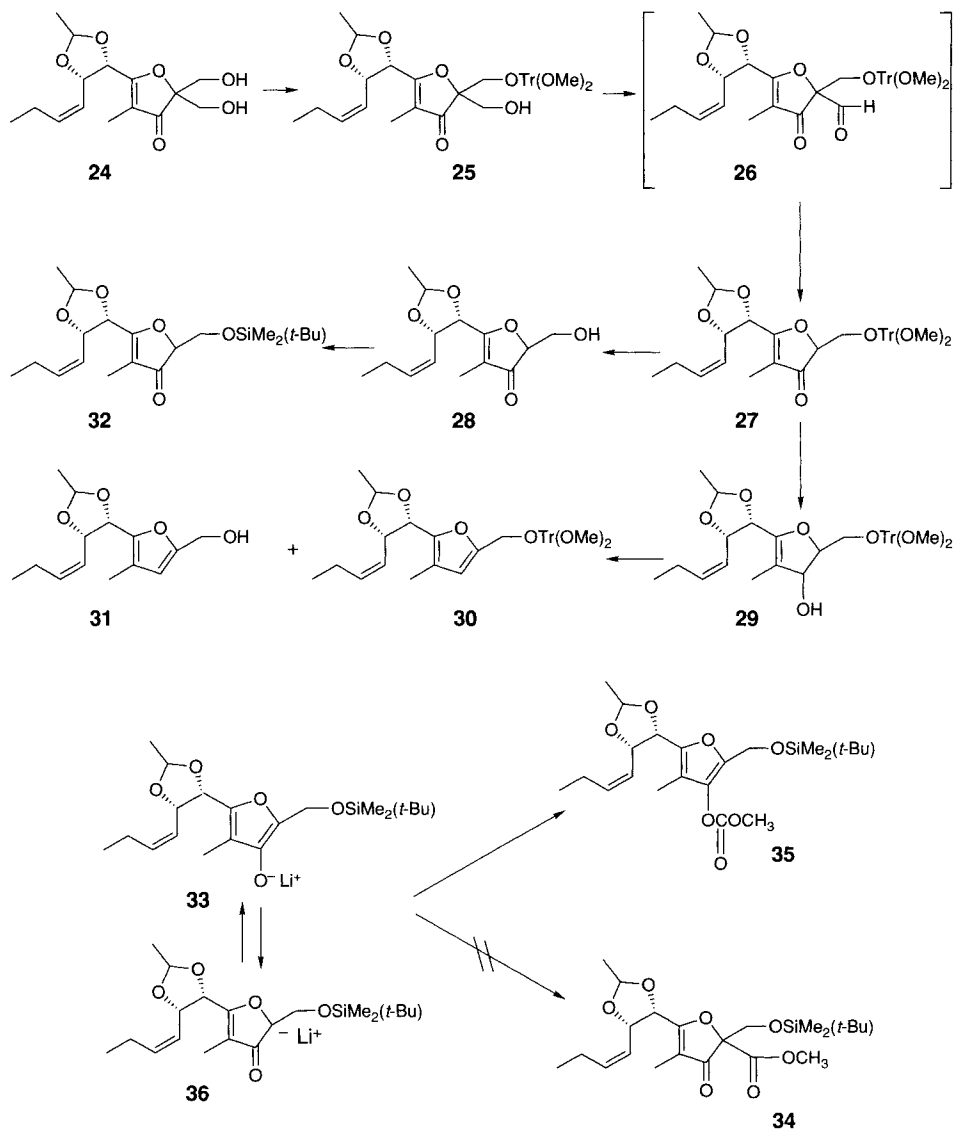
Scheme 3



For the planned attachment of the right-hand moiety of **1** to **24**, *i.e.* the spirocyclization (see [1]), differentiation of the two CH₂OH 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 CH₂OH 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] ($\rightarrow$ **29** in 76% yield). However, protection of the newly formed OH group by treatment with Me_3SiCl or $(t\text{-Bu})\text{Me}_2\text{SiCl}$ 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 $(t\text{-Bu})\text{Me}_2\text{Si}$ ether ($\rightarrow$ **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. However, 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 ($\text{C}=\text{O}$), 1440, 1250, 1200, 1160, 1040, 880, 850, 760. $^1\text{H-NMR}$ (60 MHz): 0.0 (s, Me_3Si); 3.6 (s, 2 MeO); 4.5 (s, $\text{H-C}(2)$).

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 ($\text{C}=\text{O}$), 1440, 1250, 1200, 1180, 1080,

1030, 870, 840, 760. ¹H-NMR (60 MHz): 0.0 (s, Me₃Si); 0.8 (t, *J* = 7, CH₃CH₂CO); 2.4 (q, *J* = 7, CH₃CH₂CO); 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-2H-pyran and a few drops of SOCl₂ were added. The mixture was stirred under Ar and cooled with a H₂O-bath for 2 h. Then, 150 ml of Et₂O were added, and the mixture was washed with 1M KHCO₃. Distillation (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. ¹H-NMR (60 MHz): 1.1 (t, *J* = 6, CH₃(4)); 1.3–2.2 (m, 6 H of Thp, CH₂(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)Me₂SiCl 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 Et₂O, the mixture was washed with ice/H₂O and evaporated, and the residue filtered over silica gel (CH₂Cl₂): 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. ¹H-NMR (60 MHz): 0.0 (s, 2 Me₃Si); 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-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 Et₂O, washed with ice/H₂O, and evaporated. Filtration over silica gel (Et₂O) gave 6.41 g (13.1 mmol) of crude **13** as ochre-coloured oil. A sample was purified by CC (CH₂Cl₂) for characterization. IR (film): 3450 (OH), 2960, 2860, 1470, 1260, 1080, 1030, 840, 780. ¹H-NMR (60 MHz): 0.0 (s, Me₃Si); 0.8 (s, 2 *t*-BuSi); 1.1 (t, *J* = 6, CH₃CH₂); 1.3–2.0 (m, 6 H of Thp, CH₃CH₂); 3.4–3.8 (m, 2 H of Thp, 2 CH₂OSi); 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 Et₂O, washed with brine, and evaporated. CC (petroleum ether/Et₂O 1:1) gave 3.86 g (61% referring to **11**) of **14**. ¹H-NMR (60 MHz): 0.0 (s, 2 Me₃Si); 0.8 (s, 2 *t*-BuSi); 1.0 (t, *J* = 7, CH₃CH₂); 1.5–2.0 (m, CH₃CH₂); 2.9 (s, OH); 3.6 (AB, *J* = 10, 2 CH₂OSi); 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 Et₂O, washed with brine, and evaporated. Purification on silica gel (CH₂Cl₂) gave 0.77 g (81%) of **15** as colourless oil. IR (film): 3470 (OH), 2960, 2860, 1710 (C=O), 1460, 1260, 1100, 840, 780. ¹H-NMR (60 MHz): 0.0 (s, 2 Me₃Si); 0.8 (s, 2 *t*-BuSi); 1.0 (t, *J* = 7, CH₃(5)); 2.6 (q, *J* = 7, CH₂(4)); 3.6 (AB, *J* = 10, 2 CH₂OSi); 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 Me₃SiCl in 10 ml of dry pyridine, 0.43 g (1.1 mmol) of **15** was added. After 24 h, the mixture was poured into Et₂O, washed with ice/H₂O, and evaporated. Filtration over silica gel (CH₂Cl₂) 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. ¹H-NMR (60 MHz): 0.0 (s, 2 Me₃Si); 0.1 (s, Me₃Si); 0.8 (s, 2 *t*-BuSi); 1.1 (t, *J* = 7, CH₃(5)); 2.6 (q, *J* = 7, CH₂(4)); 3.6 (s, 2 CH₂OSi); 4.6 (s, OH). ¹³C-NMR (22.63 MHz): –5.4 (q, Me₃Si); 2.4 (q, Me₃Si); 7.3 (q, C(5)); 18.4 (s, (CH₃)₃CSi); 26.0 (q, (CH₃)₃CSi); 32.7 (t, C(4)); 66.5 (t, CH₂OSi); 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 Et₂O, washed with cooled H₂O, and evaporated. CC (petroleum ether/Et₂O) 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. ¹H-NMR (60 MHz): 0.0 (s, Me₃Si); 0.1 (s, Me₂Si); 1.0 (s, 2 *t*-BuSi); 1.4 (d, *J* = 7, CH₃–C(2)); 3.9 (m, 2 CH₂OSi); 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 Et₂O, washed with brine, and evaporated. The colourless powder (**9**) obtained was then immediately reacted with 0.15 g (1 mmol) of (*t*-Bu)Me₂SiCl 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 Et₂O and washed with cooled H₂O. After CC

(CH₂Cl₂), 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. ¹H-NMR (60 MHz): 0.0 (s, 2 Me₂Si); 0.8 (s, 2 *t*-BuSi); 1.9 (s, CH₃-C(4)); 3.9 (AB, *J* = 10, 2 CH₂OSi); 7.4–8.0 (*m*, 5 arom. H). ¹³C-NMR (22.63 MHz): –5.4 (*q*, Me₂Si); 7.2 (*q*, CH₃-C(4)); 18.2 (s, (CH₃)₂CSi); 25.8 (*q*, (CH₃)₂CSi); 64.0 (*t*, CH₂OSi); 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)).

(6*S*,7*S*,*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/Et₂O), 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. ¹H-NMR (90 MHz): 0.0–0.2 (2 s, 2 Me₂Si, Me₃Si); 0.8 (s, 2 *t*-BuSi); 1.0–1.3 (*m*, CH₃(11), CH₃CHO₂, CH₃-C(4)); 1.8–2.2 (*m*, CH₂(10)); 2.7–2.8 (br., OH); 3.4–4.2 (*m*, H-C(4), H-C(5), H-C(6), 2 CH₂OSi); 4.7–5.0 (*m*, CH₃CHO₂, H-C(7)); 5.3–5.7 (*m*, H-C(8), H-C(9)).

(6*S*,7*S*,*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/Et₂O 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. ¹H-NMR (90 MHz): 0.0 (2 s, 2 Me₂Si); 0.2 (s, Me₃Si); 0.9, (2 s, 2 diastereoisotopic *t*-BuSi); 1.0–1.2 (*m*, CH₃(11), CH₃CHO₂); 1.45 (*d*, *J* = 4, CH₃-C(4)); 1.9–2.3 (*m*, CH₂(10)); 3.8 (*d*, *J* = 3, 2 CH₂OSi); 4.0 (2 *m*, *J* = 5, H-C(7)); 4.6 (*d*, *J* = 5, H-C(6)); 4.8–5.2 (2 *m*, CH₃CHO₂, H-C(4)); 5.5–5.9 (*m*, H-C(8), H-C(9)). ¹³C-NMR (22.63 MHz): –5.5 (2 *q*, Me₂Si); 2.1 (*q*, Me₃Si); 11.4 (*q*, CH₃-C(4)); 13.8 (*q*, C(11)); 18.2, 18.5 (2 s, (CH₃)₂CSi); 19.2 (*q*, CH₃CHO₂); 21.1 (*t*, C(10)); 25.9 (2 *q*, (CH₃)₂CSi); 55.2 (*d*, C(4)); 67.1, 67.5 (2 *t*, CH₂OSi); 74.9 (*d*, C(7)); 82.6 (*d*, C(6)); 88.4 (s, C(2)); 102.2 (*d*, CH₃CHO₂); 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-[(1*S*,2*S*,*Z*)-1,2-bis[[*tert*-butyl]dimethylsilyloxy]hex-3-enyl]-4-methylfuran-3(2*H*)-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 Et₃N. The solvent was evaporated and the residue dried under high vacuum. To the crude **21**, 320 mg (2.2 mmol) of (*t*-Bu)Me₂SiCl 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 Et₂O, washed with brine, and evaporated. After CC (CH₂Cl₂), 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. ¹H-NMR (90 MHz): 0.00 (s, 4 Me₂Si); 0.90 (*m*, 4 *t*-BuSi, CH₃(6)); 1.70 (s, CH₃-C(4)); 1.8–2.1 (*m*, CH₃(5)); 3.70, 3.85 (2 AB, *J* = 8, 2 CH₂OSi); 4.4–4.7 (*m*, H-C(1'), H-C(2')); 5.3–5.6 (*m*, H-C(3'), H-C(4')). ¹³C-NMR (22.63 MHz): –4.0–5.0 (*m*, 4 Me₂Si); 6.1 (*q*, CH₃-C(4)); 14.0 (*q*, C(6)); 18.4, 18.5 (2 s, 4 (CH₃)₂CSi); 21.6 (*t*, C(5)); 26.0 (s, 4 (CH₃)₂CSi); 63.8, 64.0 (2 *t*, 2 CH₂OSi); 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-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3(2*H*)-one (**23**). At r.t., 1.038 g (1.68 mmol) of **20** were stirred with 136 mg of K₂CO₃ in 50 ml of MeOH. After 18 h, the mixture was poured into 50 ml of Et₂O, washed with ice/H₂O, evaporated, and purified by CC (petroleum ether/Et₂O 20:3): 758 mg of **23** (85%) as mixture of diastereoisomers. UV (MeOH): 279 (3.881). IR (CHCl₃): 2960, 2940, 2860, 1700 and 1630 (C=C–C=O), 1470, 1260, 1100, 840. ¹H-NMR (90 MHz): 0.0 (s, 4 Me₂Si), 0.8 (s, 2 *t*-BuSi), 0.95 (*t*, CH₃(6)); 1.45 (*d*, CH₃CHO₂); 1.7 (s, CH₃-C(4)); 1.85–2.4 (*m*, CH₃(5)); 3.85 (*q*, 2 AB, 2 CH₂OSi); 4.63 (*d*, H-C(1')); 4.95 (*t*, H-C(2')); 5.25 (*q*, CH₃CHO₂); 5.55 (*d*, H-C(3')); 5.75 (2 *td*, H-C(4')). ¹³C-NMR (22.63 MHz): –5.5, –5.6 (2 *q*, 2 Me₂Si); 5.1 (*q*, CH₃-C(4)); 14.1 (*q*, C(6)); 18.1, 18.2 (2 s, (CH₃)₂CSi); 19.6 (*q*, CH₃CHO₂); 21.2 (*t*, C(5)); 25.7 (*q*, 2 (CH₃)₂CSi); 63.6, 63.7 (2 *t*, 2 CH₂OSi); 76.6, 77.3 (2 *d*, C(1'), C(2')); 92.7 (s, C(2)); 103.0 (*d*, CH₃CHO₂); 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 (NH₃): 527 (*[M* + H]⁺), 483 (*[M* – 44]⁺), 469 (*[M* – HC(CH₃)₃]⁺), 425, 401, 385, 343, 301, 281, 197, 171, 132 (*[HOSi(CH₃)₂C(CH₃)₃]⁺*), 106, 90, 72, 58, 44.

5-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-2,2-bis(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**24**). To a soln. of 290 mg (0.55 mmol) of **23** in 1 ml of THF, 0.5 ml of Bu₄NF soln. (1*M* in THF) was added. After 20 min, the mixture was filtered immediately over a silica-gel column (Et₂O/MeOH 18:1): 154.3 mg (94%) of **24** as colourless oil. IR (CHCl₃): 3490 (OH), 2980, 2940, 2880, 1700 and 1630 (C=C–C=O), 1450, 1400, 1380, 1150, 1090, 1050, 1020, 900, 845. ¹H-NMR (90 MHz): 0.93 (*t*, *J* = 7.4, CH₃(6)); 1.47 (*d*, *J* = 4.7, CH₃CHO₂); 1.68 (s, CH₃-C(4)); 1.97–2.17 (*m*, CH₃(5)); 2.8–3.2 (br., 2 OH); 3.85 (br., 2 CH₂OSi); 4.62 (*d*, *J* = 7.5, H-C(1')); 4.93 (*t*, *J* = 7.8, H-C(2')); 5.37 (*q*, *J* = 4.8, CH₃CHO₂); 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*, $\text{CH}_3\text{-C(4)}$); 14.1 (*q*, C(6')); 19.7 (*q*, CH_3CHO_2); 21.3 (*t*, C(5')); 62.8 (2 *t*, 2 CH_2OSi); 76.2, 77.0 (2 *d*, C(1'), C(2')); 91.6 (*s*, C(2)); 103.6 (*d*, CH_2CHO_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-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**25**). *Method A*: A soln. of 128 mg (0.43 mmol) of **24**, 145 mg (0.43 mmol) of (MeO)₂TrCl, 81 μl (0.058 mmol) of Et₃N and 1 mg (0.008 mmol) of 4-(dimethylamino)pyridine in CH_2Cl_2 was stirred under Ar at r.t. for 30 min. The mixture was poured into H₂O and extrated with CH_2Cl_2 . The org. layer was washed with a 4*M* aq. NH_4Cl soln. and H₂O. CC (petroleum ether/Et₂O 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)₂TrCl 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 H₂O 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. ^1H -NMR (90 MHz): 0.85 (*t*, *J* = 7.4, $\text{CH}_3(6')$); 1.51 (*d*, *J* = 4.7, CH_3CHO_2); 1.73 (*s*, $\text{CH}_3\text{-C(4)}$); 1.85–2.4 (*m*, $\text{CH}_2(5')$); 2.52 (br., OH); 3.35 (AB, CH_2O); 3.75 (*s*, 2 CH_2O); 3.84 (*s*, CH_2O); 4.71 (*d*, H-C(1')); 5.22 (*t*, H-C(2')); 5.45 (*q*, *J* = 4.8, CH_3CHO_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*, $\text{CH}_3\text{-C(4)}$); 14.1 (*q*, C(6')); 19.8 (*q*, CH_2CHO_2); 21.2 (*t*, C(5')); 55.2 (*q*, CH_2O); 63.2, 64.3 (2 *t*, CH_2OH , CH_2O); 76.4, 76.5 (2 *d*, C(1'), C(2')); 86.4 (*s*, C(2)); 91.0 (*s*, arom. C); 103.5 (*d*, CH_2CHO_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-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran-3(2*H*)-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 Et₃N gave 116 mg of crude **26/27**. CC (petroleum ether/Et₂O 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. ^1H -NMR (90 MHz): 0.73, 0.89 (2 *t*, *J* = 7.5, $\text{CH}_3(6')$); 1.51 (*d*, *J* = 4.8, CH_3CHO_2); 1.69, 1.73 (2 *s*, $\text{CH}_3\text{-C(4)}$); 1.80–2.21 (*m*, $\text{CH}_2(5')$); 3.38, 3.47 (AB, CH_2O); 3.78 (*s*, 2 CH_2O); 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_3CHO_2 , H-C(3'), H-C(4')); 6.76–7.50 (*m*, 13 arom. H). EI-MS: 570 (*M*⁺), 320, 303.

5-[(1*S*,2*S*,*Z*)-1,2-(Ethylidenedioxy)hex-3-enyl]-2-(hydroxymethyl)-4-methylfuran-3(2*H*)-one (**28**). *Method A*: A soln. of **27** (35.4 mg, 0.062 mmol) in 1 ml of $\text{CHCl}_3/\text{MeOH}$ 7:3 was stirred with 2% of TsOH for 1 h at 0°. The mixture was then washed with 5% aq. Na_2CO_3 soln. and H₂O. After evaporation and CC (petroleum ether/Et₂O 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% $\text{CHCl}_3/\text{COOH}$ in CH_2Cl_2 . After 1 h, the mixture was poured into 5% aq. NaHCO_3 soln. and extrated with CH_2Cl_2 . The org. soln. was washed with H₂O. 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. ^1H -NMR (90 MHz): 0.97 (*t*, *J* = 7.5, $\text{CH}_3(6')$); 1.50 (*d*, *J* = 4.5, CH_3CHO_2); 1.72 (*s*, $\text{CH}_3\text{-C(4)}$); 1.82–2.4 (*m*, $\text{CH}_2(5')$, OH); 3.95 (*d*, *J* = 5, CH_2O); 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_3CHO_2). ^{13}C -NMR (101 MHz): 5.4 ($\text{CH}_3\text{-C(4)}$); 14.1 (C(6')); 19.7 (CH_3CHO_2); 21.3 (C(5')); 61.7 (CH_2OH); 74.7, 75.0 (C(1'), C(2')); 84.0 (C(2)); 102.6 (CH_2CHO_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-[(1*S*,2*S*,*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/Et₂O 1:1): 26.5 mg (76%) of **29**. IR (film): 3450 (OH), 1600, 1500, 1250, 1170. ^1H -NMR (400 MHz): 0.78, 0.94 (2 *t*, *J* = 7.0, $\text{CH}_3(6')$); 1.44 (*d*, *J* = 4.5, CH_3CHO_2); 1.73, 1.75 (2 *s*, $\text{CH}_3\text{-C(4)}$); 1.80–2.20 (*m*, $\text{CH}_2(5')$); 3.36–3.70 (*m*, CH_2O); 3.79 (*s*, 2 CH_2O); 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_3CHO_2); 6.8–7.5 (*m*, 13 arom. H).

2-[(4,4'-Dimethoxytrityloxy)methyl]-5-[(1*S*,2*S*,*Z*)-1,2-(ethylidenedioxy)hex-3-enyl]-4-methylfuran (**30**) and 5-[(1*S*,2*S*,*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)₂NEt in 0.2 ml of CH_2Cl_2 at r.t. for 14 h. The mixture was poured into 10 ml of CH_2Cl_2 , washed with 4*M* aq. NH_4Cl and H₂O, and evaporated. CC (petroleum ether/Et₂O 1:1) gave 1.5 mg (54%) of **31** and

2.0 mg (36%) of **30**. ¹H-NMR for **30** (400 MHz): 0.79 (*t*, *J* = 7.5, CH₃(6')); 1.45 (*d*, *J* = 4.8, CH₃CHO₂); 1.80–2.10 (*m*, CH₂(5')); 2.00 (*s*, CH₃–C(4)); 3.81 (*s*, 2 CH₃O); 4.56 (*s*, CH₂O); 4.57 (*d*, *J* = 7.7, H–C(1')); 5.05 (*m*, H–C(2')); 5.42–5.47 (*m*, H–C(3'), CH₃CHO₂); 5.63–5.69 (*m*, H–C(4')); 6.12 (*s*, H–C(3)); 6.83–7.33 (*m*, 13 arom. H). ¹H-NMR for **31** (400 MHz): 0.79 (*t*, *J* = 7.5, CH₃(6')); 1.45 (*d*, *J* = 4.9, CH₃CHO₂); 1.80–2.10 (*m*, CH₂(5')); 2.00 (*s*, CH₃–C(4)); 4.56 (*s*, CH₂O); 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'), CH₃CHO₂); 5.63–5.70 (*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)Me₂SiCl, 45 µl of Et₃N, 1.5 mg of 4-(dimethylamino)pyridine, and 1 ml of CH₂Cl₂. CC (petroleum ether/Et₂O 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. ¹H-NMR (90 MHz): 0.0, 0.05 (2 *s*, Me₂Si); 0.70–1.15 (*m*, CH₃(6'), *t*-BuSi); 1.45 (*d*, *J* = 4.5, CH₃CHO₂); 1.65 (*s*, CH₃–C(4)); 1.85–2.30 (*m*, CH₂(5')); 3.75–4.15 (*m*, CH₂O); 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'), CH₃CHO₂). CI-MS (NH₃): 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/Et₂O 1:1) yielded 16.7 mg (66%) of **35**. IR (film): 2960, 2940, 2860, 1780 (–O–C=O), 1440, 1250, 1090, 840, 780. ¹H-NMR (90 MHz): 0.0 (*s*, Me₂Si); 0.8 (*m*, CH₃(6'), *t*-BuSi); 1.35 (*d*, *J* = 4.5, CH₃CHO₂); 1.80 (*s*, CH₃–C(4)); 1.70–2.30 (*m*, CH₂(5')); 3.80 (*s*, CH₃O); 4.45–4.50 (*m*, H–C(1'), CH₃OSi); 4.98 (*t*, *J* = 7.5, H–C(2')); 5.25–5.72 (*m*, H–C(3'), H–C(4'), CH₃CHO₂). CI-MS (NH₃): 458 ([*M* + NH₄]⁺), 441 ([*M* + H]⁺), 383, 309, 265, 251, 225, 199, 112, 91, 83, 74, 44.

REFERENCES

- [1] M. Dolder, X. Shao, Ch. Tamm, *Helv. Chim. Acta* **1990**, 73, 63.
- [2] S. G. Cohen, E. Khedouri, *J. Am. Chem. Soc.* **1961**, 83, 4228.
- [3] E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, 94, 2549.
- [4] H. I. Skulnick, W. Wirenger, *J. Org. Chem.* **1979**, 44, 310.
- [5] R. Bentely, M. Makita, C. C. Sweely, W. W. Wells, *J. Am. Chem. Soc.* **1963**, 85, 2497.
- [6] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, 94, 6190.
- [7] S. Huang, A. J. Mancuso, D. Swern, *J. Org. Chem.* **1978**, 43, 2480.
- [8] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.* **1979**, 95.
- [9] E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, 399.
- [10] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
- [11] R. A. Dagnault, E. L. Eliel, 'Organic Synthesis' Coll. Vol. V, p. 303.
- [12] A. E. Dann, J. B. Davis, M. J. Nagler, *J. Chem. Soc., Perkin Trans. 1* **1979**, 158.
- [13] a) S. Katsumura, S. Fujiwara, S. Isoe, *Tetrahedron Lett.* **1987**, 1193; b) K. E. Wilson, R. T. Seidner, S. Masamune, *J. Chem. Soc., Chem. Commun.* **1970**, 213.
- [14] E. J. Corey, J. L. Gras, P. Ulrich, *Tetrahedron Lett.* **1976**, 809.
- [15] J. D. Aebi, D. Seebach, *Helv. Chim. Acta* **1985**, 68, 1507.
- [16] a) E. Pretsch, T. Clerc, I. Seibl, W. Simon, 'Tabellen zur Strukturaufklärung organischer Verbindungen', Springer Verlag, Berlin-Heidelberg-New York, 1981, 2. Aufl.; b) C. J. Pouchert, J. R. Campbell, 'Aldrich NMR Spectra', *Aldrich Chemical Company Inc.*, 1974, Vol. III, 6A.