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A Novel One-Pot Synthetic Method for α-Methylenation of Lactones and Cycloalkanones Based on Thiophosphates

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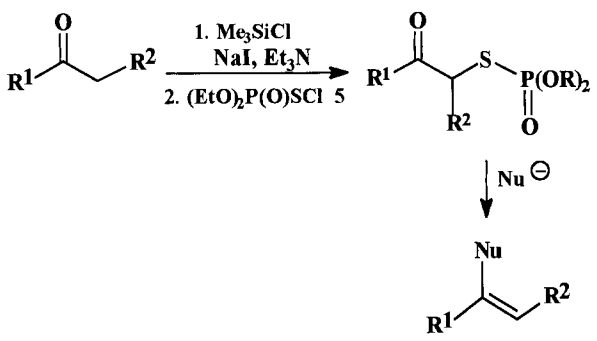
ABSTRACT: *A variety of lactones and cycloalkanones have been converted into their α-methylene derivatives using a one-pot procedure. In our approach, the key steps involve the formation of readily available thiophosphates and their reactions with sodium borohydride under very mild conditions.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:353–361, 2000

INTRODUCTION

The α-methylene-γ-lactone structural unit is an integral building block of many natural products and exhibits interesting biological properties [1]. α-Methylene ketones are highly reactive, and hence various efforts have been devoted to development of an effective synthetic method for α-methylenation of carbonyl compounds. Some of the more commonly used ones for this transformation include α-methylenation through direct hydroxymethylenation-elimination [2], employing Eschenmoser's salt [3] (reaction of lactone enolates with dimethyl-(methylene)ammonium iodate) or Stille's and other reagents in a decarboxylative methylenation [4,5], use of organosulfur reagents [6] and organoselenium reagents [7] as precursors of the double bond and palladium catalyzed decarboxylation-deacetoxylation of allyl α-acetoxymethyl-β-keto carboxylates [8]. However, many of these procedures seem to suffer from some synthetic limitations, so a new method of α-methylenation of carbonyl compounds would be useful.

We have reported a novel strategy for the stereoselective conversion of carbonyl compounds into (*Z*)-olefins. The key steps in this synthesis involve the formation of *S*-(β-oxoalkyl)thiophosphates and their reactions with appropriate nucleophiles [9] (Scheme 1). Thiophosphates were readily prepared from the appropriate carbonyl compounds, generally in very high yields. The carbonyl compounds were converted into silyl enol ethers, then addition of diethoxyoxophosphoranesulfenyl chloride **5** afforded thiophosphates. It is noteworthy that conversion of silyl enol ethers to final product can be performed as a "one-pot" procedure.

We have demonstrated that this methodology is very useful for the synthesis of a variety of unsaturated compounds [10].



SCHEME 1

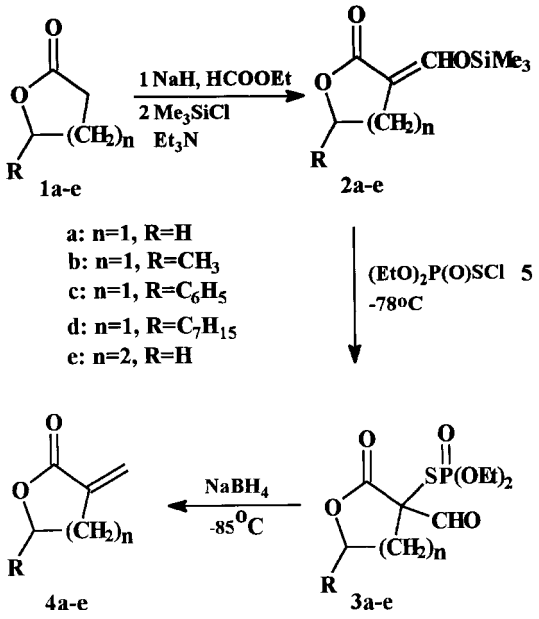
In this article, we describe an extension of this methodology, which gives a new "one-pot" procedure for α-methylenation of lactones, including the synthesis of racemic frullanolide, and for α-methylenation of cycloalkanones.

RESULTS AND DISCUSSIONS

The method of α-methylenation of lactones developed in this laboratory is shown in Scheme 2.

The lactones **1** are first formylated [12] and selectively *O*-silylated by the action of trimethylsilyl chloride in the presence of triethylamine in a nonpolar solvent [13]. Then thiophosphorylation of **2** using diethoxyoxophosphoranesulfenyl chloride **5** in CH_2Cl_2 under very mild conditions ($-78°C$) affords new thiophosphates **3** in high yield. Sulfenyl chlorides **5** (one of the best thiophosphorylation agents) are readily available from commercial materials and can be used without isolation [14]. Fully selective reduction of the aldehyde function of **3** using $NaBH_4$ proceeds smoothly at $-85°C$, providing α-methylene-γ-lactones and δ-lactone **4a–e** in good yield (Scheme 2).

The utility of this method was further demonstrated by its application to α-methylenation of the tricyclic lactone **6**, giving a racemic frullanolide **9.** The compound **9** is a typical allergenic eudesmanolide that occurs in certain plants Frullania genus [15,16]. Lactone **6** was prepared by the method described by Yoshikoshi [16]. Previously its α-methylenation providing frullanolide was performed according to Greco and Hiroi [16,17] (lithium diisopropylamine, formaldehyde, methanesulfonyl chloride, pyridine, and DBU) but gave a yield of only 35%. In our one-pot procedure, **6** afforded frullanolide **9** in 60% overall yield (Scheme 3).



SCHEME 2

Our approach can be also applied to α-methylene cycloalkanones **14** (Scheme 4).

New thiophosphates **12** have been obtained in a similar manner as the thiophosphates **3.** Cycloalkanones **10** with different *R* substituents in the ring were first formylated [13] and *O*-silylated [13] and then thiophosphorylated using **5** to provide synthesis of thiophosphates **12.** Selenophosphates **13** have been prepared by the treatment of formylated cycloalkanones [13,18] with **15** [14b] in the presence of pyridine. Selective reduction of the aldehyde function of phosphates **12** and **13** using $NaBH_4$ also proceeded smoothly to give α-methylene cycloalkanones **14** in good yield. Best results were obtained when conversion of compounds **1, 6,** and **10** to **4, 9,** and **14** was performed as a one-pot procedure (see Experimental). The identity of all α-methylene lactones and α-methylene cycloalkanones of Table 1 were confirmed by spectral data and, in most cases, by their comparison to published data.

Transformation of the thiophosphates **3, 8** into α-methylene-lactones **4** and **9** as well as thiophosphates **12** and selenophosphates **13** into α-methylene cycloalkanones **14** is exemplified in Scheme 5.

Reaction of the thiophosphate **8** with sodium borohydride results in the formation of oxyanion **16.** This intermediate anion rearranges with migration of a phosphoryl group from sulfur to oxygen affording the thiolate anion **17.** Subsequent cyclization via nucleophilic attack at carbon with elimination of phosphate anion gives episulfide. It loses sulfur spontaneously to provide frullanolide **9**.

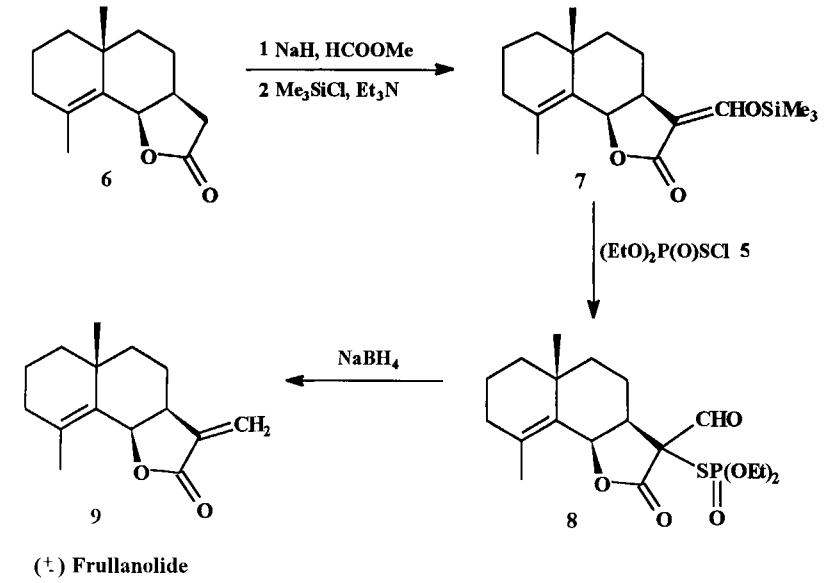
The thiophosphates **3, 8, 12** and selenophosphates **13** are presented in Table 2.

CONCLUSION

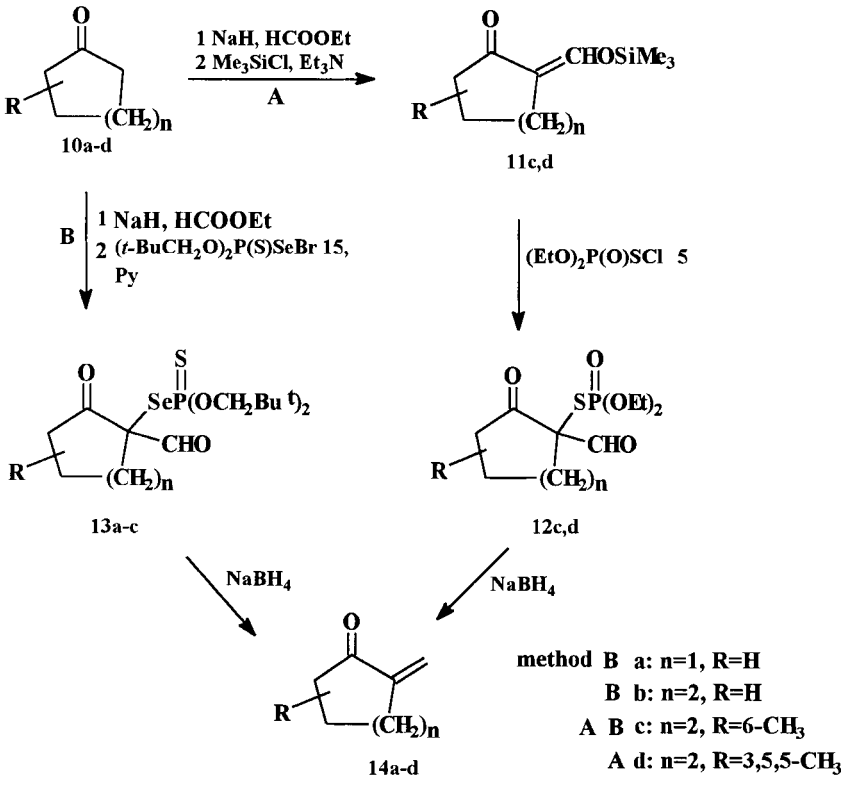
The simple one-pot protocol and mild conditions make the method described here an attractive alternative to others already known for the α-methylenation of carbonyl compounds. Our approach gives also ready access to racemic frullanolide in high yield and should be applicable to the synthesis of other eudesmanolides.

EXPERIMENTAL

All reactions were performed under argon. The solvents and reagents were purified by standard procedures excepted as noted. *n*-Hexane and Et_2O were



SCHEME 3



SCHEME 4

dried by distillation from sodium/benzophenone ketyl, and EtOH was dried by distillation from magnesium. Flash chromatography was carried out using silica gel (70-230 mesh; Merck). Thin-layer chromatography (TLC) was performed on silica gel (Kieselgel 60 F_{254}, Merck). The lactones **1** and cycloalkanones **10** [purchased from commercial suppliers (the EGA-Chemie, the Aldrich Chemical Co., the Jansen-Chimica, the Fluka Chemica, the PPH "POCh" SA)] were purified by distillation prior to

TABLE 1 Preparation of α-Methylene Lactones **4, 9,** and α-Methylene Cycloalkanones **14**

Product	*Time*[a] (*h*)	*Yield*[b] (%)
4a	1.5	77 (A)
4b	2	60 (A)
4c	3	50 (A)
4d	2.5	62 (A)
4e	2	40 (A)
9	2.5	60 (A)
14a	2	53 (B)
14b	3	63 (B)
14c	3.5	53 (B)
14c	2.5	69 (A)
14d	3.5	40 (A)

[a]Time required for the conversion of thiophosphates **3, 8, 12** and selenophosphates **13** into the corresponding **4, 9,** and **14.**
[b]Yields of isolated compounds (column chromatography on silica gel) based on lactones **1, 6** and cycloalkanones **10.**

use. Diethoxyoxophosphoranesulfenyl chloride **5** [14a], dineopentoxythiophosphoraneselenyl bromide **15** [14b], and lactone **6** [16] were prepared according to the published procedure.

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker Instruments AC-200 at 200.1 (^1H), 50.32 (^{13}C), and 81.02 MHz (^{31}P), using internal TMS (^1H, ^{13}C) and external 85% H_3PO_4 (^{31}P) as reference. $CDCl_3$ was used as solvent. Mass spectra (EI, CI-isobutane) were registered on Finnigan MAT 95 and LKB 2091 spectrometer. Microanalysis obtained on a Carlo Erba CHNS-OEA 1108 Elemental Analyzer. Boiling and melting points were uncorrected.

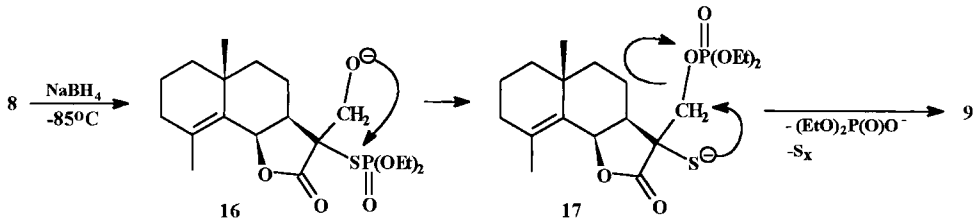
α-Methylene Lactones **4** *from Lactones* **1**, *Frullanolide* **9** *from Lactone* **6**, *and α-Methylene Cycloalkanone* **14** *from Cycloalkanone* **10** *via Thiophosphates* **3, 8**, *and* **12** (*Method A*)

The formylation of lactones **1a–e** was performed as described in Ref. [12], and that of cycloalkanones **10c,d** as described in Ref. [13]. To the mixture of formylated lactone or formylated cycloalkanone (10 mmol) with dry Et_3N (14 mmol) and dry hexane (20 mL), Me_3SiCl (19.5 mmol) was added dropwise. The mixture was stirred overnight and filtered with hexane washing. The solvent and volatiles were removed from the filtrate under reduced pressure (0.05 mmHg) to give crude silyl enol ether **2** or **11.** A solution of SO_2Cl_2 (9.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the stirred solution of *O,O,O*-triethylphosphorothioate (9.5 mmol) in CH_2Cl_2 (15 mL) at −30°C. Stirring was continued for 20 minutes at rt. After removal of about 50% of solvent, the crude diethoxyoxophosphoranesulfenyl chloride **5** was added dropwise with stirring to **2** or **11** dissolved in CH_2Cl_2 (40 mL) at −78°C. The mixture was stirred and allowed to warm slowly to ambient temperature. The solvent and trimethylsilyl chloride were removed in vacuo (0.05 mmHg). Crude thiophosphate **3** or **12** dissolved in CH_2Cl_2 (15 mL) was added by syringe to a suspension of $NaBH_4$ (28 mmol, approx. 3 eq.) in CH_2Cl_2/EtOH (50 mL, in the ratio 3.5:1.5) at −85°C [19]. The mixture was stirred at the same temperature until TLC analysis indicated complete consumption of thiophosphate (see Table 1). Then 0.5 mL of acetaldehyde was added and the resulting mixture was stirred for an additional 30 minute at −85°C. Then the mixture was treated with ice water, the organic layer separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried ($MgSO_4$), solvent was removed in vacuo at 0°C, and the residue was purified by flash chromatography (short column) with petroleum ether/ethyl acetate (10:1 to 3:1, gradient elution).

α-Methylene Cycloalkanones **14** *from Cycloalkanones* **10** *via Selenophosphates* **13** (*Method B*)

The formylation of cyclopentanone **10a** was performed as described in Ref. [18a], of cyclohexanone **10b** as described in Ref. [18b], and of 2-methylcyclohexanone **10c** as described in Ref. [13]. To a suspension of the triethylammonium salt of *O,O*-dineopentyl phosphoroselenothioate (10 mmol) in CH_2Cl_2 (20 mL) was added dropwise with stirring at −80°C a solution of anhydrous bromine (10 mmol) in CH_2Cl_2 (10 mL). The stirring was continued at −80°C for 30 minutes and the resulting crude dineopentoxythiophosphoraneselenyl bromide **15** was added to the stirred solution of formylated cycloalkanone (11 mmol) and pyridine (11.5 mmol) in CH_2Cl_2 (25 mL) at −80°C. The mixture was stirred for 2 hours at the same temperature, and Et_2O (5 mL) was added followed by filtration of triethylamine hydrobromide and pyridine hydrobromide, and evaporation of about 50% of the CH_2Cl_2 gave the crude thioselenophosphate **13**, which was added by syringe to a stirred suspension of $NaBH_4$ (27 mmol, 3 eq.) in CH_2Cl_2/EtOH (3.5:1.5, 50 mL) at −85°C. The mixture was stirred at the same temperature until TLC analysis indicated the complete consumption of thioselenophosphate (see Table 1). Then 0.5 mL of acetaldehyde was added, and the resulting mixture was stirred for an additional 30 minutes at −85°C and allowed to warm to 0°C. The precipitated selenium was filtered off, and ice water was added. Further workup was the same as described previously.

Yields of isolated α-methylene lactones **4a–e, 9**,



SCHEME 5

TABLE 2 Yield and Selected NMR Data of Thiophosphates **3, 8, 12** and Selenophosphates **13** Prepared (coupling constants *J* in Hz)

Compound	*Yield* (%)	*Ratio*[b]	$\delta^{31}P$	$^{1}J_{PSe}$	δ ^{1}H (*CHO*)	$^{4}J_{P\text{-}H}$
3a	88		20.3		9.55 (s)	
3b	85[a]	1	19.8		9.51 (s)	
		0.5	20.6		9.40 (d)	1.2
3c	65[a]	1	19.7		9.57 (d)	1.1
		1.5	20.4		9.66 (s)	
3d	78[a]	1	20.0		9.63 (s)	
		0.5	20.8		9.51 (d)	1.3
3e	60		20.2		9.45 (d)	2.5
8	84		23.0		9.2 (brs)	
12c	88[a]	1	21.0		9.57 (s)	
		3	22.5		9.87 (d)	0.7
12d	55[a]	1	22.1		9.66 (d)	1.0
		3.5	22.4		9.81 (s)	
13a	78.2		78.3	489.9	9.56 (s)	
13b	62.2		78.2	493.0	9.87 (s)	
13c	68		77.1	493.4	9.92 (d)	0.9

[a]Overall yield of both diastereoisomers.
[b]Ratio of diastereoisomers as determined by ^{31}P and ^{1}H NMR.

and α-methylene cycloalkanones **14a–d** are listed in Table 1. The known α-methylene lactones and α-methylene cycloalkanones were characterized by ^{1}H NMR and MS data.

3-Methylene-dihydrofuran-2-one **4a** *[12,20].* Yield 77%, light brown liquid, R_f = 0.57 (hexane/ethyl acetate 1:1). ^{1}H NMR: δ = 2.97 (tt, 2H, J = 2.7, 7.3 Hz, CH_2), 4.37 (t, 2H, J = 7.3 Hz, OCH_2), 5.67 (t, 1H, J = 2.5 Hz, $C=CH_2$), 6.25 (t, 1H, J = 2.9 Hz, $C=CH_2$). MS (CI, capillary column): *m/z* (%) = 100 (5) [$M^+ + 2$], 99 (100) [$M^+ + H$], 68 (1) [$M^+ - CH_2O$].

Dihydro-5-methyl-3-methylene-2(3H)-furanone **4b** *[21].* Yield 60%, light yellow liquid, R_f = 0.60 (hexane/ethyl acetate 1:1). ^{1}H NMR: δ = 1.43 (d, 3H, J = 5.9 Hz, CH_3), 2.27–3.53 (m, 2H, CH_2), 4.56 [sextet, J = 5.9 Hz, 1H, *CH*(CH_3)], 5.61 (t, 1H, J = 2.5 Hz, $C=CH_2$), 6.21 (t, 1H, J = 2.9 Hz, $C=CH_2$). MS (EI, 15 eV): *m/z* (%) = 112 (5) [M^+], 67 (80) [$M^+ - HCO_2$], 43 (100) [CH_3CO].

Dihydro-3-methylene-5-phenyl-2-(3H)-furanone **4c** *[5,22].* Yield 50%, yellow solid [m.p. = 47°C, (lit. [5] m.p. = 48–51°C)], R_f = 0.75 (hexane/ethyl acetate 1:1.5). ^{1}H NMR: δ = 2.93 (ddt, 1H, J = 2.9, 9.5, 17.1 Hz, CH_2), 3.42 (ddt, 1H, J = 2.4, 8.0, 17.1 Hz, CH_2), 5.42 [dd, 1H, J = 6.2, 10 Hz, *CH*(C_6H_5)], 5.69 (t, 1H, J = 2.5 Hz, $C=CH_2$), 6.31 (t, 1H, J = 2.8 Hz, $C=CH_2$). MS (CI, isobutane): *m/z* (%) = 175 (100) [$M^+ + H$], 129 (2) [$M^+ - CO_2H$], 91 (1) [$CH_2C_6H_5$], 68 (3) [$M^+ - C_6H_5CHO$]. MS (EI, 15 eV): *m/z* (%) = 174 (20) [M^+], 147 (15), 129 (30), 91 (33), 77 (28), 68 (100).

Dihydro-5-heptyl-3-methylene-2-(3H)-furanone **4d** *[23].* Yield 62%, colorless oil, R_f = 0.72 (hexane/ethyl acetate 1:1). ^{1}H NMR: δ = 0.87–0.9 (m, 3H, CH_3), 1.27 (brs, 10H, CH_2), 1.53–1.86 (m, 2H, CH_2), 2.40–2.52 (m, 10 lines, 1H, J = 2.2, 6.7, 14.8 Hz, CH_2), 2.9 (ddt, 1H, J = 7.7, 14.8 Hz, CH_2), 4.34–4.6 [m, 1H, *CH*(C_7H_{15})], 5.56 (t, 1H, J = 2.2 Hz, $C=CH_2$), 6.2 (t, 1H, J = 2.8 Hz, $C=CH_2$). MS (CI, isobutane): *m/z* (%) = 197 (50) [$M^+ + H$], 149 (30), 125 (42) [$M^+ - C_5H_{11}$], 97 (100) [$M^+ - C_7H_{15}$].

3-Methylene tetrahydropyran-2-one **4e** *[20].* Yield 40%, yellow liquid, R_f = 0.55, (hexane/ethyl acetate 1:1). ^{1}H NMR: δ = 2.08–2.33 (m, 2H, CH_2), 3.03 (tt, 2H, J = 4.6, 7.2 Hz, CH_2), 4.55 (t, 2H, J = 4.9 Hz, OCH_2), 5.62 (m, 1H, $C=CH_2$), 6.47 (d, 1H, J = 1.2 Hz, $C=CH_2$). MS (EI, capillary column): *m/z* (%) = 112 (100) [M^+], 83 (35) [$M^+ - CHO$], 66 (30), 55 (23).

6-Methyl-2-methylenecyclohexanone **14c** *[24,25].* Yield 69% (method A), 53% (method B), colorless liquid, R_f = 0.7 (hexane/ethyl acetate 1:1). ^{1}H NMR: δ = 1.02 (d, 3H, J = 6.86 Hz, CH_3), 1.34–1.98 (m, 4H, CH_2), 2.15–2.38 (m, 2H, CH_2), 2.40–2.70 [m, 1H, *CH*(CH_3)], 4.95 (brs, 1H, $C=CH_2$), 5.40 (brs, 1H, $C=CH_2$). MS (CI, capillary column): *m/z* (%) = 124 (5) [$M^+ + H$], 109 (7) [$M^+ - CH_3$], 89 (80), 81 (50) [$M^+ - CH_3CO$], 79 (40), 71 (65), 69 (100), 67 (60).

3,5,5-Trimethyl-2-methylenecyclohexanone **14d.** Yield 40%, light yellow oil, R_f = 0.82 (hexane/ethyl

acetate 1:1). ^{1}H NMR: δ = 0.92 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.16 (d, 3H, J = 6.6 Hz, CH_3CH), 1.52 (dd, 1H, J = 2.4, 5.6 Hz, CH_2), 1.59 (dd, 1H, J = 2.4, 5.6 Hz, CH_2), 2.13 (d, 1H, J = 10.0 Hz, CH_2), 2.14 (d, 1H, J = 10 Hz, CH_2), 2.5–2.77 [11 lines, 1H, J = 2.2, 6.2, 11.6 Hz, CH(CH_3)], 5.26 (brs, 1H, C=CH_2), 5.84 (d, 1H, J = 1.6 Hz, C=CH_2). ^{13}C NMR: δ = 21.14 (CH_3), 25.33 (CH_3), 31.06 (CH_3), 31.94 (C-3), 35.17 (C-5), 45.47 (C-4), 47.10 (C-6), 112.27 (CH_2=C), 145.99 (CH_2=C), 186.40 (C=O). MS (CI, isobutane): m/z (%) 153 (5.5) [M^+ +H], 138 (9), 123 (18), 122 (3), 107 (100) [M^+ −C_3H_9], 45 (50). Anal. calcd for $C_{10}H_{16}O$ (152.2): C 78.89, H 10.59; found: C 79.31, H 9.96.

2-Methylenecyclopentanone **14a** *[6,26].* Yield 53%, colorless liquid, R_f = 0.66 (benzene/ethyl acetate 1:1). ^{1}H NMR: δ = 1.49–1.70 (m, 2H, CH_2), 1.72–1.98 (m, 2H, CH_2), 2.26–2.43 (m, 2H, CH_2), 5.50 (brs, 1H, C=CH_2), 6.05 (brs, 1H, C=CH_2). MS (EI, capillary column): m/z (%) = 96 (75) [M^+], 95 (58) [M^+ −H], 78 (32), 77 (23), 67 (100) [M^+ −CHO], 41 (39), 39 (59).

2-Methylenecyclohexanone **14b** *[24].* Yield 63%, colorless liquid, R_f = 0.65 (benzene/ethyl acetate 1:1). ^{1}H NMR: δ = 1.63–1.67 (m, 2H, CH_2), 2.08–2.16 (m, 2H, CH_2), 2.2–2.31 (m, 2H, CH_2), 5.08 (d, 1H, J = 2 Hz, C=CH_2), 5.75 (d, 1H, J = 1.9 Hz, C=CH_2). MS (EI, capillary column): m/z (%) = 110 (15) [M^+], 67 (100) [M^+ −CH_3CO], 54 (60), 41 (45).

[3a(R,S)-(3aα,5aβ,9bα)]-3a,4,5,5a,6,7,8,9b-Octahydro-5a,9-dimethyl-3-methylene-naphthol[1,2-b]furan-2-(3H)-one [(±)Frullanolide] **9** *[16,27].* According to the procedure described previously (method A) from 2,3,3aα,4,5,5a,6,7,8,9bα-decahydro-5a-β,9-dimethyl-2-oxonaphtho[1,2-b] furan **6** [16] (33 mg, 0.15 mmol) the title compound **9** (21 mg, 0.09 mmol) was obtained (flash chromatography, hexane/ethyl acetate (15:1 elution). Yield 60%, white solid [m.p. 92.0–92.5°C (lit. [27] 93.0–93.5°C)]. ^{1}H NMR: δ = 1.01 (s, 3H, CH_3), 1.20–1.90 (m, 8H), 1.67 (s, 3H, CH_3), 2.03 (brs, 2H), 3.02 (brs, 1H), 5.11 (brs, 1H), 5.73 (d, 1H, J = 1.1 Hz, C=CH_2), 6.24 (s, 1H, C=CH_2). Anal. calcd for $C_{15}H_{20}O_2$ (232.3): C 77.55, H 8.68; found. C 77.17, H 8.39.

Thiophosphates **3, 8***, and* **12***: General Procedure*

To the appropriate pure silyl enol ether **2, 7,** or **11** (5 mmol) in CH_2Cl_2 (20 mL) solution the freshly prepared diethoxyoxophosphoranesulfenyl chloride **5** (4.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise with stirring at −78°C. The mixture was stirred and allowed to warm slowly to ambient temperature. Then the solvent and volatile products were removed in vacuo (0.05 mmHg) to afford crude thiophosphates **3, 8,** or **12.** No analytically pure compounds were obtained owing to their instability during purification.

Thiophosphoric Acid O,O-diethyl S-(3-formyl-2-oxo-tetrahydrofuran-3-yl) Ester **3a**. Yield 88% colorless oil. ^{31}P NMR: δ = 20.3. ^{1}H NMR: δ = 1.38 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.34 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.62–2.77 (m, 5 lines, 1H, J = 7.4 Hz, CH_2), 3.17 (ddd, 1H, J = 5.4, 7.4, 13.9 Hz, CH_2), 4.09–4.30 (m, 4H, OCH_2CH_3), 4.30–4.54 (m, 2H, OCH_2), 9.55 (s, 1H, CHO). ^{13}C NMR: δ = 15.81, 15.82 (CH_3CH_2O), 31.32 (C-4), 63.72 (C-5), 65.04, 65.14 (CH_3CH_2O), 75.22 (C-3), 167.02 (C=O), 189.78 (CHO). MS (CI, isobutane): m/z (%) = 283 (20) [M^+ +H], 237 (5) [M^+ −CO_2H], 155 (100) [$(EtO)_2P(O)OH_2$].

Thiophosphoric Acid O,O-diethyl S-(3-formyl-5-methyl-2-oxo-tetrahydrofuran-3-yl) Ester **3b**. Yield 85%, colorless viscous oil. ^{31}P NMR: δ = 19.8 (56.6%), 20.55 (28.3%). ^{1}H NMR: δ = 1.26 (t, 6H, J = 7.1 Hz, OCH_2CH_3, major), 1.26 (t, 6H, J = 7.1, OCH_2CH_3, minor), 1.36 (d, 3H, J = 6.4 Hz, CH_3, major), 1.39 (d, 3H, J = 6.4 Hz, CH_3, minor), 2.21 (ddd, 1H, J = 1.0, 9.2, 13.5 Hz, CH_2, minor), 2.66 (dAB, 2H, J = 6.5, 14.5 Hz, CH_2 major), 3.20 (dd, 1H, J = 6.0, 13.5 Hz, CH_2, minor), 3.99–4.17 (m, 4H, OCH_2CH_3, major and minor), 4.57 [ddq, 1H, J = 6.1, 6.1, 9.1 Hz, $CH(CH_3)$, minor], 4.78 [ddq, J = 6.3, 6.5, 8.1 Hz, 1H, CH(CH_3), major], 9.40 (d, 1H, $^4J_{PH}$ = 1.2 Hz, CHO, minor), 9.51 (s, 1H, CHO, major). ^{13}C NMR: δ = 15.58, 15.70 (CH_3CH_2O), 20.06 (CH_3 major), 20.66 (CH_3, minor), 36.99 (C-4, major), 39.50 (C-4, minor), 64.73 (J_{PC} = 9.9 Hz, OCH_2CH_3), 65.03 (J_{PC} = 5.4 Hz, OCH_2CH_3), 74.30 (C-3), 75.38 [OCH(CH_3), major], 76.28 [OCH(CH_3), minor], 152.00 (C=O), 189.19, 190.32 [CHO minor and major]. MS (CI, isobutane): m/z (%) = 298 (4.8) [M^+ +2H], 297 (41) [M^+ +H], 257 (21) [M^+ −CHO], 189 (8), 171 (53), 129 (25), 155 (100, $(EtO)_2P(O)OH_2$). HRMS: $C_{10}H_{18}O_6PS$ calcd for (M + H) 297.0561, found 297.0551.

Thiophosphoric Acid O,O-diethyl S-(3-formyl-2-oxo-5-phenyl-tetrahydrofuran-3-yl) Ester **3c**. Yield 65%, dark yellow oil. ^{31}P NMR: δ = 19.7 (26%), 20.4 (39%). ^{1}H NMR: δ = 1.36 (t, J = 7.1, 6 H, OCH_2CH_3), 2.65–2.92 (m, 9 lines, 1H, J = 6.4, 8.0 Hz, CH_2 major + minor), 3.21–3.38 (m, 5 lines, 1H, J = 8.3 Hz, CH_2 minor), 3.56 (dd, 1H, J = 6.2, 13.5, CH_2 major), 4.17–4.26 (m, 4H, OCH_2CH_3), 5.45–5.54 (m, 5 lines, 1H, J

= 6.4, 10.0 Hz, *CH*(C_6H_5) major + minor), 7.25–7.36 (m, 5H, C_6H_5), 9.57 (d, 1H, $^4J_{PH}$ = 1.1 Hz, CHO, minor), 9.66 (s, 1H, CHO, major). ^{13}C NMR: δ = 15.54, 15.65 (*CH*$_3$CH$_2$O), 30.50 (C-4, major), 31.97 (C-4, minor), 63.43 (J_{PC} = 5.0 Hz, O*CH*$_2$CH$_3$), 65.15 (J_{PC} = 4.8 Hz, O*CH*$_2$CH$_3$), 78.26 (C-3), 79.82 (*CH*C_6H_5, minor), 81.05 (*CH*C_6H_5, major), 125.00 (*meta*-C_6H_5), 128.02 (*ortho*-C_6H_5), 128.39 (*para*-C_6H_5), 139.02, 140.58 (*ipso*-C_6H_5, major and minor), 173.82 (C=O), 189.01, 189.86 (CHO major and minor). MS (EI, 15 eV): *m/z* (%) = 358 (7.8) [M^+], 328 (30) [$M^+ - C(O)H_2$], 281 (15), 267 (100) [$M^+ - CH_2C_6H_5$], 155 (45) [$(EtO)_2P(O)OH_2$], 91 (80), 77 (20) [C_6H_5].

Thiophosphoric Acid O,O-diethyl S-(3-formyl-5-heptyl-2-oxo-tetrahydrofuran-3-yl) Ester **3d**. Yield 78%, yellow oil. ^{31}P NMR: δ = 20.0 (52%), 20.8 (26%). ^{1}H NMR: δ = 0.87 (t, 3H, J = 6.3 Hz, CH_3), 1.26 (brs, 10H, CH_2), 1.36 (t, 3H, J = 7.1 Hz, OCH$_2$*CH*$_3$) and 1.37 (t, 3H, J = 7.1 Hz, O*CH*$_2$*CH*$_3$) (major and minor), 1.59–1.93 (m, 2H, CH_2), 2.35–2.42 (m, 1H, CH_2,minor), 2.52 (dd, 2H, J = 6.5, 9 Hz, CH_2, major), 3.28 (dd, 1H, J = 6.0, 13.4 Hz, CH_2, minor), 4.03–4.31 (m, 4H, O*CH*$_2$CH$_3$), 4.64–4.78 [m, 8 lines, 1H, J = 5.6, 7.4 Hz, *CH*(C_7H_{15}), major and minor], 9.51 (d, 1H, $^4J_{PH}$ = 1.3 Hz, CHO, minor), 9.63 (s, 1H, CHO, major). ^{13}C NMR: δ = 13.93 (CH_3), 15.82, 15.90 (*CH*$_3$CH$_2$O), 22.48, 25.09, 28.76, 29.56, 31.57 (CH_2), 34.69 (C-4), 35.45 (*CH*$_2$CHO), 63.63, 65.12 (CH$_3$*CH*$_2$O), 79.22 (C-3), 80.98 [O*CH*(C_7H_{15})], 162.30 (C=O), 177.25 (CHO). MS (EI, 15 eV): *m/z* (%) = 380 (0.8) [M^+], 351 (2), 287 (2), 263 (3), 170 (4), 155 (10) [$(EtO)_2P(O)OH_2$)], 128 (15), 99 (20) [C_7H_{15}], 85 (100) [C_6H_{13}], 55 (9).

Thiophosphoric Acid O,O-diethyl S-(3-formyl-2-oxo-tetrahydropyran-3-yl) Ester **3e**. Yield 60%, colorless oil. ^{31}P NMR: δ = 20.2. ^{1}H NMR: δ = 1.17 (m, 14 lines, 6H, J = 7.3 Hz, OCH$_2$*CH*$_3$), 1.53 (brs, 2H, CH_2), 1.66–1.82 (m, 2H, CH_2), 2.17–2.30 (m, 2H, CH_2), 3.97–4.45 (m, 6H, O*CH*$_2$CH$_3$ and H_2CO), 9.45 (d, 1H, J = 2.47 Hz, CHO). MS (EI, 15 eV): *m/z* (%) = 296 (0.5) [M^+], 226 (13), 211 (18), 171 (5), 155 (100) [$(EtO)_2P(O)OH_2$].

Thiophosphoric Acid O,O-diethyl S-(1-formyl-3-methyl-2-oxo-cyclohexyl) Ester **12c**. Yield 88%, slightly yellow oil. ^{31}P NMR: δ = 21.0 (22%), 22.5 (66%). ^{1}H NMR: δ = 0.99 (d, 3H, J = 6.4 Hz, CH_3, major), 1.04 (d, 3H, J = 6.4 Hz, CH_3, minor), 1.30 (t, 6H, J = 7.1 Hz, OCH$_2$*CH*$_3$), 1.69–1.89 (m, 2H, CH_2, major + minor), 1.91–2.14 (m, 3H, CH_2, major + minor), 2.18–2.64 (m, 1H, CH_2, major + minor), 3.06 (q, 1H, J = 7.2 Hz, C*H*$(CH_3)_{minor}$), 3.23 (sextet, 1H, J = 6.3 Hz, C*H*(CH_3), major), 3.99–4.28 (m, 4H, O*CH*$_2$CH$_3$), 9.57 (s, 1H, CHO, minor), 9.87 (d, 1H, $^4J_{PH}$ = 0.7 Hz, CHO, major). ^{13}C NMR: δ = 13.79 (CH_3, major), 14.15 (CH_3, minor), 15.69, 15.81 (*CH*$_3$CH$_2$O), 22.75, 23.49 (C-5, major and minor), 32.81, 33.51 (C-4, minor and major), 35.34, 36.59 (C-6, minor and major), 40.27 [*CH*(CH_3) minor], 41.38 [*CH*(CH_3), major], 64.22 (J_{PC} = 10.2 Hz, O*CH*$_2$CH$_3$), 64.56 (J_{PC} = 6.9 Hz, O*CH*$_2$CH$_3$), 83.28 (C-1), 186.44 (C=O), 193.52 (CHO, minor), 195.23 (CHO, major). MS (CI, isobutane): *m/z* (%) = 309 (100) [M^+ + H], 280 (2), 171 (17), 139 (7), 126 (2). HRMS: $C_{12}H_{21}O_5PS$ calcd for (M + H) 309.0925, found 309.0926.

Thiophosphoric Acid O,O-diethyl S-(1-formyl-4,4,6-trimethyl-2-oxo-cyclohexyl) Ester **12d**. Yield 55%, yellow viscous oil. ^{31}P NMR: δ = 22.1 (12.2%), 22.4 (36.7%). ^{1}H NMR: δ = 0.89 (s, 3H, CH_3, minor), 0.97 (s, 3H, CH_3, minor), 0.98 (s, 3H, CH_3, major), 1.01 (d, 3H, J = 6.4 Hz, CH_3, minor), 1.06 (s, 3H, CH_3, major), 1.15 (d, 3H, J = 6.6 Hz, CH_3, major), 1.33 (t, 6H, J = 6.9 Hz, OCH$_2$*CH*$_3$), 1.44–2.84 (m, 3H, CH_2 + *CH*(CH_3), major and minor), 2.93 (d, 2H, J = 13.4 Hz, *CH*$_2$C(O), minor), 3.15 (d, 2H, J = 13.3 Hz, *CH*$_2$C(O), major), 4.01–4.31 (m, 4H, CH$_3$*CH*$_2$O), 9.66 (d, 1H, $^4J_{PH}$ = 1 Hz, CHO, minor), 9.81 (s, 1H, CHO, major). MS (EI, 15 eV): *m/z* (%) = 337 (1.3) [M^+ + H], 336 (10), [M^+], 321 (5), 306 (6), 291 (30), 181 (100), 155 (40) [$(EtO)_2P(O)OH_2$].

Thiophosphoric Acid O,O-diethyl S-(3a-formyl-3aα,5,aβ,9bα-octahydro-5a,9-dimethyl-2-oxo-naphtho[1,2-b]furan-3-yl) ester **8**. Yield 84%, white solid mass. ^{31}P NMR: δ = 23.0. ^{1}H NMR: δ = 1.22 (s, 3H, CH_3), 1.37 (t, 3H, J = 7.1 Hz, OCH$_2$*CH*$_3$), 1.38 (t, 3H, J = 7.1 Hz, OCH*CH*$_3$), 1.51–1.98 (m, 8H), 2.26 (t, 2H, J = 7.4 Hz), 3.12 (d, 1H, J = 10.0 Hz), 4.08–4.34 (m, 4H, O*CH*$_2$CH$_3$), 5.18–5.32 (m, 1H), 9.2 (brs, 1H, CHO). MS (CI, isobutane): *m/z* (%) = 417 (60) [M^+ + H], 155 (100), [$(EtO)_2P(O)OH_2$].

Selenophosphates **13***: General Procedure*

Dineopentoxythiophosphoraneselenyl bromide **15** (10 mmol) in CH_2Cl_2 (25 mL), freshly prepared from the triethylammonium salt of *O,O*-dineopentyl phosphoroselenothioate with anhydrous bromine was added by syringe to the stirred solution of the appropriate formylated cycloalkanone (11 mmol) and pyridine (11.5 mmol) in CH_2Cl_2 (30 mL) at −78°C. Filtration of precipitated pyridine hydrobromide, followed by evaporation of solvents in vacuo (0.01 mmHg), afforded crude selenophosphates **13.** No analytically pure compounds were obtained owing to their instability during purification.

Selenothiophosphoric Acid O,O-dineopentyl Se-(1-formyl-2-oxo-cyclopentyl) Ester **13a**. Yield 78.2%, yellow oil. ^{31}P NMR: δ = 78.3, $^{1}J_{PSe}$ = 489.9 Hz. ^{1}H NMR: δ = 0.92 (s, 18H, *t*-Bu), 1.89–2.51 (m, 5H, CH_2), 2.7–2.86 (m, 1H, CH_2), 3.59–3.70 (m, 4H, OCH_2 *t*-Bu), 9.56 (s, 1H, CHO). MS (EI, 15 eV): *m/z* (%) = 426 (0.47) [M^+ (^{78}Se)], 428 (0.71) [M^+ (^{80}Se)], 318 (4.6) [$M^+ - CHO$], 112 (13.4) [$C_6H_8O_2$], 79 (100).

Selenothiophosphoric Acid O,O-dineopentyl Se-(1-formyl-2-oxo-cyclohexyl) Ester **13b**. Yield 62.2%, yellow oil. ^{31}P NMR: δ = 78.2, $^{1}J_{PSe}$ = 493.0 Hz. ^{1}H NMR: δ = 0.96 (s, 18H, *t*-Bu), 1.66–2.06 (m, 4H, CH_2), 2.22–2.54 (m, 2H, CH_2), 3.13 (dAB, 2H, *J* = 5.0, 7.3 Hz, CH_2), 3.62–3.72 (m, 10 lines, 4H, OCH_2 *t*-Bu), 9.87 (s, 1H, CHO). MS (EI, 15 eV): *m/z* (%) = 440 (0.22) [M^+ (^{78}Se)], 442 (0.48) [M^+ (^{80}Se)], 411 (9) [$M^+ - CHO$], 125 (40) [$C_7H_3O_2$], 81 (100).

Selenothiophosphoric Acid O,O-dineopentyl Se-(1-formyl-3-methyl-2-oxo-cyclohexyl) Ester **13c**. Yield 68%, yellow oil. ^{31}P NMR: δ = 77.1, $^{1}J_{PSe}$ = 493.4 Hz. ^{1}H NMR: δ = 0.91 (s, 18H, *t*-Bu), 1.10 (d, 3H, *J* = 7.0 Hz, CH_3), 1.46–1.90 (m, 2H, CH_2), 1.92–2.12 (m, 2H, CH_2), 2.16–2.40 (m, 2H, CH_2), 3.08 [dq, 1H, *J* = 4.9, 7.2 Hz, $-CH(CH_3)$], 3.60–3.87 (m, 4H, OCH_2*t*-Bu), 9.92 (d, 1H, *J* = 0.9 Hz, CHO). MS (EI, 15 eV): *m/z* (%) = 454 (0.25) [M^+ (^{78}Se)], 456 (0.56) [M^+ (^{80}Se)], 426 (15) [$M^+ - C(O)H_2$], 218 (18), 79 (100).

Trimethylsilylenol Ethers **2** *and* **11**

Analytically pure silyl enol ethers **2** and **11** were obtained by distillation using Kugelrohr or by crystallization.

Dihydro-3-(trimethylsilyl)oxymethylene-2(3H) furanone **2a** *[28].* Yield 98%, colorless liquid (ot 60°C/0.05 mmHg). ^{1}H NMR: δ = 0.23 [s, 9 H, $Si(CH_3)_3$], 2.82 (dt, 2H, *J* = 7.5, 2.6 Hz, CH_2), 4.29 (t, 2H, *J* = 7.5 Hz, CH_2), 7.40 (t, 1H, *J* = 2.6 Hz, C=CHOSi). MS (EI, 70 eV): *m/z* (%) = 186 (0.5) [M^+], 171 (5), 147 (34), 86 (80), 66 (100).

Dihydro-5-methyl-3-(trimethylsilyl)oxymethylene-2-(3H)-furanone **2b**. Yield 97.5%, colorless liquid (ot 100°C/0.05 mmHg). ^{1}H NMR: δ = 0.27 [s, 9H, $Si(CH_3)_3$], 1.20 (d, 3H, *J* = 6.3 Hz, CH_3), 2.41 (ddd, 1H, *J* = 2.7, 5.9, 16.4 Hz, CH_2), 3.00 (ddd, 1H, *J* = 2.5, 8.0, 16.4 Hz, CH_2), 4.64 [ddq, 1H, *J* = 6.0, 6.2, 8.0 Hz, C*H*(CH_3)], 7.42 (t, 1H, *J* = 2.6 Hz, C=CHOSi). MS (EI, 70 eV): *m/z* (%) = 200 (1.5) [M^+], 185 (10), 157 (15), 127 (60), 99 (100). Anal. calcd. for $C_9H_{16}O_3Si$ (200.3): C 53.96, H 8.05; found: C 53.28, H 7.88.

Dihydro-5-phenyl-3-(trimethylsilyl)oxymethylene-2-(3H)-furanone **2c**. Yield 90%, white solid (m.p. 95°C). ^{1}H NMR: δ = 0.28 [s, 9H, $Si(CH_3)_3$], 2.78 (ddd, 1H, *J* = 2.4, 6.3, 16.5 Hz, CH_2), 3.34 (ddd, 1H, *J* = 2.4, 8.6, 16.5 Hz, CH_2), 5.51 (dd, 1H, *J* = 6.3, 8.6 Hz, C*H*C_6H_5), 7.26–7.41 (m, 5H, C_6H_5), 7.50 (t, *J* = 2.6 Hz, C=CHOSi). MS (EI, 70 eV): *m/z* (%) = 262 (26) [M^+], 247 (23), 172 (19), 171 (20), 156 (93), 113 (100) [$C_5H_5O_3$]. Anal. calcd for $C_{14}H_{18}O_3Si$ (262.38): C 64.09, H 6.91; found: C 64.14, H 6.76.

5-Heptyl-dihydro-3-(trimethylsilyl)oxymethylene-2-(3H)-furanone **2d**. Yield 96%, colorless oil (ot 170°C/0.05 mmHg). ^{1}H NMR: δ = 0.25 [s, 9 H, $Si(CH_3)_3$], 0.84 (t, 3H, *J* = 6.3 Hz, CH_3), 1.24 (brs, 10H, CH_2), 1.53–1.9 (m, 2H, CH_2), 2.50 (ddd, 1H, *J* = 2.5, 6.5, 13.3 Hz), 2.95 (ddd, 1H, *J* = 2.5, 8.1, 16.4 Hz), 4.50 [m, 1H, $CH(C_7H_{15})$], 7.40 (t, *J* = 2.6 Hz, C=CHOSi). MS (EI, 70 eV): *m/z* (%) = 285 (0.8) [M^+ + 1], 284 (2.2) [M^+], 269 (15), 254 (11), 241 (18), 219 (25), 185 (80), 126 (100) [$C_6H_6O_3$]. Anal. calcd for $C_{15}H_{28}O_3Si$ (284.46): C 63.33, H 9.92; found. C 62.92, H 9.85.

Tetrahydro-3-(trimethylsilyl)oxymethylene-2-pyranone **2e**. Yield 92%, colorless liquid (ot 68°C/0.1 mmHg). ^{1}H NMR: δ = 1.84 (tt, 2H, *J* = 5.8, 6.5 Hz, CH_2), 2.44 (dt, 2H, *J* = 2.1, 6.4 Hz, CH_2), 4.26 (m, 7 lines, 2H, *J* = 5.3 Hz, OCH_2), 7.64 (t, 1H, *J* = 2.1 Hz, C=CHOSi). MS (EI, 70 eV): *m/z* (%) = 200 (9) [M^+], 185 (20), 155 (22), 127 (100) [$C_6H_7O_3$].

6-Methyl-2-(trimethylsilyloxymethylene)cyclohexanone **11c** *[29].* Yield 96%, light yellow liquid (ot 100°C/0.05 mmHg). ^{1}H NMR: δ = 0.22 [s, 9H, $Si(CH_3)_3$], 1.10 (d, 2.7H, *J* = 6.9 Hz, CH_3), 1.17 (d, 0.3H, *J* = 7.1 Hz, CH_3), 1.40–1.67 (m, 2H), 1.73–2.01 (m, 2H), 2.15–2.34 (m, 2H), 2.51–2.56 [m, 0.8H, 1H, C*H*(CH_3)], 2.57–2.67 [m, 0.2H, 1H, C*H*(CH_3)], 7.38 (t, 0.9H, *J* = 2.0 Hz, C=CHOSi), 9.99 (s, 0.1H, CHO). MS (EI, 70 eV): *m/z* (%) = 212 (8.7) [M^+], 197 (42), 169 (15), 147 (14), 73 (100) [$M^+ - C_7H_9O_2$]. Anal. calcd for $C_{11}H_{20}O_2Si$ (212.36): C 62.21, H 9.49; found: C 61.97, H 9.32.

3,5,5-Trimethyl-2-trimethylsilyloxymethylene-cyclohexanone **11d**. Yield 85%, yellow oil (ot 180°C/0.05 mmHg). ^{1}H NMR: δ = 0.26 [s, 9H, $Si(CH_3)_3$], 0.92 (s, 2.1H, CH_3), 0.93 (s, 0.9H, CH_3), 0.98 (s, 2.1H, CH_3), 1.05 (s, 0.9H, CH_3), 1.13 (d, 2.1H, *J* = 6.7 Hz, CH_3), 1.17 (d, 0.9H, *J* = 6.7 Hz, CH_3), 1.50–1.75 (m, 2H), 2.00–2.12 (m, 2H), 2.51–2.68 [m, 0.3H, C*H*(CH_3)], 2.79–2.92 [m, 0.7H, C*H*(CH_3)], 7.48 (d, 0.7H, *J* = 2.2 Hz, C=CHOSi), 10.10 (s, 0.3H, CHO). MS (EI, 70 eV): *m/z* (%) = 240 (1.5) [M^+], 225 (5),

210 (8), 197 (10), 173 (20), 90 (100) [$M^+ - C_9H_{10}O_2$]. Anal. calcd for $C_{13}H_{24}O_2Si$ (240.4): C 64.95, H 10.59; found: C 65.03, H 9.91.

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