The First Convenient Entry to δ-Formyl-δ-valerolactone Precursor for the Synthesis of Statins via Lactonized Side Chain

Zdenko Časar,*[a] Janez Košmrlj[b]

[a] Lek Pharmaceuticals, d.d., Sandoz Development Center Slovenia, API Development, Organic Synthesis, Kolodvorska 27, 1234 Mengeš, Slovenia
Fax +386(1)7237382; E-mail: zdenko.casar@sandoz.com

[b] Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia

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Abstract: (4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-formyltetrahydro-2*H*-pyran-2-one has been prepared for the first time by oxidation of alcohol (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-one. The oxidation of the alcohol was performed with Dess–Martin periodinane in up to 95% yield. Because of limited stability of the aldehyde, it was isolated in the form of hydrate for isolation and storage purposes. The latter can be dehydrated back to the aldehyde quantitatively by simple dissolution in an apolar organic solvent followed by removal of volatiles. The aldehyde was demonstrated to undergo Wittig olefination in high yield. Presented findings set a key platform for statin synthesis via lactonized side chain.

Key words: lactones, aldehydes, oxidations, drugs, statins

Cholesterol-lowering drugs, dominated by statins, represent a group of the most efficient and frequently prescribed drugs in the treatment of lipid disorders,[1] and are the second largest by revenue in pharmaceutical sector with a market value of more than US$30 billion in 2007. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, crucial in the biosynthesis of cholesterol.[2] Commenced from the discovery of the first HMGCoA reductase inhibitor compactin,[3] new analogues have rapidly been developed. From early examples, including lovastatin,[4] pravastatin,[5] and simvastatin,[6] derived from microorganisms through partial synthesis, this class of drugs has been expanded by even more potent purely synthetic compounds. Representative examples are the world best-selling drug atorvastatin,[7] a new blockbuster rosuvastatin,[8] fluvastatin,[9] and pitavastatin.[10] As shown in Figure 1, these molecules are comprised of a heterocyclic core attached to a chiral 3,5-dihydroxy-6-heptenoic (-heptanoic for atorvastatin) acid side chain, a hydrolyzed form of β-hydroxy-δ-valerolactone. Essentially, this side chain is a key element for the bioactivity of statins[11] (Figure 1).

The preparation of synthetic statins has been achieved by different approaches in which the key step is frequently Wittig-type olefination of derivatized heterocyclic core with a fully O-protected 3,5-dihydroxy-6-oxohexenoic acid derivatives.[12,13] Some 6-formyltetrahydro-2*H*-pyran-2-ols (lactols) have also been applied in olefination.[14]

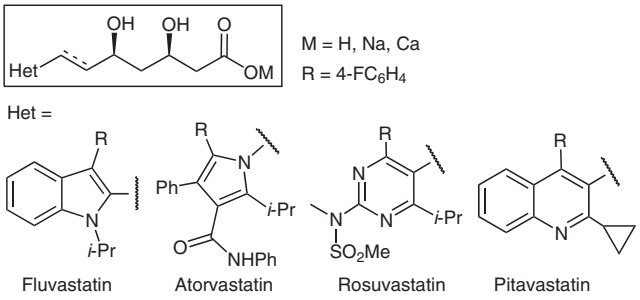
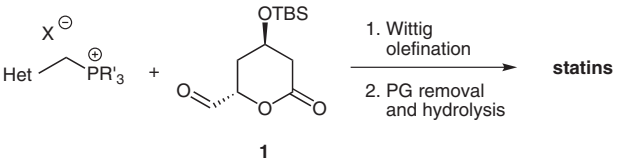


Figure 1 General structure of synthetic statins

Several drawbacks are associated with these aldehydes, including their availability in optically pure forms, long multistep preparation sequences, and often a tedious deprotective workup required after the olefination step to get the final statin. In contrast, we believe that (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-formyltetrahydro-2*H*-pyran-2-one (**1**) is the precursor of choice (Scheme 1). Provided that **1** can readily be prepared in the desired optically pure form, after being installed to the heterocyclic core, it should easily provide the final statin molecule by a simple one-pot deprotection and lactone hydrolysis reaction. The use of aldehyde **1** would reduce many synthetic steps and would enable a major breakthrough in efficiency, cost reduction, and consequently ecological issues in the production of these drugs.



Scheme 1 Retrosynthetic analysis of statins synthesis via aldehyde **1**

A logical and industrial acceptable pathway to aldehyde **1** is oxidation of (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-one (**2**), which can be prepared from ethyl (*S*)-4-chloro-3-hydroxybutanoate via halolactone **3a** in an efficient seven-step sequence.[15] Conveniently, halolactone **3b** is also accessible in efficient and highly stereoselective approach based on enzymatically catalyzed aldol condensation from achiral materials followed by chemical oxidation (Scheme 2).[16] Surprisingly, despite the fact that the synthesis of alcohol

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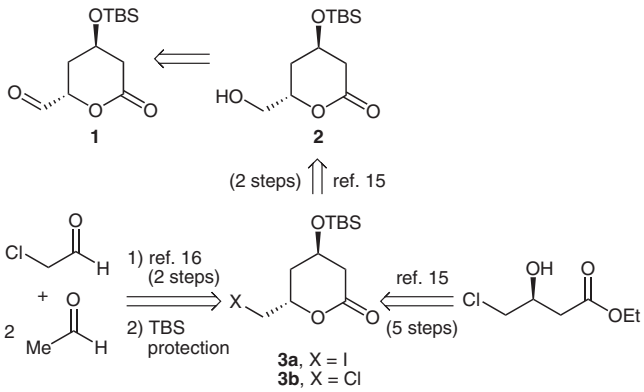
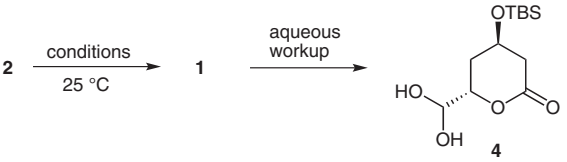
2 has previously been precedented,[17] there is only a single, yet unsuccessful attempt of its oxidation to aldehyde **1**.[18] It has been reported that the oxidation of **2** by NaOCl/TEMPO failed to provide **1** and it was discouragingly concluded that intermediates **2** and **3** are of no use for the preparation of statins.[18] Other attempts for the preparation of aldehyde **1** were equally unsuccessful.[13] Two decades ago, the synthesis of (4*S*,6*R*)-4-(*tert*-butyldimethyl-silyloxy)-6-formyltetrahydro-2*H*-pyran-2-one (*ent*-**1**) has been achieved in thirteen steps from D-glucose. Low overall yield, the use of highly toxic reagents, such as OsO_4, and the availability and price of L-glucose, which would be required for the preparation of **1**, render this approach industrially unacceptable. It should also be noted that, because of its instability, *ent*-**1** has not been isolated and that characterization has been done for its semicarbazone derivative.[19]

Being interested in statin chemistry, the above facts inevitably prompted us to survey the oxidation of alcohol **2**, and herein we disclose preliminary results on the synthesis and chemical properties of aldehyde **1**.



Scheme 2 Retrosynthesis of **1**

Initially, we attempted the oxidation of alcohol **2** with pyridinium chlorochromate (PCC), and pyridinium dichromate (PDC, Scheme 3, Table 1, entries 1, 2), previously used for the oxidation of some 5-hydroxymethyl-δ-valerolactones.[20] Both reagents afforded complex mixtures of products in which aldehyde **1** could not be detected. This led us to test a considerably milder oxidant, Dess–Martin periodinane (DMP).[21] The first experiment was conducted with 1.5 equivalents of DMP in dichloromethane at room temperature (entry 3). After three hours the reaction was quenched and the product was extracted into methyl *tert*-butyl ether (MTBE) and the solution was dried with magnesium sulfate. Evaporation of volatiles afforded white crystalline solid. Based on NMR, mass spectra, and combustion analysis, the structure of this compound was elucidated as hydrate **4**. Reducing the amount of DMP to 1.2 equivalents did not change the yield of **4** (81%, entry 4). In the next step, optimizing the reaction time, we found out that performing the oxidation for 30 minutes resulted in even higher isolated yield of hydrate **4** (94–95%, entries 5, 6) as mentioned above.



Scheme 3 Dess–Martin periodinane oxidation of alcohol **2**

Compound **4**[22] arises from intermediately formed aldehyde **1** by addition of water molecule to the aldehyde carbonyl group during the aqueous workup, as shown in Scheme 3. It is stable and can be stored at 8 °C for several months without decomposition. This is interesting as the 'carbonyl water' adducts are usually unstable to be isolated. Exceptions are hydrates, functionalized with strong electron-withdrawing groups, such as ninhydrin, glyoxal hydrate, chloral hydrate, and similar.[23] Whereas very few organic hydrate forms have been observed in the case of γ-formyl-γ-butyrolactones,[24] to the best of our knowledge, there are no unambiguous reports on hydrates of δ-formyl-δ-valerolactones.

Table 1 Dess–Martin Periodinane Oxidation of Alcohol **2**

Entry	Oxidant (equiv)	Solvent (mL/mmol of **2**)	Time (h)	Yield of **1**/**4** (%)
1	PCC (1.5)	CH_2Cl_2 (7.8)	3	0/0
2	PDC (2.0)	CH_2Cl_2 (7.8)	3	0/0
3	DMP (1.5)	CH_2Cl_2 (26)	3	0/81
4	DMP (1.2)	CH_2Cl_2 (26)	3	0/81
5	DMP (1.2)	CH_2Cl_2 (26)	0.5	0/95
6	DMP (1.1)	CH_2Cl_2 (26)	0.5	0/94

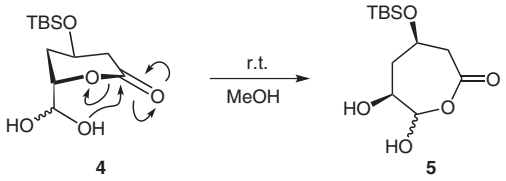
In solution, the structure of hydrate **4** was elucidated by 1D and 2D NMR spectra. In freshly prepared THF-d_8 solution, the ^{13}C NMR spectrum of **4** contained signals belonging to the lactone skeleton and TBS group. An additional resonance at δ = 91.7 ppm was observed for the exocyclic carbon atom attached to C-6, indicating that the aldehyde group was hydrated. In HSQC spectrum the signal at δ = 91.7 ppm correlated with a proton at δ = 4.83–4.91 ppm (CHOH), which was coupled (COSY) with H-6 (δ = 4.35–4.45 ppm) and two diastereotopic D_2O exchangeable geminal OH (*gem*-OH) protons at δ = 5.14 and 5.22 ppm. In the solid state the hydrate structure of **4** was confirmed by IR spectroscopy by the appearance of broad hydrogen bonded O–H stretching band centering at 3380 cm^{-1}. The MS (ES^+) showed an $[M + H]^+$ ion peak at *m/z* = 277.2, corresponding to the molecular formula $C_{12}H_{24}O_5Si$, which was also confirmed by combustion analysis.

After the above THF-d_8 solution of **4** was let to stand for a prolonged time, an additional set of signals appeared in the NMR spectra, assigned to aldehyde **1** (Figure 2). Indicative of the latter was CHO resonance at δ = 9.65 ppm

and the absence of *gem*-OH resonances. Equilibrium between **1** and **4** was reached at the ratio of 47:53 after three days (Figure 2). Dehydration of **4** is solvent-polarity dependent. In strongly polar solvents such as D_2O, the equilibrium is shifted towards **4** whereas in less polar chlorinated, aromatic, and aliphatic solvents (acetone-d_6, CD_2Cl_2, $CDCl_3$, toluene-d_8, cyclohexane-d_{12}), the aldehyde form of **1** is favorable. The kinetics of facile dehydration of **4** to **1** in CD_2Cl_2 is demonstrated in Figure 2.

On the other hand, in methanol-d_4 solution of hydrate **4**, the presence of aldehyde **1** could not be detected. Instead, within 2.5 days it completely transformed into a new compound, the structure of which has been suggested as oxepan-2-one derivative **5** (Scheme 4).[25] Compound **5** is presumably formed by an intramolecular transesterification with geminal hydroxy groups, as suggested in Scheme 4.

The above results clearly indicate that the aldehyde **1** could simply be obtained by dissolution of hydrate **4** in an appropriate solvent. Thus, stirring of **4** in dichloromethane for 1 day followed by evaporation of volatiles afforded the desired product in a quantitative yield.[26] The HRMS (TOFMS$^+$) of aldehyde **1** showed an $[M + H]^+$ ion peak at m/z = 259.1366 corresponding to the molecular formula $C_{12}H_{23}O_4Si^+$. In addition, only a single set of resonances in ^{1}H NMR and ^{13}C NMR spectra for aldehyde **1** indicated that it was obtained in optically pure form without epimerization at C-6 or silanol elimination.[27] It is noteworthy that attempts to isolate aldehyde **1** directly after the oxidation of alcohol **2**, followed by extractive workup and drying with magnesium sulfate, failed to provide aldehyde **1** and hydrated form **4** was always obtained. It appears also that aldehyde **1** degrades in contact with strong drying agents such as molecular sieves and calcium chloride while magnesium sulfate was ineffective[22] for dehydration of **4**.



Scheme 4 Rearrangement of hydrate **4** to substituted oxepan-2-one **5**

In the final stage of this work we were prompted to ascertain that the aldehyde **1** is amenable to undergo Wittig olefination. To this end, yilide **6**, prepared in situ from benzyltriphenylphosphonium bromide and NaHDMS, was let to react with aldehyde **1** (Scheme 5). The TBS-protected olefinic precursor of mevinic acid analogue **7**[28] was obtained in 74% isolated yield as a mixture of *E*/*Z* isomers in molar ratio of 63:37 (HPLC), which were separated for analysis.[29] It is important to note that no protecting group removal or lactone ring opening could be detected during the Wittig reaction. No attempts were made at this point of the research to optimize the *E*/*Z* ratio.

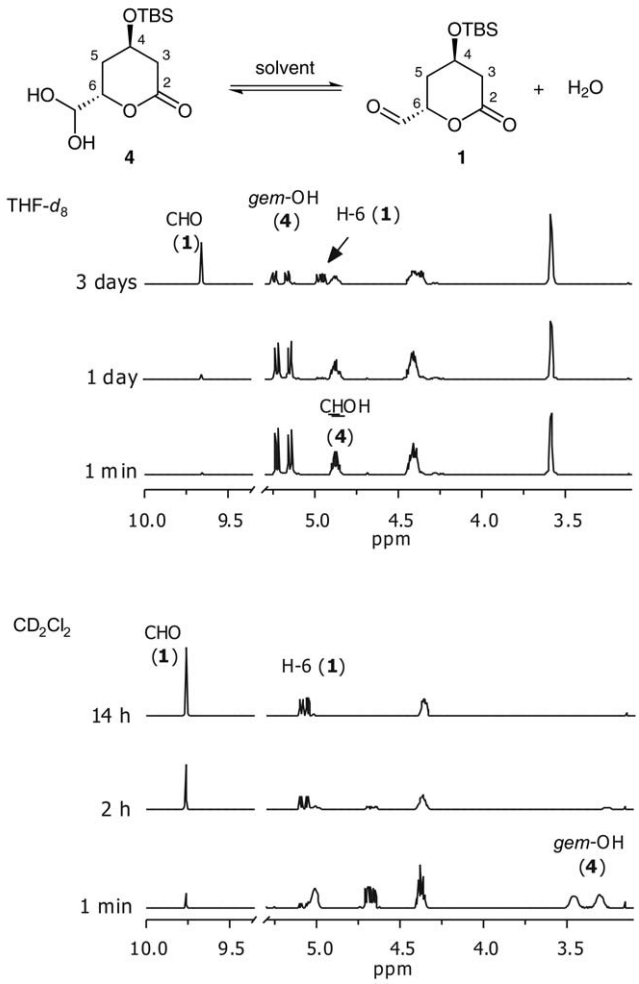
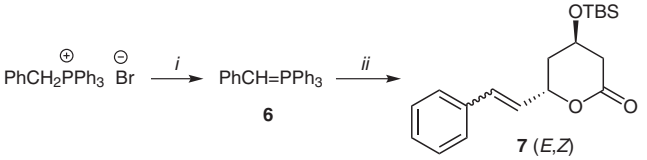


Figure 2 Hydrate **4** to aldehyde **1** interconversion with selected atom numbering scheme (top) and the corresponding ^{1}H NMR kinetic study in THF-d_8 (middle) and CD_2Cl_2 (bottom); selected illustrative regions of proton spectra are shown

In conclusion, we have reported the first synthesis of aldehyde **1** and demonstrated its utility in Wittig reaction, which opens new horizons in statin chemistry. We have shown that aldehyde **1** forms stable 'carbonyl water' adduct, hydrate **4**, which enables its stabilization and isolation. Powered by the recent discovery on highly stereoselective enzymatic synthesis of halolactole precursors, results presented herein lay down foundation for the first formation of statins with lactonized statin side chain. Future endeavors will focus on utilization of the aldehyde in Wittig reaction with corresponding heterocyclic derivatives to form statins. Our preliminary results with various



Scheme 5 Wittig reaction of aldehyde **1** and ylide **6**. *Reagents and conditions*: (*i*) NaHDMS (1.05 equiv), toluene, r.t., 2.25 h; (*ii*) **1** (1.1 equiv), 65 °C, 5 min.

heterocyclic phosphonium ylides are highly encouraging and will be presented in due course.

Acknowledgment

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(22) **Synthesis of (4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-(dihydroxymethyl)tetrahydro-2*H*-pyran-2-one (4)**
A mixture of **2**[15] (500 mg, 1.92 mmol) and DMP (896 mg, 2.11 mmol) in CH_2Cl_2 (50 mL) was stirred at 26 °C for 30 min. The mixture was diluted with MTBE (35 mL) and washed with sat. $NaHCO_3$ (45 mL). The organic phase was separated. The water phase was additionally extracted with MTBE (3 × 25 mL). Combined organic layers were washed with sat. aq $Na_2S_2O_3$ (2 × 25 mL), sat. $NaHCO_3$ (2 × 25 mL), H_2O (70 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give pure hydrate **4** (498 mg, 94%) as a white crystalline powder; mp 73–75 °C. ^{1}H NMR (300 MHz, THF-d_8): δ = 0.10 (s, 6 H, CH_3Si), 0.91 (s, 9 H, CH_3C), 1.80–2.00 (m, 2 H, H-5), 2.39 (dd, *J* = 17.1, 3.9 Hz, 1 H, H-3), 2.58 (dd, *J* = 17.1, 4.2 Hz, 1 H, H-3), 4.35–4.45 (m, 2 H, H-4, H-6), 4.83–4.91 [m, 1 H, CH(OH)], 5.14 (d, *J* = 6.0 Hz, 1 H, OH), 5.22 (d, *J* = 6.0 Hz, 1 H, OH). ^{13}C NMR (75 MHz, THF-d_8): δ = –4.79 (CH_3Si), –4.74 (CH_3Si), 18.7 (CCH_3), 26.2 (CH_3C), 31.0 (C-5), 40.4 (C-3), 65.1 (C-4), 79.1 (C-6), 91.7 [CH(OH)], 168.8 (C-2). IR (KBr): ν = 1697 cm^{-1}. MS (ES$^+$): *m/z* (%) = 851.6 (10) [3 M + Na]$^+$, 575.4 (58) [2 M + Na]$^+$, 570.4 (13) [2 M + NH_4]$^+$, 299.2 (35) [M + Na]$^+$, 294.2 (100) [M + NH_4]$^+$, 277.2 (88) [M + 1]$^+$, 259.2 (73), 145.1 (8). Anal. Calcd (%) for $C_{12}H_{24}O_5Si$: C, 52.14; H, 8.75. Found: C, 52.45; H, 9.18.

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(25) **(4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxyoxepan-2-one (5)**
Hydrate **4** (50 mg, 0.18 mmol) was dissolved in MeOH (2 mL) and left to stand at r.t. for 2.5 d. The solvent was evaporated to dryness to give **5** (50 mg, 100%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 0.14 (s, 6 H, CH_3Si), 0.94 (s, 9 H, CH_3C), 1.87–2.06 (m, 2 H, H-5), 2.52 (ddd, *J* = 17.5, 2.9, 2.0 Hz, 1 H, H-3), 2.72 (dd, *J* = 17.5, 3.8 Hz, 1 H, H-3), 4.42–4.52 (m, 1 H, H-4), 4.56–4.70 (m, 2 H, H-6, H-7). ^{13}C NMR (75 MHz, CD_3OD): δ = –4.82 (CH_3Si), –4.76 (CH_3Si), 18.9 (CH_3C), 26.2 (CH_3C), 30.7 (C-5), 31.0 (C-5), 40.5 (C-3), 64.9 (C-4), 79.0, 79.5, 98.6, 98.8, 172.58

(C-2), 172.60 (C-2). Two sets of ^{13}C resonances are observed in the intensity ratio of 1:1. HRMS (ES^+): *m/z* calcd for $C_{12}H_{24}O_5SiNa^+$ $[M + Na]^+$: 299.1291; found: 299.1299. Anal. Calcd (%) for $C_{12}H_{24}O_5Si$: C, 52.14; H, 8.75. Found: C, 52.35; H, 8.97.

(26) **(4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-formyltetrahydro-2*H*-pyran-2-one (1)**
A solution of hydrate **4** (500 mg, 1.81 mmol) in CH_2Cl_2 (30 mL) was left to stand for 1 d. The solvent was evaporated to afford quantitatively aldehyde **1** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 6 H, CH_3Si), 0.90 (s, 9 H, CH_3C), 1.80–1.91 (m, 1 H, H-5), 2.13 (ddd, *J* = 14.0, 4.2, 4.2 Hz, 1 H, H-5), 2.55–2.70 (m, 2 H, H-3), 4.37 (m, 1 H, H-4), 5.07 (dd, *J* = 11.3, 3.9 Hz, 1 H, H-6), 9.83 (s, 1 H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9 (CH_3Si), 17.9 (CCH_3), 25.6 (CH_3C), 31.4, 39.6, 63.0, 79.2, 167.9 (C-2), 199.3 (CHO). IR (NaCl): ν = 1739, 1697 cm^{-1}. $[\alpha]_D^{20}$ –12.2 (*c* 1, $CHCl_3$). MS (ES^+): *m/z* (%) = 517.3 (20) $[2 M + H]^+$, 259.1 (100) $[M + 1]^+$, 246.1 (11), 233.1 (15), 221.1 (31), 205.1 (34), 183.1 (9), 169.1 (16), 153.1 (14), 129.1 (33), 127.0(27). HRMS ($TOFMS^+$): *m/z* calcd for $C_{12}H_{22}O_4Si^+$ $[M + H]^+$: 259.1366; found: 259.1366.

(27) β-Substituted δ-lactone ring is unstable and readily undergoes elimination to unsaturated compounds. For example, see ref. 13, 18.

(28) Sabitha, G.; Sudhakar, K.; Srinivas, C.; Yadav, J. S. *Synthesis* **2007**, 705.

(29) **(4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-styryltetrahydro-2*H*-pyran-2-one (7)**
Benzyltriphenylphosphonium bromide (0.130 g, 3.00 mmol) was dissolved in dry toluene (70 mL) and NaHDMS (5.25 mL, 3.15 mmol, 0.6 M in toluene) was added at r.t. The reaction mixture was stirred at r.t. for 2.25 h to give ylide **6**. Then the solution of ylide **6** was warmed up to 65 °C within 10 min. At this temperature a solution of pre-dried aldehyde **1** (853 mg, 3.30 mmol) in toluene (25 mL), prepared from hydrate **4** (913 mg, 3.30 mmol) and toluene, was added. The resulting reaction mixture was stirred at 65 °C for 5 min quenched with EtOH and allowed to cool down to r.t. The solvent was evaporated, and the residue was subjected to flash chromatography with ARMEN INSTRUMENT Spot® apparatus on SiO_2 [gradient elution; EtOAc–hexane (3:97) over 10 min; from 3:97 to 5:95 over 15 min, from 5:95 to 15:85 over 10 min, and from 15:85 to 100:0 over 5 min; flow rate 60 mL/min] to obtain a mixture of (*E*)-**7**/(*Z*)-**7** in the ratio of 63:37 (740 mg, 74%). For analysis, the isomers were separated by the second flash chromatography under the same conditions as described above.

Data for Compound (*E*)-7
White solid; mp 57.5 °C (DSC onset). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, CH_3Si), 0.81 (s, 9 H, CH_3C), 1.73–1.82 (m, 1 H), 1.87–1.95 (m, 1 H), 2.48–2.61 (m, 2 H), 4.22–4.29 (m, 1 H), 5.21–5.28 (m, 1 H), 6.12 (dd, *J* = 6.4, 15.9 Hz, 1 H), 6.59 (d, *J* = 15.9 Hz, 1 H, CHPh), 7.14–7.32 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 (CH_3Si), –4.9 (CH_3Si), 17.9, 25.6, 36.9, 39.3, 63.4, 76.1, 126.6, 126.8, 128.1, 128.6, 132.0, 135.9, 169.8. IR (NaCl): ν = 2927, 1727, 1348, 1233, 1165, 1090, 1072, 693 cm^{-1}. HRMS (CI^+): *m/z* calcd for $C_{15}H_{19}O_3Si^+$ $[M - C_4H_9]^+$: 275.1104; found: 275.1110.

Data for Compound (*Z*)-7
White solid; mp 65.8 °C (DSC onset). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, CH_3Si), 0.81 (s, 9 H, CH_3C), 1.80–2.00 (m, 2 H), 2.52–2.69 (m, 2 H), 4.29–4.35 (m, 1 H), 5.64–5.76 (m, 2 H), 6.67 (d, *J* = 10.5 Hz, 1 H, CHPh), 7.22–7.36 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 (CH_3Si), –5.0 (CH_3Si), 17.8, 25.5, 36.6, 39.2, 63.6, 72.4, 127.6, 128.4, 128.5, 129.0, 133.0, 135.7, 169.8. IR (NaCl): ν = 2927, 1737, 1359, 1239, 1160, 1084, 1065, 697 cm^{-1}. HRMS (CI^+): *m/z* calcd for $C_{15}H_{19}O_3Si^+$ $[M - C_4H_9]^+$: 275.1104; found: 275.1110.