A New Synthesis of an Important Prostaglandin Intermediate by Selective Oxidation of a Trimethylsilylated Primary Alcohol to the Corresponding Aldehyde

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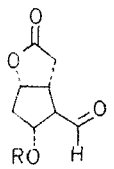
The bis(trimethylsilyl) ether of the prostaglandin precursor rac-**3** was oxidized with high selectivity to the trimethylsilylated Corey aldehyde rac-**1f** using Collins reagent (chromium(VI) oxide/pyridine) in dichloromethane. This unstable compound was subjected without isolation to a twophase Horner olefination by adding the dimethyl phosphonate **4** and concentrated aqueous sodium hydroxide to the oxidation mixture. Thus, the prostaglandin intermediate *rac*-**5** was obtained in a yield of 35–40% in a convenient one-pot procedure.

The aldehydes **1a**,[1-3] **1b**,[4,6] **1c**,[7-10] **1d**,[11,12] and **1e**[13] are key intermediates in one of the most frequently applied strategies for the synthesis of prostaglandins.[1] When the easily available diol **2**[13] is used as a precursor of these aldehydes the problem of the selective oxidation of a primary alcohol to an aldehyde in the presence of a secondary hydroxy group has to be solved.

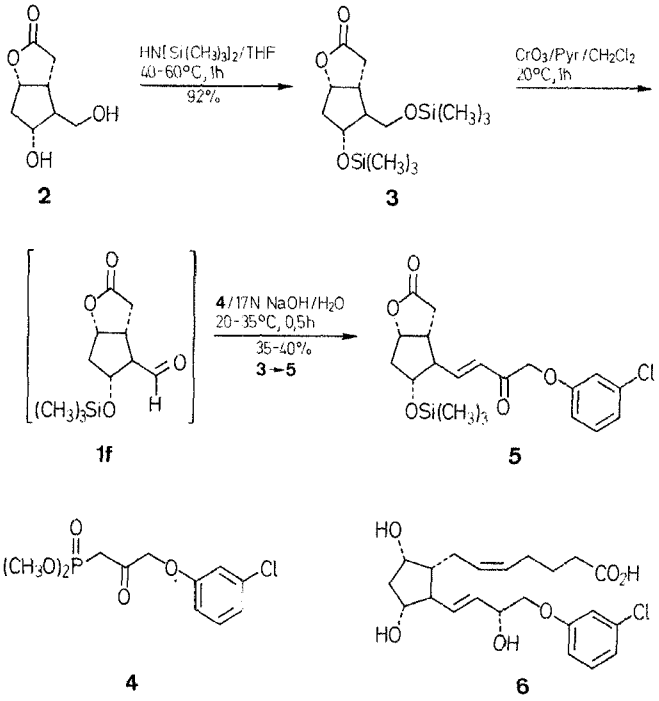


1a-e

1	R
a	CH_3CO
b	C_6H_5CO
c	4-$C_6H_5C_6H_4CO$
d	
e	H

This can be accomplished by oxidants such as thioanisole/chlorine[13] or dicyclohexylcarbodiimide/dimethyl sulfoxide.[13] $RuCl_2(PPh_3)_2$[14] or cyclohexanone/Cp_2ZrH_2[15] also may be suitable reagents for this purpose. The selectivity of commonly used chromium(VI) compounds, however, is too low and, in most cases, secondary hydroxy groups are oxidized preferentially.[14,16] The favored route from the diol **2** to aldehydes of structure **1** consists in a multistep procedure starting with a selective protection of the primary hydroxy group followed by a different protection of the secondary one. Then the primary hydroxy group is deprotected and, finally, oxidized to an aldehyde.[13]

Recently, we have found that bis(trimethylsilyloxy) compounds derived from diols with a primary and a secondary hydroxy group can be oxidized selectively to the corresponding trimethylsilyloxy aldehydes.[17] Herein we report the application of this procedure to the synthesis of the trimethylsilylated Corey aldehyde *rac*-**1f** and its transformation into the α,β-unsaturated ketone *rac*-**5**, an important intermediate[18] in the synthesis of cloprostenol **(6)**, a prostaglandin derivative used in veterinary medicine.



2 **3** **1f** **5** **4** **6**

The diol *rac*-**2** was converted into the bis(trimethylsilyl) ether *rac*-**3** by treatment with hexamethyldisilazane in tetrahydrofuran. The reaction of this compound with Collins reagent in dichloromethane at 20 °C for 1 hour afforded after work-up the aldehyde *rac*-**1f** as an oil. Due to its instability, this crude product was used immediately for further transformations such as the aldol reaction with heptan-2-one[19] or the Reformatsky reaction with hept-2-yn-1-yl zinc bromide.[20] For a Horner olefination, the aldehyde *rac*-**1f** can be used without isolation from the reaction mixture. In this case the selective oxidation of the bis(trimethylsilyl) ether of *rac*-**3** and the subsequent olefination are advantageously performed in a one-pot procedure. For example, the addition of the dimethyl phosphonate **4**[21] and concentrated aqueous solution of sodium hydroxide to the reaction mixture, obtained from the oxidation of *rac*-**3** with

Collins reagent in dichloromethane, afforded the cloprostenol intermediate *rac*-**5** in the form of colorless crystals. An overall yield of 35–40% related to the silyl ether *rac*-**3** documents the efficiency of this procedure.

(1*SR*,5*RS*,6*SR*,7*RS*)-7-Trimethylsilyloxy-6-trimethylsilyloxymethyl-2-oxabicyclo[3.3.0]octan-3-one (*rac*-3):
Hexamethyldisilazane (322.8 g, 2 mol) is added slowly at 40 °C to a solution of the diol *rac*-**2**[13] (172 g, 1 mol) in THF (500 mL). The mixture is stirred for 1 h at 40–60 °C and then concentrated under reduced pressure affording crude *rac*-**3** as an oil.

Distillation yields the product in pure form;
yield: 291 g (92%); b.p. 152 °C/4 mbar; m.p. 24–26 °C.

$C_{14}H_{28}O_4Si_2$	calc.	C 53.12	H 8.91
(316.5)	found	53.20	8.80

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.40 (d, 2H, J = 7 Hz, CH_2OSi); 4.0 (q, 1H, J = 5.5 Hz, CHOSi); 4.83 (m, 1H, CH–O–CO).

(1*SR*,5*RS*,6*RS*,7*RS*)-7-Trimethylsilyloxy-3-oxo-2-oxabicyclo[3.3.0]octane-6-carbaldehyde (*rac*-1f):
Carefully dried chromium(VI) oxide (6.0 g, 60 mmol) is added with vigorous stirring to a solution of absolute pyridine (8.1 g, 100 mmol) in thoroughly purified CH_2Cl_2 (200 mL). The solution obtained is agitated at 20 °C for 1 h. Subsequently, a solution of the bis(trimethylsilyl) ether of *rac*-**3** (3.2 g, 10 mmol) in purified CH_2Cl_2 (20 mL) is added and stirring is continued for a further hour. Thereafter the reaction mixture is filtered and the filter cake is washed with CH_2Cl_2 (2 × 30 mL). The combined filtrates are extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL) and NH_4Cl (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure at a bath temperature below 25 °C, yielding crude aldehyde *rac*-**1f** as an oil (2.1 g). This is used immediately for further reactions. R_f = 0.48 (hexane/Et_2O/CH_2Cl_2, 2:3:4).

(1*SR*,5*RS*,6*RS*,7*RS*)-6-[4-(3-Chlorophenoxy)-3-oxo-1(*E*)-butenyl]-7-trimethylsilyloxy-2-oxabicyclo[3.3.0]octan-3-one (*rac*-5):
According to the foregoing procedure, the aldehyde *rac*-**1f** is prepared by addition of the bis(trimethylsilyl) ether of *rac*-**3** (62.8 g, 0.2 mol) dissolved in CH_2Cl_2 (100 mL) to a solution of Collins reagent prepared from chromium(VI) oxide (160.0 g, 1.6 mol) and pyridine (252.0 g, 3.2 mol) in CH_2Cl_2 (3000 mL). All solvents have to be carefully purified and dried. After vigorous agitation for 1 h at 20 °C, TLC indicates the absence of the bissilyl ether of *rac*-**3**. Then dimethyl 3-(3-chlorophenoxy)-2-oxopropylphosphonate **4**[21] (43.8 g, 0.15 mol) is added in one portion to the oxidation mixture followed by the addition of a 17 normal aqueous solution of NaOH (188 mL, 3.2 mol) within 10 min at 20–35 °C. The reaction mixture is filtered 20 min after complete addition. The filtrate is washed with water (3 × 300 mL, dried (Na_2SO_4), and concentrated in vacuo. Remaining traces of pyridine are removed by addition of toluene (3 × 100 mL) and evaporation under reduced pressure. The residue is dissolved in toluene (200 mL) and filtered through Al_2O_3. The Al_2O_3 is washed with toluene (500 mL). The combined filtrates are concentrated *in vacuo*. The residue is recrystallized from EtOAc/*n*-hexane; yield: 28 g (35%); m.p. 77–79 °C.

$C_{20}H_{25}ClO_5Si$	calc.	C 58.73	H 6.16	Cl 8.67
(409.0)	found	58.50	6.38	8.92

^{1}H-NMR ($CDCl_3$/TMS): δ = 4.10 (t, 1H, J = 7 Hz, CHOSi); 4.70 (s, 2H, CH_2O); 4.96 (m, 1H, CH–O–CO); 6.48 (d, 1H, J = 16 Hz, =CH–CO); 6.70–7.30 (m, 5H, arom. and –CH=CH–CO).

^{13}C-NMR ($CDCl_3$/TMS): δ = –0.52 (q, $(CH_3)_3Si$–); 34.02 (t, C-8); 41.10 (t, C-4); 41.77 (d, C-6); 56.78 (d, C-5); 71.80 (t, $-CH_2O$–); 76.82 (d, C-7); 82.30 (d, C-1); 113.67 (d, C_{arom}-6); 115.12 (d, C_{arom}-2); 121.39 (d, C_{arom}-4); 127.40 (d, =CH–CO); 130.82 (d, C_{arom}-5); 134.54 (s, C_{arom}-3); 147.11 (d, –CH=CH–CO); 159.41 (s, C_{arom}-1); 175.98 (s, C-3); 193.75 (s, C=O).

MS (70 eV): m/e = 408 (M^+), 393, 378, 318, 267, 177.

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