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A NEW PROCEDURE FOR HOMOLOGATION OF CARBONYL COMPOUNDS TO α-HYDROXY-CARBOXYLIC ESTERS BY MEANS OF DIETHYL-[TRIMETHYLSILYLETHOXYMETHYL]PHOSPHONATE

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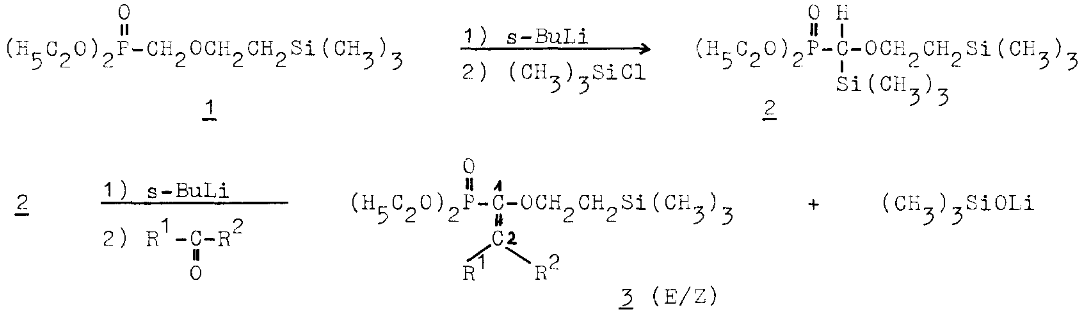
Summary: A synthesis of α-hydroxyesters 5 using the Peterson olefination of the α-trimethylsilyl-substituted phosphonate 2 to vinylphosphonates 3 followed by hydroxylation with catalytical amounts of OsO_4 has been developed.

Among numerous methods[1)] for the conversion of aldehydes and ketones to homologous carboxylic acids the Wittig-Horner procedure with suitable α-substituted phosphonates is most important[2)]. The remarkable fact that O,O-dialkylacetals of formylphosphonates cannot be lithiated even if t-BuLi is used[2c)], was the reason for the development of dialkoxymethyl diphenylphosphinoxides as homologation reagents[3)]. Another possibility for stabilizing carbanionic centres of an alkoxymethyl-phosphonate should be the additional introduction of a trimethylsilyl group at the α-C-atom. In this case the Peterson olefination should be preferred to the Wittig-Horner olefination[4)].

In this paper we report on a suitable derivative of the title reagent 1[5)] which can be employed for a homologation procedure leading to one carbon elongated carboxylic esters furnished with an additional α-hydroxy group.



$$(H_5C_2O)_2\overset{O}{\overset{\|}{P}}\text{-}CH_2OCH_2CH_2Si(CH_3)_3 \xrightarrow[2)\ (CH_3)_3SiCl]{1)\ s\text{-}BuLi} (H_5C_2O)_2\overset{O}{\overset{\|}{P}}\text{-}\underset{Si(CH_3)_3}{\overset{H}{C}}\text{-}OCH_2CH_2Si(CH_3)_3$$

$$2 \xrightarrow[2)\ R^1\text{-}\underset{O}{\underset{\|}{C}}\text{-}R^2]{1)\ s\text{-}BuLi} (H_5C_2O)_2\overset{O}{\overset{\|}{P}}\text{-}\overset{1}{C}(=\overset{2}{C}R^1R^2)\text{-}OCH_2CH_2Si(CH_3)_3 + (CH_3)_3SiOLi$$

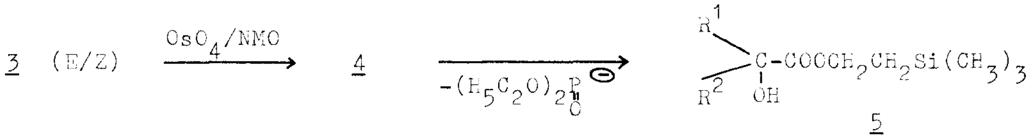
Scheme 1

Phosphonate 1 is transferred to its α-trimethylsilyl-derivative 2[6)] (70%) using the inverse strategy[7)] of adding the carbanion of 1 to $(CH_3)_3SiCl$ in order to avoid disilylation.

In contrast to the instability of the phosphonate carbanion of 1 even at

-70°C, the carbanion of phosphonate 2 is much more stable because of the stabilizing effect of the α-trimethylsilyl group. A sample prepared by deprotonation of 2 with s-BuLi at -30°C, shows a 99% incorporation of deuterium at the α-C-atom after having quenched the carbanion with D_2O after 30 min.

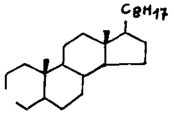
The Peterson olefination of 2 yields 1-(2-trimethylsilyl)ethoxy-vinylphosphonates 3 as E/Z mixtures (Scheme 1). Vinylphosphonates 3 represent starting materials not only for homologous carboxylic acids[8], but also for the more useful preparation of the homologous α-hydroxy-carboxylic acids. Hydroxylation of 3 with OsO_4-N-methylmorpholin-N-oxide (NMO)[9] leads via the non-isolable diastereomeric mixture of 1,2-dihydroxyphosphonates 4 (not drawn in Scheme 2) to esters 5[10] according to the well documented[11] cleavage of α-hydroxyphosphonates into carbonyl compounds and dialkylphosphite (Scheme 2). Other methods concerning the transformation of carbonyl compounds into homologous α-hydroxy acids are listed in lit.cit. 1.



Scheme 2

An interesting detail is the appearance of the 2-trimethylsilylethyl residue in 5, a selectively removable carboxyl protecting group[12]. The following Table summarizes some characteristic data and observations of phosphonates 3 and α-hydroxyesters 5.

Table

	Phosphonate 3[i] R^1	R^2	b.p. [°C]*	Yield [%]	α-Hydroxyester 5 b.p. [°C] (mm Hg) or m.p. [°C]	Yield [%]
a	$-(CH_2)_5-$ [ii]		90-95	88	b.p. 100-105 (2mm)	55
b			non crystallized	85	m.p. for the C-3 isomers 95-97[iv] 108-111	85
c	$-CH(CH_3)_2$	H	65-75	61	not distilled	50
d	p-MeO-Ph	H	115-125	80	b.p. 85-90 (0.001)	40[iii]
e	m-MeO-Ph	H	110-120	77	b.p. 80-83 (0.005)	40[iii]
f	Ph	CH_3	100-105	40	b.p. 60-65 (0.005)	25

* bulb to bulb distillation (0.001 mm Hg)

i) The E/Z ratio for compounds 3a-3f is approximately 1/1

ii) Diethyl-[(2-trimethylsilyl)ethoxy-cyclohexyliden-methyl]phosphonate 3a
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.00 (s, 9H, $SiMe_3$), 1.03 (m, 2H, CH_2SiMe_3), 1.33 (t, 6H, J=7.2 Hz, $2xOCH_2CH_3$), 1.58 (bs, 6H, $-(CH_2)_3-$), 2.32 (bs, 2H, two allylic protons), 2.58 (bs, 2H, remaining two allylic protons), 3.72 (m, 2H, $-OCH_2CH_2$), 4.093 and 4.1 (quint. and quint., 2H and 2H, 2x $-OCH_2CH_3$).
The spectral properties of compounds 3b-3f are fully in agreement with the indicated structure. The ^{1}H-NMR patterns of 3b-3f are more complicated because of E/Z mixtures.

iii) Starting aldehyde was isolated too (25-30%).

iv) Both C-3 isomers, (3RS)-3-hydroxy-cholestanic-3-carboxylic acid-(2-trimethylsilyl)-ethylester, could be obtained in pure form after chromatography (petroleum ether/ethyl acetate = 20/1); their ^{1}H-NMR spectra exhibit no real differences; a stereochemical assignment of both isomers using the shift reagent $Eu(dpm)_3$ was impossible.

References and Notes

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6) Diethyl-[(2-trimethylsilyl)ethoxy-trimethylsilyl-methyl] phosphonate 2:
To a solution of 1.2 equiv. of s-BuLi in 30 ml dry THF was added phosphonate 1 (5g, 18.6 mmol) in THF (10 ml) at -78°C under argon atmosphere. After stirring for about 30 min. at -78°C, the solution of the anion was added by cannula and argon pressure to a solution of an excess trimethylsilylchloride (28 mmol) in dry THF (10 ml) at -78°C. The reaction mixture was warmed to room temperature and poured into a saturated aqueous solution of NH_4Cl. Crude 2 was purified by flash chromatography (CH_2Cl_2/ethyl acetate ~10/1) and distillation to give a colourless liquid: B.p. 90-95°C (0.001 mm); yield: 70%. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.00 (s,9H, $SiMe_3$), 0.13 (s, 9H, $SiMe_3$), 0.90-0.95 (m, 2H, CH_2SiMe_3), 1.30 and 1.31 (t and t, 3H and 3H, J=7.3 Hz, 2x OCH_2CH_3), 3.23 (d, J_{HP}=14.6 Hz, 1H, $CHSiMe_3$), 3.37-3.98 (m, 2H, OCH_2CH_2-), 4.10 and 4.11 (quint. and quint., 2H and 2H, $J_{HH}=J_{HP}$=7.3 Hz, $2xOCH_2CH_3$).

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8) These results will be published soon.

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10) General Procedure for the Conversion of 3 → 5:
To vinylphosphonates 3 (0.80 mmol) in THF/acetone/water = 9/1/1 were added about 30 mg OsO_4 (THF solution) and 3.3 equiv. of N-methylmorpholin-N-oxide. Temperature (25°-70°C) and the period for stirring varied with the nature of the substituents R^1, R^2 of 3. When compound 3 was completely consumed (T.L.C.) sodium hydrosulfite, Florisil (60-100 mesh; Sigma Chemical Company) and water were added. After stirring and a short-path filtration (celite) followed an extraction with chloroform/ethyl acetate. Compounds 5 were chromatographed and often further purified by distillation.

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