2-(1,3-Dioxan-2-yl)-ethylidenetriphenylphosphorane, A New Three-Carbon Homologating Agent

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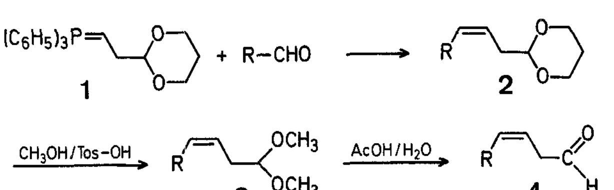
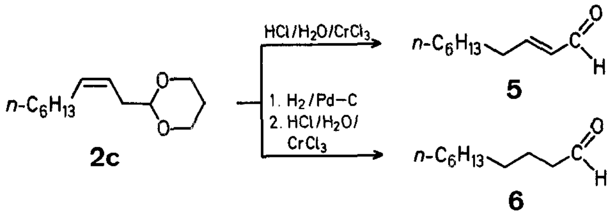
Several organometallic reagents are available for extending carbon chains by three carbons with an aldehyde function at the new terminus[1–6]. We wish to introduce a convenient new reagent for this purpose which also offers the alternatives of providing α,β- or β,γ-unsaturation as well. We have found that the Wittig reagent **1** derived from the readily available 2-(2-bromoethyl)-1,3-dioxane is thermally stable[7], and reacts with aldehydes to give cyclic acetals of *cis*-3-alkenals (**2**) in yields up to 76%. The stereoselectivity is greater than 95% when the phosphorane **1** is generated using potassium *t*-butoxide[8].



a R = C_2H_5
b R = n-C_4H_9
c R = n-C_6H_{13}
d R = n-C_8H_{17}

Certain *cis*-3-alkenals are common volatile flavor constituents in foods. The earlier general, but lengthy synthetic routes to these compounds are based on chain extension of *cis*-2-butenediol[9,10], or of butadiyne via 1-methoxy-1-butene-3-yne[11]. *trans*-3-Alkenals have been prepared using methoxycyclopropyllithium[12]. We have prepared free *cis*-3-alkenals (**4**) from their 1,3-propanediol acetals (**2**) by a two-step process. The six-membered ring acetal has a high equilibrium stability such that simple acid hydrolysis is unfavorable. However, trans-acetalization in acidic methanol gives the dimethyl acetal **3** in high yield without isomerization of the β,γ-unsaturation. The dimethyl acetal can then be hydrolyzed at room temperature in aqueous acetic acid to give the *cis*-3-alkenal **4** containing none of the α,β-unsaturated isomer[13,14] (2-alkenal). The product is quite sensitive to heat. For instance, simple steam distillation of *cis*-3-decenal caused rapid isomerization to the α,β-unsaturated isomer. If the stable 2-alkenals (e.g. **5**) are desired, the cyclic acetals **2** may be hydrolyzed with concomitant isomerization[15] using hot aqueous acid plus chromium(III) chloride to complex the diol[16].

Finally, the saturated aldehydes (e.g. **6**) may be obtained by hydrogenation of **2** followed by hydrolysis again using aqueous acid plus chromium(III) chloride.



For the α,β-unsaturated and the saturated aldehydes, a mixture of *cis* and *trans* Wittig products is suitable. This is made conveniently using butyllithium in tetrahydrofuran. This mixture was used also for comparisons to show the exclusive *cis* nature of the products **2** above. The *cis*/*trans* isomer ratio in the cyclic acetals can be estimated by examination of the 100 MHz ^{1}H-N.M.R. signal (triplet) for the acetal proton at δ≈4.5 ppm. The signal of the *trans* isomer appears 0.025 ppm upfield from the *cis* signal. The configurational assignment is based on ^{13}C-N.M.R. spectra where the signals of the allyl C atoms in *cis*-**2b** appear 4.5 and 7.1 ppm upfield from the signals of the corresponding *trans* isomer[17]. Also, the *cis* isomer is normally expected from a Wittig reaction in the absence of lithium salts[8].

2-(2-Bromoethyl)-1,3-dioxane:

An excess of hydrogen bromide is bubbled into a solution of acrolein (56 g, 1.0 mol) in dichloromethane (300 ml) at room temperature. Excess hydrogen bromide is removed with a stream of nitrogen. 1,3-Propanediol (76 g, 1.0 mol) and *p*-toluenesulfonic acid hydrate (1 g) are added to the crude 3-bromopropanal and the mixture is stirred under nitrogen for 8 h. The resulting solution is neutralized with saturated sodium hydrogen carbonate, washed with water, and dried with potassium carbonate. The solvent is evaporated and the residual product distilled in vacuo; yield: 155 g (80%); b.p. 68–70°/3 torr (Ref. [18], b.p. 68–74°/4.8 torr).

2-(1,3-Dioxan-2-yl)-ethyltriphenylphosphonium Bromide:

A solution of 2-(2-bromoethyl)-1,3-dioxane (94.1 g, 0.482 mol) and triphenylphosphine (200 g, 0.762 mol) in cyclohexane (250 ml) is heated at reflux with stirring for one day. The resulting solid is ground to a powder, washed with ether and then pentane (1000 ml each), and dried under vacuum; yield: 212 g (96%); m.p. 205–208°. If seed crystals of the product are added at the beginning of the reaction, the product is more easily isolated.

Table. 2-(*cis*-2-Alkenyl)-1,3-dioxanes (**2**):

2	R	Yield [%]	b.p./torr	Molecular formula[a]	^{1}H-N.M.R. δ [ppm]
a	C_2H_5	41	31–34°/0.4	$C_9H_{16}O_2$ (156.2)	(60 MHz, CCl₄): 0.93 (t, 3H); 1.32 (m, 1H); 1.8–2.3 (m, 5H); 3.3–4.2 (m, 4H); 4.36 (t, 1H); 5.31 (m, 2H)
b[b]	n-C_4H_9	60	103°/4	$C_{11}H_{20}O_2$ (184.3)	(100 MHz, CDCl₃): 0.86 (t, 3H); 1.30 (m, 5H); 1.99 (m, 3H); 2.30 (m, 2H); 3.72 (dt, 2H); 4.03 (dd, 2H); 4.45 (t, 1H); 5.40 (m, 2H)
c	n-C_6H_{13}	72	134°/5	$C_{13}H_{24}O_2$ (212.3)	(60 MHz, CCl₄): 0.88 (t, 3H); 1.30 (m, 7H); 1.8–2.5 (m, 5H); 3.4–4.2 (m, 4H); 4.49 (t, 1H); 5.44 (m, 2H)
d	n-C_8H_{17}	69	140–142°/1.2	$C_{15}H_{28}O_2$ (240.4)	(100 MHz, CDCl₃): 0.85 (t, 3H); 1.22 (m, 13H); 1.99 (m, 3H); 2.30 (m, 2H); 3.66 (dt, 2H); 4.01 (dd, 2H); 4.43 (t, 1H); 5.35 (m, 2H)

[a] The microanalyses of compounds **2a, c, d** were in good agreement with the calculated values: C, ±0.18; H, ±0.14. **2b:** C, −0.42; H, −0.03.

[b] ^{13}C-N.M.R. (25.2 MHz, CDCl₃): δ = 14.0, 22.4, 25.8, 27.2, 31.75, 33.5, 67.0, 102.1, 123.0, 132.6 ppm.

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2-(*cis*-2-Alkenyl)-1,3-dioxanes (2); General Procedure:

A 0.5 molar solution of potassium *t*-butoxide in tetrahydrofuran (100 ml, 50 mmol) is added to a stirred solution of 2-(1,3-dioxan-2-yl)-ethyltriphenylphosphonium bromide (22.8 g, 50 mmol) in dry dimethyl sulfoxide or tetrahydrofuran (50 ml) to give the orange phosphorane **1**. Stirring is continued at room temperature for 30 min and the aldehyde (100 mmol) is added dropwise. The mixture is stirred for 2 h and then poured into water (500 ml). The product is extracted with ether, the extract dried, the solvent evaporated, and the residue distilled in vacuo.

***cis*- and *trans*-2-(2-Alkenyl)-1,3-dioxanes; General Procedure:**

A 1.6 molar solution of butyllithium in hexane (11 ml, 17.5 mmol) is added to a stirred suspension of 2-(1,3-dioxan-2-yl)-ethyltriphenylphosphonium bromide (7.98 g, 17.5 mmol) in dry tetrahydrofuran (50 ml) at −20°. The resultant solution of the orange phosphorane **1** is stirred at −20° for 1 h and then the aldehyde (18 mmol) is added. Stirring is continued for 12 h at room temperature, the mixture is poured into water (500 ml), and extracted with ether. The extract is dried, the solvent evaporated, and the residue distilled in vacuo to give compounds **2a–d** containing up to 40% of the corresponding *trans* isomers; yield: 65–76%.

The ^{13}C-N.M.R. spectrum of 2-(2-heptenyl)-1,3-dioxane thus obtained showed the signals for the *cis* isomer as listed above along with the following peaks for the *trans* isomer: $\delta = 14.1$, 22.3, 31.7, 32.4, 38.9, 102.3, 123.9, 133.6 ppm.

***cis*-3-Decenal Dimethyl Acetal (3c):**

A solution of 2-(*cis*-2-nonenyl)-1,3-dioxane (**2c**; 4.64 g, 21.9 mmol) and *p*-toluenesulfonic acid (0.15 g, 0.8 mmol) in methanol (200 ml) is heated at reflux for 2 h, cooled, and neutralized with anhydrous sodium carbonate. After evaporation of the methanol, the product is taken up in dichloromethane, washed with water, rotary-evaporated, and distilled; yield: 3.83 g (88%); b.p. 109–111°/11 torr (Ref. [11], b.p. 108–110°/14 torr).

^{1}H-N.M.R. (60 MHz, CDCl$_3$): $\delta = 0.9$ (t, 3H); 1.24 (m, 8H); 2.0 (m, 2H); 2.3 (t, 2H); 3.28 (s, 6H); 4.32 (t, 1H); 5.38 ppm (m, 2H).

The N.M.R. shows a trace of cyclic acetal remaining, but if necessary this can be removed by a second treatment with acidic methanol.

***cis*-3-Dodecenal Dimethyl Acetal (3d):**

Prepared as above from **2d** (2.4 g, 0.1 mol); yield: 2.03 g (89%); b.p. 84°/0.4 torr (Ref. [11], b.p. 62–63°/0.001 torr); n_D^{22}: 1.4442 (Ref. [11], n_D^{20}: 1.4446).

^{1}H-N.M.R. (100 MHz, CDCl$_3$): $\delta = 0.86$ (t, 3H); 1.24 (m, 12H); 1.98 (m, 2H); 2.30 (t, 2H); 3.24 (s, 6H); 4.27 (t, 1H); 5.33 ppm (m, 2H).

***cis*-3-Decenal (4c):**

A solution of *cis*-3-decenal dimethyl acetal (**3c**; 1.21 g, 6.05 mmol) in acetic acid (24 ml) and water (6 ml) is stirred at room temperature for 4 h, neutralized with cold saturated sodium hydrogen carbonate, taken up in dichloromethane, and dried with potassium carbonate. The solvent is rotary-evaporated to give **4c** containing a small amount of unhydrolyzed **3c**, but none of the isomeric 2-decenal; yield: 0.683 g (73%).

I.R. (neat): $\nu_{max} = 1730$, 740 cm^{-1}.

^{1}H-N.M.R. (60 MHz, CDCl$_3$): $\delta = 0.9$ (t, 3H); 1.25 (m, 8H); 2.0 (m, 2H); 3.1 (m, 2H); 5.2–5.7 (m, 2H); 9.51 ppm (t, 1H).

***trans*-2-Decenal (5):**

A solution of chromium(III) chloride hexahydrate (2.6 g, 9.8 mmol) in 4 molar hydrochloric acid (75 ml) is added to 2-(*cis*-2-nonenyl)-1,3-dioxane (**2c**; 0.59 g, 2.8 mmol), the mixture is heated at reflux for 15 min, and then steam-distilled. The wet mixture of 2-decenal and 3-decenal thus obtained is added to 4 molar hydrochloric acid (75 ml), the mixture is heated at reflux for 30 min, and then steam-distilled. The distillate is extracted with pentane, the extract is dried with potassium carbonate; and rotary evaporated; yield of **5** (homogeneous by G.L.C.): 0.37 g (86%); semicarbazone, m.p. 167° (Ref. [19], m.p. 168.5°).

^{1}H-N.M.R. (60 MHz, CDCl$_3$): $\delta = 0.8$ (t, 3H); 1.2 (m, 10H); 2.2 (m, 2H); 5.90 (ddt, 1H); 6.72 (dt, 1H); 9.30 ppm (d, 1H).

Decanal (6):

2-Nonyl-1,3-dioxane: A solution of 2-(*cis*-2-nonenyl)-1,3-dioxane (**2c**; 0.68 g, 3.2 mmol) in ethanol (40 ml) is hydrogenated over 5% palladium on carbon (4.9 mg) at 1 atm for 25 min. The resultant mixture is filtered and evaporated; yield: 0.68 g (99%); b.p. 99–100°/0.6 torr.

Decanal (**6**): A solution of chromium(III) chloride hexahydrate (15.6 g, 58.5 mmol) in 4 molar hydrochloric acid (100 ml) is added to 2-nonyl-1,3-dioxane (2.59 g, 12.1 mmol), the mixture is heated at reflux for 15 min, and then steam-distilled. The distillate is extracted with pentane, the extract is dried with potassium carbonate and evaporated to give **6**; yield: 1.75 g (92%); semicarbazone, m.p. 102° (Ref. [19], m.p. 102°).

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