Two-Carbon Chain Extension of Chiral Aldehydes via 2-Alkenylthiazoles: Synthesis of γ-Functionalized Alkanals

Alessandro Dondoni,* Pedro Merino, Jesus Orduna, Daniela Perrone
Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy

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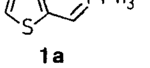
The reaction of 2-thiazolylmethylenetriphenylphosphorane (**1a**) in benzene with various aldehydes gives 2-alkenylthiazoles in variable *E*/*Z* ratios. Application of the thiazole-to-formyl deblocking protocol to the mixture of the olefins leads to saturated aldehyde homologues having two more carbon atoms.

The thiazole to formyl equivalence[1] makes the thiazole armed ylid **1a** a convenient surrogate of the formylmethylene phosphorane **1b** for the two-carbon chain extension of aldehydes via Wittig olefination. The reagent **1a** which can be prepared in multigram quantities from the now readily available 2-formylthiazole,[2] has been employed in synthetic routes to biologically active carbohydrates.[1] In one of these routes, the reduction of the ethylenic double bond taking place in the course of the aldehyde releasing sequence, was exploited for the synthesis of dideoxy sugars.[3] We now report the application of this reductive two-carbon homologation sequence to various chiral aldehydes **2** to give synthetically useful functionalized saturated homologues **4**.



1a

$Ph_3P{=}CH{-}CHO$

1b

Recent reports from different laboratories have described the use of chiral γ-functionalized alkanals[4] and alcohols[5] as convenient building blocks for the construction of complex molecular arrays. Selected chiral alkoxy- and *N*-protected amino aldehydes **2a–j** available in our laboratory from previous work,[6] were converted into the corresponding homologues **4a–j** (Scheme 1).

The results of Table 1 indicate that in all cases examined the Wittig olefination of the aldehydes **2** with the phosphorane **1a** leads to the corresponding alkenylthiazoles **3** in good yields although with variable *E*/*Z* selectivity.[7] This was not surprising in view of the semistabilized nature of this ylid.[8] Also the subsequent step involving the aldehyde liberation from the thiazole ring and concomitant carbon–carbon double bond reduction, transformed **3** into the saturated aldehyde homologue **4** in good overall yield. The aldehyde **4a** and the alcohol **5b** obtained by reduction of **4b** (Scheme 2), showed specific rotation values in good agreement with the literature data,[5] thus indicating that no substantial racemization occurs in reactants and products. The same conclusion is likely to hold also in the other cases of Table 2.

In summary, we have presented a convenient and straightforward method to prepare functionalized alkanals of type **4** using readily available and inexpensive reagents.

The ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Gemini 300 Varian spectrometer, unless otherwise stated, using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer. Elemental analyses were performed on a Model 1106 microanalyzer (Carlo Erba). Optical rotations were measured at 20 °C using a Perkin-Elmer Model 214 polarimeter. Preparative chromatography were done on columns of

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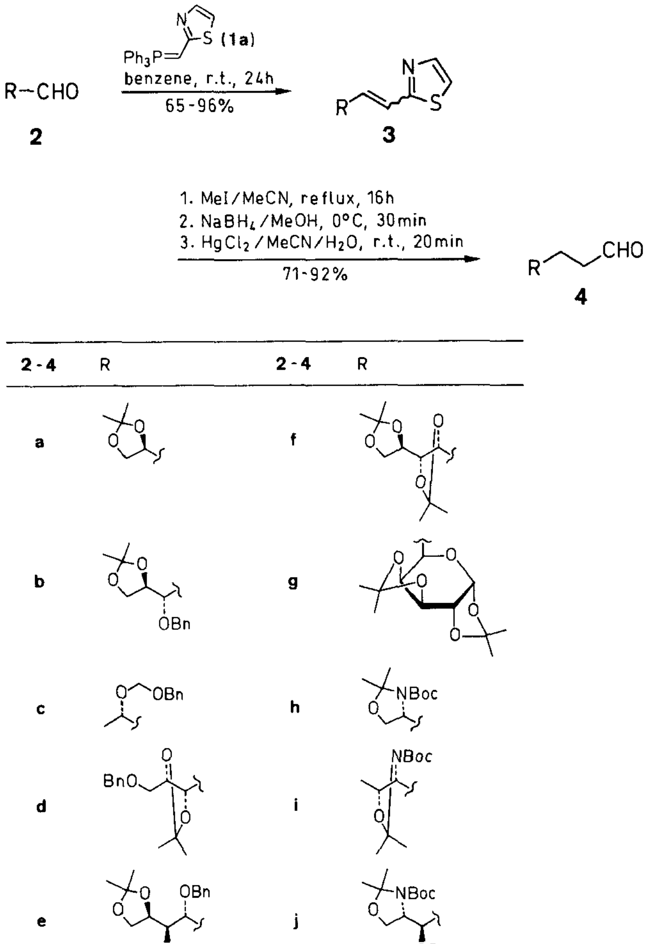
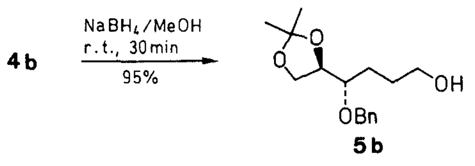


Bn = CH_2Ph; Boc = CO_2Bu-*t*

Scheme 1



Scheme 2

Table 1. 2-Alkenylthiazoles **3** Prepared

Product	Yield (%)[a]	*E* : *Z*[b]
3a	89	56 : 44
3b	80	75 : 25
3c	65	90 : 10
3d	95	60 : 40
3e	89	52 : 48
3f	96	88 : 12
3g	85	28 : 72
3h	85	≥ 95 : 5
3i	88	≥ 95 : 5
3j	82	≥ 95 : 5

[a] Isolated yields.

[b] Determinated by ^1H NMR.

silica gel (Merck 70–230 mesh). All experiments were carried out with freshly distilled and dried solvents.

2-Alkenythiazoles (3); General Procedure:

A well stirred suspension of 2-thiazolylmethylenetriphenylphosphonium chloride[2] (792 mg,2 mmol) or bromide[9] (880 mg, 2 mmol) in anhydrous benzene (25 mL) was treated with KOBu-*t* (224 mg, 2 mmol) and the mixture was stirred at r.t. for 3 h. To the yellow-orange solution of the phosphorane **1 a** formed was added the aldehyde **2** (2 mmol) in benzene (15 mL) and stirring was continued for 24 h. The mixture was quenched with hexane (30 mL) and the suspension was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue chromatographed through a short column of silica gel (hexane/Et_2O, 80 : 20) to give the alkenes **3** as a mixture of *E*- and *Z*-isomers (Table 1). The compounds **3** were used without purification in the next step.

Aldehydes (4); General Procedure:

A solution of the olefin **3** (1 mmol) and MeI (1.42 g, 10 mmol) in MeCN (50 mL) was refluxed for 16 h. The solvent was removed under reduced pressure and the residue dissolved in MeOH (50 mL). To the solution cooled at 0 °C, was added $NaBH_4$ (76 mg, 2 mmol) in small portions. The mixture was stirred for 30 min, concentrated in vacuum and partitioned between Et_2O (30 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and the solvent distilled. The residue was dissolved in MeCN (5 mL) and added to a solution of $HgCl_2$ (271 mg, 1 mmol) in MeCN/H_2O 4 : 1 (25 mL). The mixture was stirred at r.t. for 20 min and then filtered through Celite. The solvent was partially distilled under reduced pressure and the residue was dissolved in Et_2O (25 mL) and washed with sat. aq KI (2 x 25 mL). The organic phase was dried (Na_2SO_4) and the solvent distilled to give the crude aldehyde **4** which was purified by chromatography (silica gel, hexane/Et_2O, 85 : 15) (Table 2).

2,3-Dideoxy-5,6-*O*-(1-methylethylidene)-4-*O*-benzyl-D-*erythro*-hexitol (5b):

To a solution of **4b** (200 mg, 0.72 mmol) in MeOH (10 mL), was added slowly $NaBH_4$ (84 mg, 2.2 mmol) and stirred for 30 min at r.t. The solvent was distilled at reduced pressure and the residue partitioned between brine (20 mL) and CH_2Cl_2 (20 mL). The separated organic phase was dried (Na_2SO_4) and the solvent distilled in vacuo to give the crude alcohol which after purification by column chromatography (silica gel, hexane/Et_2O, 40 : 60) furnished pure **5b**; yield: 192 mg (95 %); oil: $[\alpha]_D^{20}$ + 17.9° ($c = 2.7$, $CHCl_3$) [Lit.[5], + 16.2° ($c = 2.1$, $CHCl_3$)].

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Table 2. Aldehydes **4** Prepared

Product	Yield[a,b] (%)	$[\alpha]_D^{20}$ (*c*, solvent)	Molecular Formula[c] or Lit. $[\alpha]_D$	^1H NMR ($CDCl_3$/TMS) (300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (75.5 MHz) δ
4a	75	−1.0° (0.92, CH_2Cl_2)	−0.95° (*c* = 1.42, CH_2Cl_2)[4a]	1.33 (s, 3H), 1.40 (s, 3H), 1.90 (m, 2H), 2.60 (m, 2H), 3.56 (dd, 1H, *J* = 7.8, 6.6), 4.06 (dd, 1H, *J* = 7.8, 6.1), 4.13 (dddd, 1H, *J* = 6.6, 6.1, 4.6, 4.0), 9.82 (m, 1H)	25.23, 25.72, 26.57, 39.82, 69.02, 74.85, 109.30, 201.19
4b	80	+20.3° (0.61, $CHCl_3$)	$C_{16}H_{22}O_4$ (278.3)	1.35 (s, 3H), 1.42 (s, 3H), 1.84 (m, 1H), 1.98 (m, 1H), 2.58 (m, 2H), 3.47 (ddd, 1H, *J* = 6.8, 5.8, 3.9), 3.86 (m, 1H), 4.07 (m, 2H), 4.55 (d, 1H, *J* = 11.2), 4.60 (d, 1H, *J* = 11.2), 7.32 (m, 5H), 9.83 (m, 1H)	23.09, 24.98, 26.33, 34.14, 66.61, 72.60, 72.29, 78.24, 109.51, 128.19, 128.31, 128.79, 138.43, 202.73
4c	77	+9.7° (1.08, $CHCl_3$)	$C_{13}H_{18}O_3$ (222.3)	1.19 (d, 1H, *J* = 6.2), 1.83 (m, 2H), 2.51 (m, 2H), 3.79 (pseudo q, 1H, *J* = 6.2), 4.58 (s, 2H), 4.72 (d, 1H, *J* = 7.0), 4.77 (d, 1H, *J* = 7.0), 7.36 (m, 5H), 9.75 (dd, 1H, *J* = 2.3, 1.6)	19.76, 29.00, 39.83, 69.59, 72.36, 93.11, 127.24, 128.03, 128.72, 138.25, 202.85
4d	72	−9.8° (0.42, $CHCl_3$)	$C_{16}H_{22}O_4$ (278.3)	1.32 (s, 3H), 1.34 (s, 3H), 1.77 (m, 1H), 1.92 (m, 1H), 2.56 (m, 2H), 3.50 (dd, 1H, *J* = 10.3, 4.4), 3.56 (dd, 1H, *J* = 10.3, 5.2), 3.79 (m, 2H), 4.53 (s, 2H), 7.28 (m, 5H), 9.73 (pseudo t, 1H, *J* = 2.4)	25.10, 26.64, 26.90, 39.80, 7.37, 73.56, 77.65, 79.59, 109.18, 127.93, 127.97, 128.66, 138.23, 202.25
4e	75	+10.0° (1.19, $CHCl_3$)	$C_{24}H_{30}O_5$ (398.5)	1.33 (s, 3H), 1.40 (s, 3H), 1.95 (m, 2H), 2.42 (m, 2H), 3.40 (pseudo q, 1H, *J* = 5.0), 3.51 (dd, 1H, *J* = 6.3, 5.1), 3.65 (dd, 1H, *J* = 8.5, 7.9), 3.98 (dd, 1H, *J* = 8.5, 6.6), 4.20 (ddd, 1H, *J* = 7.9, 6.6, 6.3), 4.38 (d, 1H, *J* = 11.3), 4.46 (d, 1H, *J* = 11.3), 4.73 (d, 1H, *J* = 11.9), 4.77 (d, 1H, *J* = 11.9), 7.30 (m, 10H), 9.63 (pseudo t, 1H, *J* = 2.0)	22.33, 25.16, 26.03, 39.18, 66.15, 71.65, 73.74, 77.37, 78.51, 79.62, 108.84, 127.67, 127.89, 128.02, 128.14, 128.36, 128.48, 137.90, 138.53, 202.50
4f	71	+15.6° (0.62, $CHCl_3$)	$C_{13}H_{22}O_5$ (258.3)	1.32 (s, 6H), 1.34 (s, 3H), 1.37 (s, 3H), 1.85 (m, 1H), 2.12 (dddd, 1H, *J* = 16.0, 9.0, 6.5, 3.5), 2.61 (m, 2H), 3.52 (pseudo t, 1H, *J* = 7.6), 3.90 (m, 1H), 3.93 (dd, 1H, *J* = 8.4, 5.0), 4.0 (ddd, 1H, *J* = 8.0, 6.1, 5.0), 4.11 (dd, 1H, *J* = 8.4, 6.1), 9.78 (dd, 1H, *J* = 1.2, 2.5)	24.99, 25.82, 26.46, 26.70, 26.95, 40.40, 67.80, 77.17, 79.58, 81.19, 109.32, 109.89, 202.56
4g	78	−30.0° (0.34, $CHCl_3$)	$C_{14}H_{22}O_6$ (286.3)	1.30 (s, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.90 (m, 2H), 2.39 (m, 2H), 3.74 (ddd, 1H, *J* = 9.4, 4.0, 1.8), 4.11 (dd, 1H, *J* = 8.0, 1.8), 4.26 (dd, 1H, *J* = 5.0, 2.5), 4.56 (dd, 1H, *J* = 8.0, 2.5), 5.26 (d, 1H, *J* = 5.0), 9.80 (m, 1H)	22.59, 24.15, 24.67, 25.71, 29.44, 39.80, 66.39, 70.61, 71.02, 72.83, 96.68, 108.66, 109.43, 202.78
4h	92	−13.5° (0.52, $CHCl_3$)	$C_{13}H_{23}NO_4$ (257.3)	1.46 (s, 9H), 1.56 (s, 6H), 1.90 (m, 2H), 2.43 (m, 2H), 3.67 (m, 1H), 3.92 (m, 1H), 9.76 (br s, 1H)[d]	
4i	73	−20.6° (0.57, $CHCl_3$)	$C_{14}H_{25}NO_4$ (271.3)	1.29 (d, 1H, *J* = 6.4), 1.40 (s, 9H), 1.51 (s, 3H), 1.59 (s, 3H), 2.05 (m, 2H), 2.43 (m, 2H), 3.45 (br q, 1H, *J* = 6.4), 3.90 (m, 1H), 9.47 (br s, 1H)[d]	
4j	78	−13.1° (0.67, $CHCl_3$)	$C_{21}H_{31}NO_5$ (377.4)	1.45 (s, 3H), 1.47 (s, 9H), 1.49 (s, 3H), 1.87 (m, 2H), 2.46 (m, 2H), 3.90 (m, 2H), 4.10 (m, 1H), 4.50 (m, 3H), 7.30 (m, 5H), 9.71 (br s, 1H)[d]	–

[a] Isolated yields.
[b] All compounds are oils showing IR ($CHCl_3$): ν (C=O) = 1720–1725 cm^{-1}.
[c] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.24.
[d] 80 MHz NMR at 340 K.

(6) **2a, 2b, 2d, 2g**: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. **2c**: Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784. **2e**: Dondoni, A.; Orduna, J.; Merino, P. *Synthesis* **1992**, 201. **2f**: Dondoni, A.; Merino, P. *J. Org. Chem.* **1991**, *56*, 5294. **2h, 2i, 2j**: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.

(7) Although it is beyond the scope of the present work, it is worth mentioning that a solvent effect study on the stereoselectivity of the olefination of the aldehyde **2a** with **1a** showed very small variations of the *E*/*Z* ratio (ca. 50:50) in benzene, toluene, THF, $ClCH_2CH_2Cl$, $CHCl_3$, DMF, whereas in MeOH the *E*/*Z* ratio was 20:80.

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(9) Prepared by the same procedure of the chloride: mp 265 °C (dec). 300 MHz ^1H NMR ($CDCl_3$): δ = 6.20 (d, 2H, J = 14.4 Hz), 7.35 (d, 1H, J = 3.5 Hz), 7.57 (d, 1H, J = 3.5 Hz), 7.75 (m, 15H).

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