Benzyl Esters of D- and L-Arabinals as Chiral Synthons in Organic Synthesis

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An acidic opening of the benzyl esters of D and L arabinal (1,5-anhydro-2-deoxy-*erythro*-pent-1-enitol) catalyzed by mercuric sulfate has been proposed as the key step in the preparation of chiral synthons with selectively substituted hydroxy groups.

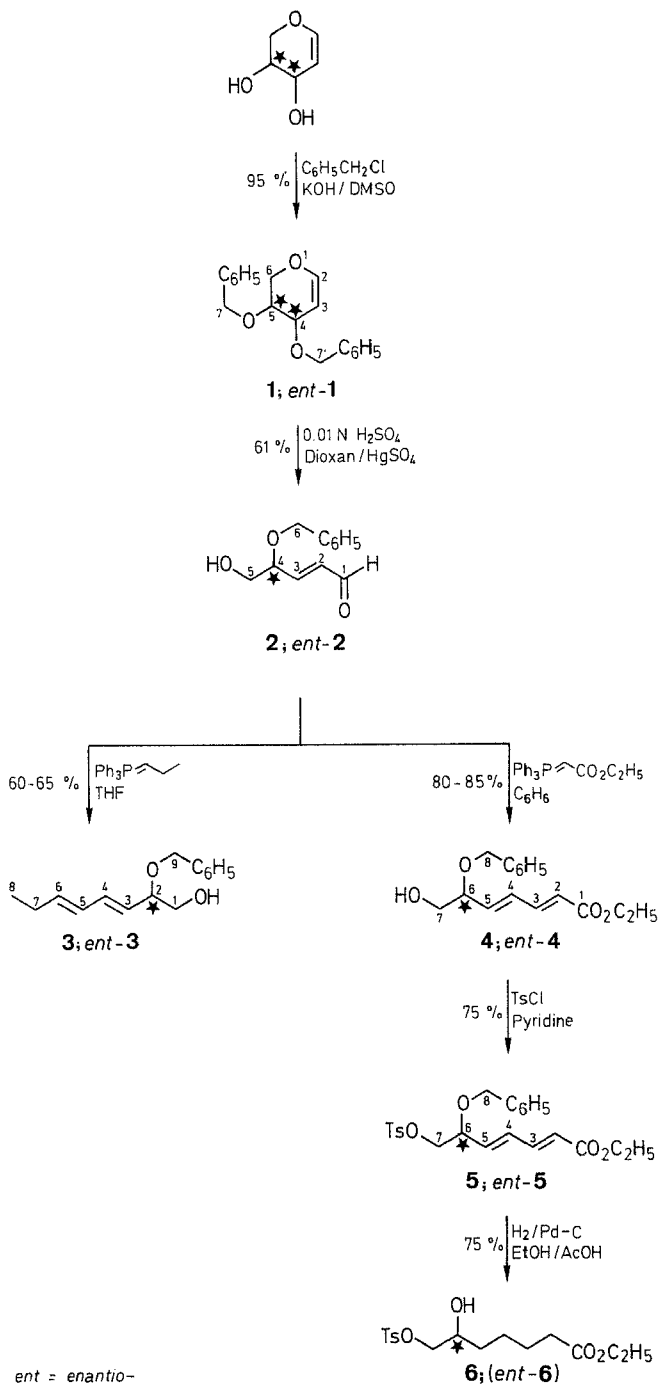
Recently, glycals (cyclic end ether derivatives of sugars) have been widely adopted in the stereospecific synthesis of natural compounds.[1-3] The α,β-unsaturated aldehydes, obtained by the acidic opening of glycal-*O*-acetates in the presence of mercuric sulfate, have attracted considerable attention.[4] The glycal-*O*-acetates, however, are not always suitable, since a mixture of partially formed acetates of hydroxy aldehyde is always obtained on acid catalyzed opening of glycal derivatives.

In an attempt to find glycal derivatives, the acidic opening of which appeared to produce the above type of compounds with selectively protected hydroxy groups, we have directed our attention to *O*-benzyl esters of glycals. (**1**; di-*O*-benzyl-D-1,5-anhydro-2-deoxy-*erythro*-pent-1-enitol)

The acidic ring opening of di-*O*-benzyl-D-arabinal (**1**) with 0.005 N sulfuric acid in dioxane in the presence of mercuric sulfate has been found[4] to proceed very slowly giving (*E*)-(4*S*)-4-benzyloxy-5-hydroxy-2-pentenal (**2**) in 15% yield. We have now managed to improve the yield of **2** from **1** up to 60–75% using 0.01 N sulfuric acid under identical conditions.

To control the optical purity of products, we have carried out a series of parallel conversions with di-*O*-benzyl-L-arabinal (*ent*-**1**; *ent* = *enantio*). The aldehydes **2** and *ent*-**2** thus obtained can be successively expanded at both ends of the molecule to produce chiral synthons suitable for the synthesis of homolypoxine B and a series of other polyhydroxy unsaturated acids and their esters.

We have reacted the aldehyde **2** and its enantiomer, *ent*-**2** with propylidenetriphenylphosphorane in tetrahydrofuran at −78 °C to give the chain extended (2*S*)- and (2*R*)-benzyloxy alcohols **3** and *ent*-**3**, respectively, in 60–65% yield.



In the same way ethyl (6*S*)- and (6*R*)-6-benzyloxy-7-hydroxy-2,4-heptadienoate **4** and *ent*-**4** were obtained in 80–85% yield from **2** and *ent*-**2** by heating with (ethoxycarbonylmethylene)triphenylphosphorane in benzene. The hydroxy esters **4** and *ent*-**4** were converted to the corresponding tosylates **5** and *ent*-**5**, which were hydrogenated with 5% palladium-on-charcoal as catalyst in ethanol/acetic acid medium to ethyl (6*S*)-hydroxy-7-tosyloxyheptanoate (**6**) and *ent*-**6** respectively.

It should be noted that a comparison of the values of optical rotation of intermediates formed from D- and L-arabinals gave a good coincidence. This evidences that a racemization does not occur in the course of the chemical transformations.

^{1}H-NMR spectra (100 MHz) were recorded on a Tesla-BS-587 spectrometer. The values of both chemical shifts and spin-spin interaction coupling constants, according to the calculated spectra, were identified by the LAOCOON-III interaction programme. The precision of those values, being determined and assigned on a spectrometer, was ± 2.35 Hz. The optical rotation were measured on a Perkin-Elmer-141 polarimeter. The products were analysed by TLC on Silufol UV-254 (CSR) plates. The products were separated and purified by column chromatography on silica gel (CSR, L 40/100, L 100/160).

Di-*O*-benzyl-D-1,5-anhydro-2-deoxy-*erythro*-pent-1-enitol (1):
To a solution of D-arabinal (6 g, 52 mmol) and benzyl chloride (13.1 g, 105 mmol) in dry DMSO (20 mL) is added finely ground KOH (5.8 g, 105 mmol). The mixture is stirred vigorously at room temperature for 3 h, diluted with water (50 mL) and the pH is brought to 5–6 by the addition of few drops of conc. HCl. The aqueous layer is extracted with $CHCl_3$ (3 × 50 mL), the combined extract is dried ($MgSO_4$), the solvent is evaporated and the residue is purified by distillation; yield: 14.5 g (95%); bp 150–152 °C/0.005 mbar; $[\alpha]_D^{20}$ + 193° (*c* = 2.2, $CHCl_3$).

$C_{19}H_{20}O_3$	calc.	C 76.99	H 6.80
(296.4)	found	77.09	6.78

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.74 (dd, 1 H, J_{gem} = 11.2 Hz, J_{vic} = 4.2 Hz, H-6); 3.90 (m, 1 H, H'-6); 4.00 (m, 1 H, H-4); 4.10 (m, 1 H, H-5); 4.55 (d, 1 H, J_{gem} = 11.6 Hz, 7'-H); 4.58 (d, 1 H, J_{gem} = 11.6 Hz, 7'-H); 4.73 (d, 2 H, J_{gem} = 11.6 Hz, 7-H', 7'-H'); 4.80 (t, 1 H, *J* = 8.7 Hz, H-3); 6.31 (d, 1 H, *J* = 8.7 Hz, 2-H); 7.32 (m, 10 H_{arom}).

*Di-O-benzyl-*L*-arabinal* (*ent*-**1**): This is prepared as described above from L-arabinal; yield: 92%; bp 150 °C/0.005 mbar; $[\alpha]_D^{20}$ − 192.8° (*c* = 1.03, $CHCl_3$).

$C_{19}H_{20}O_3$	calc.	C 76.99	H 6.80
(296.4)	found	77.00	6.76

(4*S*)-4-Benzyloxy-5-hydroxy-2-penten-1-al (2):
A mixture of **1** (1 g, 3.3 mmol), $HgSO_4$ (50 mg), 0.01 N H_2SO_4 (20 mL) and dioxane (2 mL) is stirred at room temperature for 24 h. The pH of the mixture is brought to 7 by the addition of a saturated solution of $NaHCO_3$. The aqueous layer is extracted with CH_2Cl_2 (5 × 10 mL), the combined extract dried (Na_2SO_4) and the solvent is removed. The residue is chromatographed on silica gel using EtOAc/hexane (1:1) as eluent; yield: 0.48 g (65%); R_f = 0.45 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ 52 °C (*c* = 1.36, $CHCl_3$).

$C_{12}H_{14}O_3$	calc.	C 69.90	H 6.84
(206.2)	found	69.87	6.82

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.37 (br s, 1 H, OH); 3.69 (dd, 2 H, J_{gem} = 11.0 Hz, J_{vic} = 5.6 Hz, C$\underline{H}_2$OH); 4.24 (dt, 1 H, $J_{4,3}$ = 5.52 Hz, $J_{4,5}$ = 5.6 Hz, $J_{4,2}$ = 1.05 Hz); 4.65 (d, 2 H, J_{gem} = 11.7 Hz, C$\underline{H}_2C_6H_5$); 6.35 (dd, 1 H, $J_{2,1}$ = 7.5 Hz, $J_{2,3}$ = 15.85 Hz, H-2); 6.76 (dd, 1 H, $J_{3,2}$ = 15.85 Hz, $J_{3,4}$ = 5.52 Hz, H-3); 7.34 (m, 5 H_{arom}).

(4R)-4-Benzyloxy-5-hydroxy-2-penten-1-al (*ent*-**2**); yield: 60%; $[\alpha]_D^{20}$ − 52° (*c* = 1.31, $CHCl_3$).

$C_{12}H_{14}O_3$	calc.	C 69.90	H 6.84
(206.2)	found	69.90	6.80

(2*S*)-2-Benzyloxy-3,5-octadien-1-ol (3):
To a stirred suspension of *n*-propyltriphenylphosphonium bromide (0.8 g, 2.1 mmol) in dry THF (10 mL) kept at − 78 °C under argon is added dropwise a 1.56 M hexane solution of *n*-BuLi (1.3 mL, 2.1 mmol) and the mixture is further stirred for 0.5 h. A solution of **2** (0.3 g, 1.4 mmol) in dry THF (1 mL) is added to it dropwise and the mixture is allowed to warm to room temperature. The mixture is diluted with water (10 mL), the organic layer is separated and the aqueous layer is extracted with EtOAc (3 × 10 mL). The combined extract is dried (Na_2SO_4), the solvent is removed and the residue is chromatographed on silica gel (eluent: EtOAc/hexane, 1:1); yield: 0.19 g (60%); R_f: 0.65 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ + 30° (*c* = 1, $CHCl_3$).

$C_{15}H_{20}O_2$	calc.	C 77.56	H 8.68
(232.3)	found	77.54	8.62

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.02 (t, 3 H, *J* = 7.35 Hz, CH_3); 2.20 (qt, 2 H, $J_{7,6}$ = 7.5 Hz, $J_{7,8}$ = 7.35 Hz, C$\underline{H}_2$CH$_3$); 2.30 (br s, 1 H, OH); 3.57 (d, 2 H, $J_{1,2}$ = 5.7 Hz, C$\underline{H}_2$OH); 3.97 (q, 1 H, $J_{2,1}$ = 5.7 Hz, $J_{2,3}$ = 5.7 Hz, H-2); 4.48 (d, 2 H, J_{gem} = 11.7 Hz, C$\underline{H}_2C_6H_5$); 5.51 (dt, 1 H, $J_{6,5}$ = 10.8 Hz, $J_{6,7}$ = 7.5 Hz, H-6); 5.53 (dd, 1 H, J_{32} = 5.7 Hz, $J_{3,4}$ = 15.26 Hz, H-3); 5.58 (t, 1 H, $J_{4,5}$ = 10.8 Hz, H-5); 6.58 (dd, 1 H, $J_{4,3}$ = 15.26 Hz, $J_{4,5}$ = 10.8 Hz); 7.33 (m, 5 H_{arom}).

(2R)-2-Benzyloxy-3,5-octadien-1-ol (*ent*-**3**); yield: 56%, $[\alpha]_D^{20}$ − 30°.

$C_{15}H_{20}O_2$	calc.	C 77.56	H 8.68
(232.3)	found	77.52	8.64

Ethyl (6*S*)-6-Benzyloxy-7-hydroxy-2,4-heptadienoate (4):
A mixture of **2** (0.6 g, 2.7 mmol) and (ethoxycarbonyl methylene)-triphenylphosphorane (0.95 g, 4.1 mmol) in benzene (10 mL) is refluxed for 4 h. After removal of the solvent, the residue is chromatographed on silica gel (eluent: EtOAc/hexane, 1:1); yield: 0.67 g (85%); R_f = 0.5 (EtOAc/hexane, 1:1); $[\alpha]_D^{20}$ + 57° (*c* = 2.3, $CHCl_3$).

$C_{16}H_{20}O_4$	calc.	C 69.53	H 7.29
(276.4)	found	69.48	7.23

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.29 (t, 3 H, CH_2C$\underline{H}_3$); 3.59 (d, 2 H, $J_{7,6}$ = 5.4 Hz, C$\underline{H}_2$OH); 4.03 (dt, 1 H, $J_{6,5}$ = 7.1 Hz, $J_{6,7}$ = 5.4 Hz, H-6); 4.2 (q, 2 H, C$\underline{H}_2$CH$_3$); 4.51 (d, 2 H, *J* = 11.8 Hz, C$\underline{H}_2C_6H_5$); 5.82 (d, 1 H, *J* = 11.27 Hz, H-2); 6.01 (dd, 1 H, $J_{5,4}$ = 15.26 Hz, $J_{5,6}$ = 7.1 Hz, H-5); 6.45 (dd, 1 H, $J_{3,2}$ = 11.27 Hz, $J_{3,4}$ = 10.5 Hz, H-3); 7.30 (dd, 1 H, $J_{4,3}$ = 10.5 Hz, $J_{4,5}$ = 15.26 Hz, H-4); 7.34 (m, 5 H_{arom}).

(6R)-6-Benzyloxy-7-hydroxy-2,4-heptadienoic Acid Ethyl Ester (*ent*-**4**); yield: 86%; $[\alpha]_D^{20}$ − 57.4° (*c* = 1.97, $CHCl_3$).

$C_{16}H_{20}O_4$	calc.	C 69.53	H 7.29
(276.4)	found	69.51	7.30

Ethyl (6*S*)-6-Benzyloxy-7-tosyloxy-2,4-heptadienoate (5):
A mixture of **3** (0.2 g, 0.7 mmol), tosyl chloride (0.6 g, 0.75 mmol) and dry pyridine (2 mL) is stirred at room temperature for 24 h. The mixture is taken up in EtOAc (20 mL) and washed with water (2 × 10 mL). The combined organic layer is dried (Na_2SO_4), the solvent evaporated, and the residue is chromatographed on silica gel using EtOAc/hexane as eluent; yield: 0.23 g (75%); R_f = 0.7 (EtOAc/hexane, 3:7); $[\alpha]_D^{20}$ + 53° (*c* = 2.0, $CHCl_3$).

$C_{23}H_{26}O_6S$	calc.	C 64.17	H 6.09
(430.5)	found	64.11	6.04

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.30 (t, 3 H, *J* = 7 Hz, CH_2, C$\underline{H}_3$); 2.41 (s, 3 H, ArC$\underline{H}_3$); 4.07 (m, 2 H, C$\underline{H}_2$OTs); 4.15 (m, 1 H, H-6); 4.2 (q, 2 H, *J* = 7 Hz, C$\underline{H}_2$CH$_3$); 4.48 (d, 2 H, J_{gem} = 11.7 Hz, C$\underline{H}_2C_6H_5$); 5.73 (m, 1 H, H-2); 6.41 (m, 1 H, H-3); 7.25 (m, 1 H, H-4); 7.62 (m, 9 H_{arom}).

Ethyl (6R)-6-Benzyloxy-7-tosyloxy-2,4-pentadienoate (*ent*-**5**); yield: 72%; $[\alpha]_D^{20}$ − 53.2° (*c* = 2.5, $CHCl_3$).

$C_{23}H_{26}O_6S$	calc.	C 64.17	H 6.09	S 7.45
(430.5)	found	64.12	6.05	7.43

Ethyl (6*S*)-6-Hydroxy-7-tosyloxyheptanoate (6):
Tosylate **5** (0.2 g, 0.5 mmol) is hydrogenated using 5% Pd/C (0.08 g) as catalyst in EtOH/AcOH medium (10:1, 11 mL). The mixture is filtered and the filtrate is concentrated by evaporation. The residue obtained is dissolved in EtOAc (10 mL), the organic phase is washed with 5% aqueous $NaHCO_3$ solution (5 × 5 mL) and dried (Na_2SO_4). Removal of solvent and chromatographic purification of the residue on silica gel (eluent: EtOAc/hexane, 3:7) gives **6**; yield: 0.13 g (80%); R_f = 0.52 (EtOAc/hexane, 3:7); $[\alpha]_D^{20}$ + 13.2° (*c* = 3.95, $CHCl_3$).

$C_{16}H_{24}O_6S$	calc.	C 55.80	H 7.02	S 9.31
(344.4)	found	55.75	6.99	9.29

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.12 (t, 3 H, *J* = 7 Hz, CH_2C$\underline{H}_3$9; 1.37 (m, 6 H, CHC$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$); 2.12 (t, 2 H, *J* = 7 Hz, C$\underline{H}_2$CO$_2$C$_2$H$_5$); 3.60 (br s, 1 H, OH); 4.00 (m, 2 H, C$\underline{H}_2$OTs); 4.2 (q, 2 H, *J* = 7 Hz, C$\underline{H}_2$CH$_3$); 4.37 (m, 1 H, C$\underline{H}$OH); 7.68 (m, 4 H_{arom}).

Ethyl (6R)-6-Hydroxy-7-tosyloxyhepanoate (*ent*-**6**); yield: 70%; $[\alpha]_D^{20}$ − 13.0° (*c* = 3.5, $CHCl_3$).

Received: 3 June 1987; revised: 21 September 1987

(1) Kochetkov, N.K., Sviridov, A.F., Ermolenko, M.S., Yatshunsky, D.V., Chizhov, O.S. *Uglevody v sinteze prirodnykh soedinenyi*, "*Nauka*", Moskva 1984, str. 99, 143, 223; *C.A.* **1984**, *101*, 171652.
(2) Ireland, R.E., Wuts, P.G.M., Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.
(3) Hanessian, S., Tyler, P.C., Demailly, G., Chapleur, Y. *J. Am. Chem. Soc.* **1981**, *103*, 6243.
(4) Tulshian, D.B., Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474.

Baldo, M.A., Chessa, G., Marangoni, G., Pitteri, B. *Synthesis* **1987**, 720. On p. 722, line 6, "degree of functionalization" should read "yield of binding". On the same page in the preparation of bis-hydrazone **5**, line 8, "solid product" should read "oil".

Singh, L.W., Ila, H., Junjappa, H. *Synthesis* **1988**, 89. On p. 90 in the ^{1}H-NMR data for dioxime **4**, line 2, "N_2" should read "NH_2".

Burger, K., Hübl, D., Geith, K. *Synthesis* **1988**, 194. On p. 196 in the table, for entries **4l**, **4m**, and **4n**, Y = O, and *Nu* = Cl, Br, and C_6H_5, respectively.

Tolstikov, A.G., Khakhalina, N.V., Spirikhin, L.V. *Synthesis* **1988**, 221. In the title and abstract, benzyl esters should read benzyl ethers.

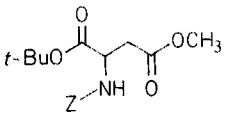
Gupta, A.K., Ila, H., Junjappa, H. *Synthesis* **1988**, 284. Compounds **4** are 1,6-dioxo-1,2,3,6-tetrahydropyrano[3,4-*c*]pyrroles; compounds **9** are 1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridines.

Keshavarz-K., M., Cox, S.D., Angus, R.O., Jr., Wudl, F. *Synthesis* **1988**, 641. On p. 642 the IR spectra shown in Figures 2 and 3 should be interchanged.

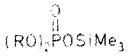
Rodriguez, J., Waegell, B. *Synthesis* **1988**, 534. On p. 535, the first line of the general procedure should read: "DMAP (0.92 g, 7.5 mmol) and then α,β-unsaturated aldehyde **1** (0.1 mol)..."

Zbiral, E., Drescher, M. *Synthesis* **1988**, 735. On p. 738 in the last procedure, the name for compounds **14** should read: (5-Oxo-5,6-dihydroimidazo[1,2-*c*]pyrimidin-3-yl)methylphosphonsäuren.

Valerio, R.M., Alewood, P.F., Johns, R.B. *Synthesis* **1988**, 786. On p. 787 formula **2** should be:



Also on p. 787 in the reaction of **5** in the scheme on the right side, the reagent should be:



Garrigues, B., Mulliez, M. *Synthesis* **1988**, 810. The title should read: Salts of *N*-(Sulfoalkyl)ureas and -thioureas.

Yokoyama, M., Watanabe, S., Seki, T. *Synthesis* **1988**, 879. On p. 880 the name of compound **3a** in the first procedure should be azido(2-benzyloxyethoxy)methane.