Convenient Synthesis of Chiral $\alpha,\beta$-Unsaturated Esters from D-Arabinose

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Acyclic sugar aldehydes 4 and 9 were obtained in 28 and 26% yields through three step reactions from D(-)-arabinose. 4 and 9 were treated with ylde Ph$_2$PCH$_2$O$_2$Me (5) to give unsaturated sugar esters (6 + 7) and (10 + 11), respectively, as inseparable mixtures of cis and trans isomers, which do not guarantee stereoselectivity at the stage of alkene formation nor the separation of the resulting mixtures. However, when D(-)-arabinose was treated with ylde 5 in the presence of catalytic amounts of benzoic acid, only trans sugar enolate 12 was obtained with good yield. The pure trans enolate 7 was obtained by acetylation of 12 in 95% yield. The overall yield for 7 (87% in two steps) was remarkably improved compared to when previous methods (25%, in four steps) were used. The pure trans enolate 11 was also obtained through 12 at good and improved yield.

Key words: $\alpha,\beta$-unsaturated esters, Wittig reaction, D-arabinose, ylde.

Michael acceptors, $\alpha,\beta$-unsaturated esters (A), have been widely used in Michael addition, Diels-Alder reaction, and 1,3-dipolar addition reaction. In asymmetric version of the above reactions, chirality in Michael acceptor controls stereoselectivity on the C = C bond in the molecule.$^{1,3}$ In particular, chirality at γ-position plays a significant role in diastereofacial selectivity. For the formation of chirality at γ-position, chiral pools in sugar have been used (Fig. 1), permitting $\alpha,\beta$-unsaturated sugar esters (B) to serve as good chiral Michael acceptors.$^{2,7}$ In connection with our studies on stereocontrols in asymmetric Michael additions of amines to $\alpha,\beta$-unsaturated sugar esters, which furnish amino sugars as precursors of glycosidase inhibitors, convenient synthesis of B were demanded. Because arabinose is the only commercially available inexpensive sugar in both D-(-) and L-(+)-forms, it was the first choice from various sugars. Facile and preparative methods for synthesis of chiral $\alpha,\beta$-unsaturated esters from D-(-)-arabinose are reported in this paper.

![Diagram](image)

Fig. 1. General structures of Michael acceptor, $\alpha,\beta$-unsaturated ester (A) and chiral Michael acceptor, $\alpha,\beta$-unsaturated sugar ester (B).

Materials and Methods

General methods. Melting points were determined using a Thomas-Hoover Unimelt apparatus. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter at 25°C unless otherwise noted. T.L.c. was performed on precoated glass plates of Silica Gel 60-254 (E. Merck), and compounds on the plate were detected by spraying with 10% H$_2$SO$_4$ solution with subsequent heating. Flash-column chromatography was performed on 230-300 mesh silica gel (Merck) as described in the literature.$^8$ $^1$H-NMR and $^13$C-NMR spectra were recorded using Bruker Avance 400 spectrometer system (9.4 T) at a temperature of 298K in CDCl$_3$, with TMS as an internal reference, unless otherwise specified. Splitting patterns are designated as: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet.

D-Arabinose diethyl ditioacetal (2). D-(-)-Arabinose (15 g, 0.1 mol) was added to 15 mL of concentrated HCl, and the mixture was stirred to give a clear solution at room temperature. The mixture was cooled down in an ice-bath, and ethanethiol (15.5 mL, 0.21 mol) was added dropwise to afford a solid. The solid was poured into 200 mL of cold water, filtered, and washed with cold water and ether successively. Recrystallization from methanol afforded 13 g of 2 (56%). $^1$H-NMR (400 MHz, Me$_2$SO-$d_6$); δ 4.54 (s, 1H, J 7.2 Hz, OH), 4.45 (s, 1H, J 5.4 Hz, OH), 4.33 (m, 2H, 2OH), 4.03 (d, 1H, J 8.6 Hz, H-1), 3.74 (t, 2H, J 7.7 Hz, H-5), 3.36-3.64 (m, 3H, H-2,3,4), 2.58-2.69 (m, 4H, 2SC$_2$H), 1.20 (t, 6H, 2SC$_2$CH$_3$), $^1$C-NMR (100 MHz, Me$_2$SO-$d_6$); δ 71.7, 71.5, 70.6, 63.6, 54.5, 24.3, 23.9 (2SC$_2$H), 14.5, 14.4 (2SC$_2$CH$_3$), 2,3,4,5-Tetra-O-acetyl- D-arabinose diethyl ditioacetal (3). To a solution of 6 g of D-arabinose diethyl ditioacetal (2, 23.4 mmol) in dry pyridine (30 mL) was added 30 mL of acetic anhydride (32.4 g, 0.32 mol) at 5°C, and the solution was
stirred at room temperature overnight. The mixture was poured into 500 ml of ice-water, and resulting precipitate was filtered off and washed several times with water. Recrystallization from methanol gave 9.2 g of a colorless solid (39%). m.p.: 79-80°C, [α]D +30.7° (c 3.6, CHCl3, lit.2 m.p.: 80°C, [α]D +30.0° (c 4.2, CHCl3), H-NMR (400 MHz); δ 5.73 (dd, 1H, J 8.0 Hz), 5.28 (dd, 1H, J 2.8 Hz), 5.12 (dd, 1H, J 8.8 Hz), 4.28 (dd, 1H, J 12.4 Hz), 4.05 (dd, 1H, J 6.0 Hz), 3.90 (d, 1H, J 8.1 Hz), 2.60-2.75 (m, 4H, 2SC(H)3), 2.12 (s, 3H, CH3), 2.11 (s, 3H, CH3), 2.06 (s, 3H, CH3), 2.05 (s, 3H, CH3), 1.21-1.28 (m, 6H, 2SC2H3CH, 13C-NMR (100 MHz); δ 170.6, 170.0, 169.8, 169.5 (4COCH3), 70.8, 69.5, 68.8 (C-2,3,4), 62.1(C-5), 51.8 (C-1), 20.9, 20.8 (double intensity), 20.6 (4COCH3), 24.8 (double intensity. 2SC(H)3), 14.3, 14.0 (2SC2H3CH).)

2,3,4,5-Tetra-O-acetyl-aldehydo-D-arabinose (4). To a solution of the acetylated dithioacetal 3 (4.5 g, 10.6 mmol) in acetone (25 ml) were added 22.5 g of CdCO3, and 5 ml of H2O, and the mixture was stirred for 30 min at room temperature. To the mixture was added a solution of HgCl2 (11.5 g, 42.4 mmol) in 35 ml of acetone, and vigorous stirring was continued overnight at room temperature. The mixture was filtered, and the filtrate was evaporated in the presence of CdCO3. The residue was extracted with warm CHCl3 (3 x 100 ml), and the combined extracts were washed successively with 10% NaI solution (4 x 50 ml) and water (4 x 50 ml). Drying (Na2SO4) followed by evaporation of organic layer gave a syrup (1.8 g, 53%). Rf 0.4 (1 : 1 EtOAc-hexanes), H-NMR (400 MHz); δ 9.54 (s, 1H), 5.42 (d, 1H, J 2.3 Hz), 5.71 (dd, 1H, J 8.5 Hz), 5.27 (m, 1H), 4.34 (dd, 1H, J 4.2 Hz), 4.18 (dd, 1H, J 12.7 Hz), 2.60-2.75 (m, 4H, 2SC(H)3), 2.18 (s, 3H, CH3), 2.07 (s, 3H, CH3), 2.06 (s, 3H, CH3), 2.05 (s, 3H, CH3), 1.21-1.28 (m, 6H, 2SC2H3CH), 13C-NMR (100 MHz) δ 193.8 (C-1), 170.5, 169.9, 169.6, 169.5 (4COCH3) 75.3, 68.0, 67.2, 61.5, 20.7 (double density), 20.4, 20.3 (COCH3).

Methyl (cis, trans)-4,5,6,7-tetra-O-acetyl-2,3-dideoxy-D-arabino-hept-2-ene-1,2-diol (6, 7). To a solution of aldehyde 4 (1.58 g, 5 mmol) in 1 ml of benzene was added methyl triphenylphosphoranylideneacetate (5, 1.74 g, 5.5 mmol), and the mixture was boiled under reflux for 1 h. The mixture showed two spots in t.l.c. (Rf 0.62; product, Rf 0.33; PhP=O = 1 : 1 EtOAc-hexanes). The solvent was evaporated to a white solid. Removal of byproduct PhP=O by flash-column chromatography gave inseparable mixture of trans (cis)-trans-2-ene-1,2-diol 6 and 7 (1.67 g, 90%, trans : cis = 7 by H-NMR). For major trans-2-ene-1,2-diol: H-NMR (400 MHz); δ 6.76 (dd, 1H, J3,1 1.8 Hz, H-3), 5.94 (dd, 1H, J3,5 15.8 Hz, H-2), 5.68 (m, 1H, J3,1 4.8 Hz, H-4), 5.38 (dd, 1H, J3,5 3.0 Hz, H-5), 5.19 (dd, 1H, J3,5 8.6 Hz, H-6), 4.24 (dd, 1H, J3,1 2.7 Hz, H-7), 4.13 (dd, 1H, J3,1 12.5, 4.7 Hz, H-7), 3.72 (s, 3H, OCH3), 2.94-2.12 (4s, 12H, 4CH3), 13C-NMR (100 MHz); δ 165.6, 140.9, 123.2, 69.7, 69.5, 68.2, 61.7 51.8, 20.7, 20.6, 20.5 (double intensity).

2,3,4,5-Di-O-isopropylidene-D-arabinose diethyl dithioacetal (8). To a suspension of D-arabinose diethyl dithioace-