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A ONE-POT SYNTHESIS OF DIMETHYL 2,3-*O*-BENZYLIDENE-L-TARTRATE FROM L-TARTARIC ACID

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ABSTRACT. An economical one-pot synthesis of (-)-dimethyl 2,3-*O*-benzylidene-L-tartrate [(4*R*,5*S*)-4,5-bis(methoxycarbonyl)-2-phenyl-1,3-dioxolane] and its enantiomer from the corresponding tartaric acids is reported in 83-91% yield. The desired benzylidene tartrate is obtained by reaction of tartaric acid and benzaldehyde (1.5 equiv) in the presence of *p*-toluenesulfonic acid in methanol followed by the addition of 3 equiv of trimethyl orthoformate, which reacts with the water generated in the reaction.

(-)-Dimethyl 2,3-*O*-benzylidene-L-tartrate and its enantiomer are versatile intermediates for the preparation of chiral tartrate-derived compounds. For example, optically active 2,3-*O*-benzylidene-L-threitol,[1] 2-*O*-benzyl-D-threitol,[2] and 2-*O*-benzyl-L-threitol[3] have been prepared by reduction of the title compound with lithium aluminum hydride and lithium aluminum hydride-aluminum chloride, respectively. The transformation of dialkyl (2*R*,3*R*)-tartrate into a number of functionalized threitol derivatives has been reported.[4-6]

A reported preparation of the title compound is acetalization of dimethyl tartrate with benzaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic

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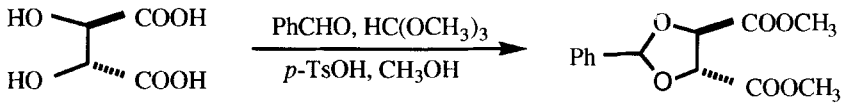
acid.[2] A disadvantage of this method is the use of 15 equiv of benzaldehyde, which minimizes possible hydrolysis of the methyl ester functionalities by water formed during the acetalization reaction; in addition, the yield of the title compound was only 63%. An alternative method that requires two separate steps to the title compound in 85% overall yield is transetherification of benzaldehyde dimethyl acetal in benzene solution and azeotropic distillation of benzene-methanol.[1]

Here we report a economical one-pot preparation of the title compound and its enantiomer (Scheme 1). The use of 3.1 equiv of inexpensive trimethyl orthoformate reported here is a more convenient and practical method to consume the water formed during acid-catalyzed esterification of tartaric acid with methanol and acid-catalyzed acetalization with the tartrate and benzaldehyde. The present method permits the preparation of both enantiomers of the title compound in a single step from L- or D-tartaric acid in one pot and in good chemical yield and high optical purity.

Scheme 1



Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Proton NMR spectra were recorded on an IBM-Bruker WP 200-MHz spectrometer, and chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5988A GC-quadrupole mas spectrometer. Optical rotations were measured in a 1-dm pathlength cell on a JASCO DIP-140 digital polarimeter.

Benzaldehyde was purified as described previously.[7] Anhydrous methanol (Fisher Scientific Co.) was dried by heating under reflux over magnesium turnings, followed by distillation. Triethylamine was dried over sodium hydroxide pellets and distilled prior to use. L- and D-Tartaric acids were purchased from Aldrich Chemical Co. and used without further purification.

(-)-Dimethyl 2,3-*O*-benzylidene-L-tartrate. An oven-dried, 1-L, round-bottomed flask equipped with a Teflon-coated stirring bar was charged with 150.09 g (1 mol) of L-tartaric acid, 159.18 g (1.5 mol) of benzaldehyde, 1.9 (10 mmol) of *p*-toluenesulfonic acid monohydrate, and 100 mL of anhydrous methanol. The mixture was shaken by hand as 329.8 g (3.1 mol) of trimethyl orthoformate was added portionwise over a 20-min period at room temperature. During the addition of trimethyl orthoformate low-boiling methyl formate is liberated; since the reaction is exothermic an efficient hood should be used. After the mixture was stirred at room temperature for 10 min, the reaction flask was equipped with a 18-in. Vigreaux column with distillation head. The mixture was heated gently in an oil bath under 120 °C to remove methyl formate and methanol as they were liberated during the reaction; oil bath temperatures higher than 120 °C cause the reaction mixture to turn dark brown. After about 320 mL of liquid was removed by distillation, the reaction mixture was cooled and 10 mL of dry triethylamine and 200 mL of chloroform were added. The mixture was filtered through a silica gel pad (100 g), which was washed with chloroform (2 X 50 mL). The solvents were removed on a rotary evaporator to leave a brown oil which was distilled under vacuum at an oil bath temperature of 155-170 °C, giving a pale yellow oil, bp 135-150 °C (0.15-0.25 mm). Recrystallization from 1:2 v/v chloroform:hexane afforded 221-242 g (83-91%) of the desired benzylidene tartrate as a white solid, mp 74-76 °C [lit.[1] mp 70-71 °C]; $[\alpha]^{25}$ -48.10° (*c* 1.02, MeOH) [lit.[1] $[\alpha]^{21}_{D}$ -47.26° (*c* 1.02, MeOH)]; IR($CHCl_3$) cm^{-1}: 3037, 3003, 2953, 2902, 2849, 1764, 1749; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.81 (s, 3H), 3.86 (s, 3H), 4.87 (d, 1H, *J* = 4.0 Hz), 4.99 (d, 1H, *J* = 4.0 Hz), 6.14 (s, 1H), 7.38-7.42 (m, 3H), 7.55-7.61

(m, 2H): EI-MS (70 eV); m/z 265 (M^+, 8%), 207 (26), 122 (74), 105 (100), 91 (77). The enantiomer was prepared in the same manner from D-tartaric acid in 88% yield; mp 74-76 °C [lit.[2] mp 73-74.5 °C]; $[\alpha]^{25}_D$ +46.70° (*c* 1.02, MeOH) [lit.[2] $[\alpha]^{23}_D$ +46.3° (*c* 1.02, MeOH)].

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