8, 25826-85-1; 9, 25826-86-2; 10, 25826-87-3; 11, 25877-02-5; chromium trioxide, 1333-82-0; pyridine, 110-86-1.

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Enantiomeric Purity of Phenylethylene Glycol and Reliability of Phenylglyoxylate Asymmetric Reductions in Configurational Assignments[1]

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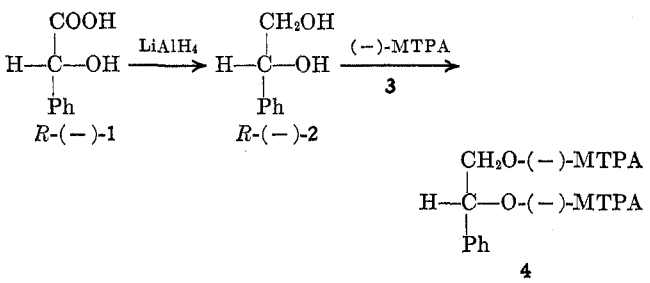
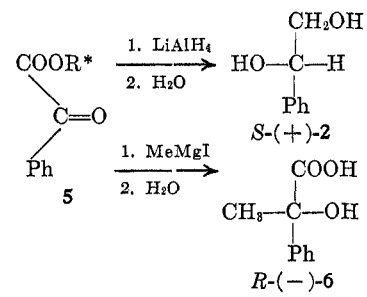
There exists a conflict in the literature concerning the maximum rotation of phenylethylene glycol.[2-6] Since this poses a crucial problem in the study of the asymmetric reduction of chiral phenylglyoxylic ester,[2] it became necessary to resolve this difficulty before we could undertake related studies.[7]

We have made use of the reagent (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (**3**, MTPA)[8] to determine the enantiomeric purity of phenylethylene glycol, and thereby to establish unequivocally its maximum rotation. The di-MTPA ester prepared

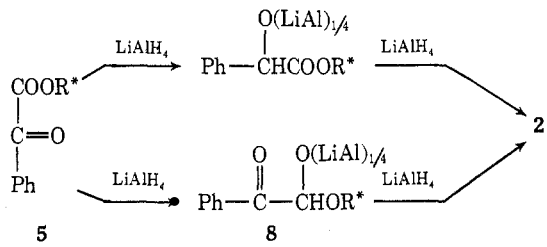


from racemic phenylethylene glycol and enantiomerically pure (*S*)-(−)-MTPA (**3**) exhibited distinct ^{19}F nmr signals for the CF_3 groups of the two diastereomers (**4** and its epimer). The signals from the CF_3 groups, belonging to the MTPA ester of the secondary alcohol function for each of the epimers, were well resolved at δ 5.10 and 4.82 (ppm downfield from the signal for trifluoroacetic acid, TFA, internal, in CCl_4 solvent, 94.1 MHz). Therefore these signals could be used for the quantitative analysis of these diastereomers in a given mixture. A sublimed sample of (*R*)-(−)-phenylethylene glycol (**2**), $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH), $[\alpha]^{25}D$ −63.7° (*c* 5.5, $CDCl_3$), prepared by lithium aluminum hydride reduction of (*R*)-(−)-mandelic acid (**1**), $[\alpha]^{24}D$ −152.3° (*c* 3.27, H_2O), gave the di-(−)-MPTA derivative **4**, the ^{19}F nmr analysis of which showed that it was 98 ± 2% stereochemically pure. Since the starting mandelic acid was 98 ± 1% enantiomerically pure, we conclude that no appreciable racemization occurs during the $LiAlH_4$ reduction of mandelic acid to phenylethylene glycol, contrary to one report[2] but in accord with previous work.[3,4,6] This finding has been independently confirmed.[9] Therefore the previously determined values for the asymmetric syntheses involving the $LiAlH_4$ reductions of chiral phenylglyoxylate esters[3-5] *need not be corrected* as suggested.[2]

Berson and Greenbaum[2] have found that the stereochemical course of the $LiAlH_4$ reduction of the phenylglyoxylate ester of phenyldihydrothebaine (**5**, R* = phenyldihydrothebainyl) giving (*S*)-(+)-phenylethylene glycol (*S*-**2**) in excess was "opposite" to that encountered for the addition of methylmagnesium iodide to the same ester giving (*R*)-(−)-atrolactic acid (*R*-**6**) in excess. This unexpected finding indicated



the need for further study of asymmetric reductions of chiral phenylglyoxylate esters before these reactions can be used with any confidence for stereochemical correlations. It was theorized[2] that the opposite stereochemical courses of these two reactions were a result of the initial reduction of the ester carbonyl group in **5**, before the keto carbonyl group, to give the keto hemiacetal derivative **8** instead of the expected mandelic ester derivative **7**. The newly created chiral center in **8** would have a different and unpredictable influence on the steric course of the further $LiAlH_4$ reduction to **2**. Thus the assumption that the



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ester group was reduced before the keto group could rationalize the stereochemical findings. The reduction of the same ester with sodium borohydride was also studied.[2] Under several reaction conditions they always obtained (+)-phenylethylene glycol, without detecting the intermediate mandelate ester.[10] These results offered direct evidence that in phenyldihydrothebainyl phenylglyoxylate the ester carbonyl is reduced more rapidly than the keto carbonyl by sodium borohydride and, by implication, by $LiAlH_4$ as well. In support of this they found that the reduction of ethyl phenylglyoxylate with excess sodium borohydride (dioxane solvent, 100°, 15 min) gave a 64% isolated yield of phenylethylene glycol; none of the intermediate ethyl mandelate was observed in the product. Under the same reduction conditions ethyl mandelate was recovered unchanged in 90% yield.[2]

We investigated a number of hydride reductions of phenylglyoxylate esters and found that the ethyl ester with less than 1 equiv of $LiAlH_4$ (ether solvent, 20 min) gave a neutral fraction, the nmr of which indicated a 56:44 ratio of ethyl phenylglyoxylate and ethyl mandelate but *no* phenylethylene glycol. When this substrate was treated with an excess of sodium borohydride (in purified dioxane, 25 min reflux), ethyl phenylglyoxylate and ethyl mandelate were observed in the product by nmr analysis in an 84:16 mol ratio with no observable (less than 3%) phenylethylene glycol. Ethyl mandelate under the same reduction conditions was observed to give an 81:19 ratio of unreacted ethyl mandelate to phenylethylene glycol. Thus both $LiAlH_4$ and sodium borohydride reduce the keto group of ethyl phenylglyoxylate before the ester group, although sodium borohydride does reduce ethyl mandelate to phenylethylene glycol slowly.

We are unable to offer any complete explanation for the differences in our results and those reported previously.[2] We concur with Berson and Greenbaum in the admonition for use of "...extreme caution in the assignment of absolute configurations on the basis of hydride reductions of phenylglyoxylates." However, with due caution and suitable controls, it would appear that the $LiAlH_4$ reduction of chiral phenylglyoxylate esters can be utilized for configurational studies, as Prelog, Wilhelm, and Bright[3] proposed.

Experimental Section

(*R*)-(−)-Phenylethylene Glycol.—An ether solution of (*R*)-(−)-mandelic acid {1.8 g, 1.2 mmol, $[\alpha]^{25}D$ −152.3° (*c* 3.27, H_2O), 98 ± 1% enantiomerically pure[11]} was added to $LiAlH_4$ (2.5 g, 6.6 mmol) in ether. After refluxing 1 hr, the mixture was hydrolyzed with hydrochloric acid and ice. The ether extracts were washed (H_2O, Na_2CO_3, H_2O), dried ($MgSO_4$), and evaporated to give an oil which was filtered through silica gel with benzene (75 ml) and methanol (100 ml). The residue from the eluate was sublimed to give 1.55 g (95% yield): mp 63–65°; $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH); $[\alpha]^{25.5}D$ −63.7° (*c* 5.45, $CDCl_3$). No impurities were detectible by nmr.

Racemic phenylethylene glycol was prepared by reduction of racemic mandelic acid by excess $LiAlH_4$:[13] the nmr spectrum was identical with that of the chiral material described above.

(*RS*)-Phenylethylene Glycol Di-(*S*)-α-methoxy-α-trifluoromethylphenylacetate.—Enantiomerically pure, distilled (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride[8] (0.1644 g, 0.65 mmol) was added to racemic phenylethylene glycol (0.0435 g, 0.31 mmol) in dry pyridine (about 1 ml). After heating the mixture for 1 hr at 45° and allowing it to remain overnight at room temperature, it was treated with water and extracted with ether. The ether extracts were washed (dilute HCl, H_2O, saturated Na_2CO_3), dried ($MgSO_4$), and evaporated to give an oil which was analyzed, without further purification, by nmr: δ 5.10 (q, 3 F), 4.82 (q, 3 F), and 4.68 (overlapping pair of quartets, 6 F) (downfield from internal TFA reference standard in CCl_4 solvent at 94.1 MHz).

(*S*)-Phenylethylene Glycol Di-(*S*)-α-methoxy-α-trifluoromethylphenylacetate.—The above experiment was duplicated except that the (−)-phenylethylene glycol, $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH), was employed. Integration of the two downfield ^{19}F signals gave relative areas of 99:1, corresponding to a 98% excess of the (−) enantiomer in the original phenylethylene glycol; the uncertainty is probably about ±1% but cannot be greater than ±2%.

Sodium Borohydride Reduction of Ethyl Phenylglyoxylate.—Following the procedure of Berson and Greenbaum,[2] a mixture of sodium borohydride (1.03 g, 2.72 mmol, Ventron Chem. Co.) in dioxane (80 ml, purified by distillation under vacuum from $LiAlH_4$, pure by nmr analysis) was heated to reflux and ethyl phenylglyoxylate (1.35 g, 0.75 mmol, pure by nmr analysis) in 20 ml of dry dioxane was removed under reduced pressure at room temperature. The residue was hydrolyzed with 4 *N* hydrochloric acid (56 ml) in the presence of ether at 0° or below. The ether extracts were washed (H_2O, saturated Na_2CO_3), dried ($MgSO_4$), and concentrated to give an oil (1.28 g) which analyzed by nmr for 16 mol % ethylmandelate and 84 mol % unreduced ethyl phenylglyoxylate; no phenylethylene glycol (less than 3%) could be detected.

Sodium Borohydride Reduction of Ethyl Mandelate.—When the identical procedure was repeated using ethyl mandelate (1.36 g, 0.75 mmol) as the substrate, the nmr analysis of the resulting oil (1.21 g) showed an 81:19 mol ratio of ethyl mandelate to phenylethylene glycol.

Reduction of Ethyl Phenylglyoxylate with Less Than 1 Equiv of Lithium Aluminum Hydride.—$LiAlH_4$ (0.0566 g, 1.48 mmol) in ether (15 ml) was added to ethyl phenylglyoxylate (1.00 g, 5.64 mmol) dissolved in ether (5 ml). The mixture was stirred for 10 min at room temperature and refluxed for 10 min, and the product was obtained by hydrolysis with hydrochloric acid followed by the usual work-up and filtration through silica gel. The purified reaction product showed by nmr a molar ratio of 44:56 of ethyl mandelate to ethyl phenylglyoxylate. No phenylethylene glycol was detected; control experiment showed that phenylethylene glycol was eluted from the column under the conditions used.

$LiAlH_4$ Reduction of (−)-Menthyl Phenylglyoxylate.—(−)-Menthyl benzoylformate (1.5 g) was treated with excess $LiAlH_4$ (1.0 g in 10 ml of ether). The hydrolyzed reaction mixture was worked up as described under the mandelic acid reduction experiment to give (*R*)-(−)-phenylethylene glycol, $[\alpha]^{19}D$ −6.5 ± 0.1° (*c* 11.22, $CDCl_3$). This corresponds to 10.4% excess of the *R* isomer, based on a maximum rotation of $[\alpha]^{25}D$ 63.7° (*c* 5.45, $CDCl_3$).

Registry No.—*R*-(−)-2, 16355-00-3; ethyl phenylglyoxylate, 7603-79-8; (−)-methyl phenylglyoxylate, 25966-98-7.

(10) Bakshi and Turner[4] however did isolate the intermediate mandelate ester upon $NaBH_4$ reduction of menthyl phenylglyoxylate.

(11) The best literature values are $[\alpha]^{23.6}D$ −154.3 ± 0.6° (*c* 1.64, H_2O);[4] $[\alpha]^{18}D$ +157.5° (*c* 3.5, H_2O);[3] $[\alpha]D$ +156.57° (*c* 2.89, H_2O).[12]

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