Proof of Configuration of (2S,3R)-(+)-Ethyl β-Methyl-*trans*-β-phenylglycidate and of (S)-(−)-2-Phenylpropanal[1]

Sharon Lwo Abidi and James L. Wolfhagen*

Department of Chemistry, University of Maine at Orono, Orono, Maine 04473

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(±)-Ethyl β-methyl-*trans*-β-phenylglycidate was resolved into its optically active enantiomers via the free acid and brucine salts. Each enantiomer was then reduced by $LiAlH_4$ to a mixture of glycols, the 1,2-glycol was destroyed by periodic acid oxidation, and the remaining 1,3-diol was reduced, via the tosylate, to the corresponding 2-phenyl-2-butanol of known configuration. In the case of one of the enantiomers, 2-phenylpropanal was recovered as the product of the periodic acid oxidation and was further oxidized to (S)-(+)-hydratropic acid.

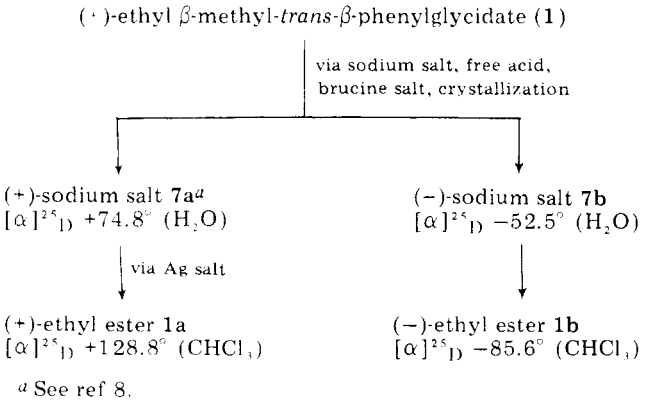
This work was undertaken in order to provide another example of an optically active glycidic ester of known absolute configuration. The reason for desiring such information was that it appeared possible to produce optically active glycidic acids or derivatives by direct epoxidation of suitably substituted unsaturated esters bearing an asymmetric *O*-alkyl group, and if the synthesis occurred as expected, one might find products with absolute configurations predictable by application of the Prelog–Cram rules.[2] The results of these attempts will be reported separately.

Harada has reported absolute configurations for (2S,3R)-(+)-*trans*-β-phenylglycidic acid and its enantiomer as well as for their ammonium salts[3] and for (2R,3S)-(−)-*trans*-β-methylglycidic acid.[4] We chose ethyl β-methyl-*trans*-β-phenylglycidate as a third candidate for resolution and structural assignment because it was structurally related to the two already known, because it appeared possible to convert the ethyl ester into a compound of known configuration, and because a closely related glycidic ester had been prepared earlier by direct epoxidation.[5] This ester also has been synthesized with the (+) form in small excess by Sisido et al.[6] via a Darzens reaction employing either (−)-menthyl chloroacetate or (+)-bornyl chloroacetate with acetophenone, followed by ethanolysis.

Racemic ethyl β-methyl-*trans*-β-phenylglycidate (**1**), prepared via the Darzens condensation of acetophenone with ethyl chloroacetate,[7] was resolved into its enantiomers **1a** and **1b** as outlined in Scheme I. Racemic **1** as prepared by the Darzens method contained about equal amounts of the cis and trans forms, but recrystallization of the sodium salts afforded the pure trans isomer for subsequent work.

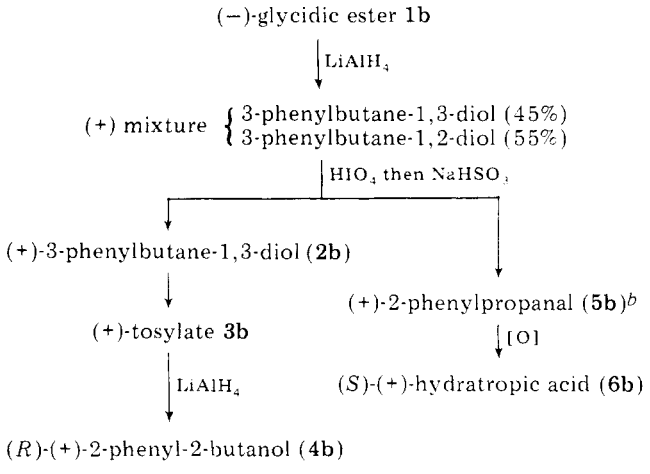
Both **1a** and **1b** exhibited properties identical with those of an authentic sample of racemic material. No attempt was made to improve the optical purity of either enantiomer. Each of the enantiomers thus obtained was treated separately as indicated in Scheme II for the transformation of **1b** to (+)-2-phenyl-2-butanol (**4b**) and to (+)-hydratropic acid (**6b**).

Scheme I. Preparation of Enantiomeric Ethyl β-Methyl-*trans*-β-phenylglycidates



[a] See ref 8.

Scheme II. Conversion of (−)-Ethyl β-Methyl-*trans*-β-phenylglycidate[a] and Derivatives to Products with Known Absolute Configuration



[a] The (+) enantiomer (**1a**) gave products which in each case were identical except for the sign of rotation. [b] The (−) enantiomer (**5a**) was inadvertently converted to what appeared to be acetal, and suffered extensive racemization on hydrolysis. Because of both low rotation and yield, (−)-hydratropic acid was not prepared.

Reduction with $LiAlH_4$ afforded what were presumably mixtures of 3-phenylbutane-1,2- and -1,3-diols.[6,9,10] Absorptions due to carbonyl groups were completely absent in the IR spectra. Each mixture comprised 44% 1,3-diol and 56% 1,2-diol by NMR, and 55% 1,2-diol by periodic acid titration.

In succeeding steps, care was taken to insure that each product was a single substance as indicated by TLC on silica gel and by NMR and IR spectroscopy. Although the reported rotations are not maximum values,[11] the magnitudes are sufficiently large to insure that we are dealing with an enantiomeric pair at each step of the sequence.

Because the absolute configurations of the 2-phenylbutanols (**5a** and **5b**)[12] and of the hydratropic acids (**6b**)[13] are already known, the configurations of all of the individual compounds involved in the reaction sequence are established, with the possible exception of the 1,2-diols obtained from the reduction of the glycidic esters. The optical rotations of these diols must be obtained by subtracting the weighted values for the 1,3-diols (**2a** or **2b**) from those of the two mixtures and are only a few degrees from 0, being −6° for the 1,2-diol derived from **1a** and +1° for that from **1b**. Table I correlates the optical rotation and absolute configuration for each substance isolated as well as for the two key compounds **4** and **6**, which have been reported by others.

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Table I. Observed Specific Rotations and Configurational Assignments of (+)- and (−)-Ethyl β-Methyl-*trans*-β-phenylglycidate and Derivatives

substance		$[\alpha]^{25}_D$,[a] deg	configuration
glycidic ester	**1a**	+128.8	2*S*, 3*R*
	1b	−85.6	2*R*, 3*S*
1,3-diol	**2a**	−32.2 (EtOH)	*S*
	2b	+22.9	*R*
monotosylates	**3a**	−7.2	*S*
	3b	+9.9	*R*
2-phenyl-2-butanol	**4a**[b]	−8.52 (EtOH)	*S*
	4b	+9.50	*R*
2-phenylpropanal	**5a**	−4.6	*R*
	5b	+130.6	*S*
hydratropic acid	**6a**[c]		*R*
	6b	+42.6	*S*
glycidic acid	**7a**	+74.8 (H_2O)	2*S*, 3*R*
	7b	−52.5 (H_2O)	2*R*, 3*S*

[a] In $CHCl_3$ unless stated otherwise. [b] Reference 12. [c] Reference 13.

Experimental Section

Temperatures are reported in °C and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer "Infracord". NMR spectra were obtained on a Varian A-60. Optical rotations were measured on a Pepol (Bellingham and Stanley, England) photoelectric polarimeter. Specific rotations are reported for solutions containing approximately 10 g of material per 100 mL of solvent, which was $CHCl_3$ except where noted otherwise. Pressures at which boiling points are recorded are uncalibrated manometer readings.

β-Methyl-β-*trans*-phenylglycidic Acid Na Salt (7). A mixture of *cis*- and *trans*-**1** (49.3 g, 0.24 mol), prepared by the Darzens method, was converted to the salt essentially as has been described,[14] except that the salt obtained was recrystallized once from aqueous ethanol to remove the last of the cis isomer: yield 19.5 g (41%); mp 256–257 °C dec (lit.[14] mp 255–257 °C); IR (Nujol) 1605 cm^{-1}.

(2*S*,3*R*)-(+)-Ethyl β-Methyl-*trans*-β-phenylglycidate (1a). A solution of 17.5 g (0.0875 mol) of the racemic salt **7** in 100 mL of H_2O was slowly acidified (chill) with 88 mL of 1 N HCl. The glycidic acid was extracted with three portions of cold ether, and the extracts were kept chilled while drying for 6 h over Na_2SO_4.

A 100-mL amount of a warm 1 M solution of (−)-brucine in 1:1 (v/v) benzene–ethanol was added with swirling and shaking to 200 mL of a 0.5 M ethereal solution of the acid prepared as above. In about 5 min a white solid appeared. After 24 h the mixture was filtered, giving 19.9 g of the brucine salt: IR (Nujol) 2400–2300, 1650, 1610–1630, 765 cm^{-1}. Following two recrystallizations from absolute ethanol, the product had mp 192–193 °C dec; $[\alpha]^{25}_D$ +19.54°.

The brucine salt (10.0 g, 0.0174 mol), dissolved in 100 mL of $CHCl_3$, was shaken with 35 mL of 0.5 N NaOH for about 10 min at 10–15 °C, and then the aqueous layer containing 3.4 g of the sodium salt was separated, $[\alpha]^{25}_D$ +74.8° (H_2O).

The solution of Na salt was then treated with an equivalent amount of aqueous $AgNO_3$ to yield 3.2 g (65%) of silver salt: mp 157–158 °C dec; IR (Nujol) 1550 cm^{-1}. The Ag salt was refluxed for 12 h with 20 mL of C_2H_5I in 20 mL of anhydrous ether. Following filtration and removal of solvent, distillation afforded 1.9 g (83%) of (+)-**1a**: $[\alpha]^{25}_D$ +128.8°; bp 84 °C (2 torr); IR and NMR spectra were identical with those of the racemic trans ester.

(2*R*,3*S*)-(−)-Ethyl β-Methyl-*trans*-β-phenylglycidate (1b). The mother liquor from the isolation of the (−)-brucine–glycidic acid salt was evaporated to a sticky solid at reduced pressure. After the same sequence of treatments as described for the preparation of **1a**, there was isolated 46 g of salt which led to a yield of 8.2 g of **1b**: $[\alpha]^{25}_D$ −85.6°; bp 84 °C (2 torr); IR and NMR spectra were identical with those of **1a**.

Reduction of 1a and 1b to Mixed Diols. A solution of 6.64 g (0.0322 mol) of **1a** in 50 mL of anhydrous ether was added dropwise to a vigorously stirred slurry of 0.0644 mol of $LiAlH_4$ in anhydrous ether. After overnight stirring at room temperature, the excess hydride was decomposed with ethyl acetate. Following hydrolysis with 10% Na_2CO_3 solution, filtration, extraction of the organic products with ether, drying (Na_2SO_4), and evaporation of the ether, there remained 4.6 g (85.5%) of a viscous material which exhibited strong IR absorption at 3500–3300 cm^{-1} and which showed no trace of the epoxy or carbonyl bands that were present in the starting material. After three developments on a TLC plate (SiO_2, 1:3 ethyl acetate–hexane, room temperature), two spots of about equal density and R_f 0.080 and 0.133 were observed: $[\alpha]^{25}_D$ −17.9°; NMR ($CDCl_3$) δ 1.30 (d, 2.4 H, CH_3 of 1,2-diol), 1.51 (s, 1.9 H, CH_3 of 1,3-diol). The ratio of protons for the two methyl groups requires 56% 1,2-diol and 44% 1,3-diol.

A 0.100-g sample of the diol mixture was allowed to stand in a water–dioxane solution that contained excess H_5IO_6 for an hour. The excess H_5IO_6 was determined in the usual manner with KI and then titration with $Na_2S_2O_3$. The result showed 55% 1,2-diol.

A similar reduction procedure applied to 9.5 g (0.046 mol) of **1b** in 70 mL of anhydrous ether afforded 6.5 g (86%) of mixed diols with $[\alpha]^{25}_D$ +10.9°; R_f 0.093 and 0.143; NMR and IR spectra were identical with those of the product from **1a**.

(*S*)-(−)-3-Phenylbutane-1,3-diol (2a). A 4.58-g (0.0275-mol) portion of the (−)-diol mixture prepared by the reduction of **1a** was stirred with 290 mL of 1.1 M periodic acid for 12 h at room temperature, and then the mixture was saturated with NaCl and extracted several times with ether. The extract was washed with 100 mL of 10% $Na_2S_2O_3$ and then with 50 mL of 10% $NaHCO_3$ and dried over anhydrous $MgSO_4$. The IR spectrum of the residue obtained after filtration and evaporation of the ether showed two new bands, one at 1720 cm^{-1} and one a doublet at 2800 cm^{-1} (–CHO).

The residual oil was stirred with 50 mL of 10% $NaHSO_3$ for 30 min, and more solid $NaHSO_3$ was added until the mixture was saturated. Then the suspension was extracted once with 50 mL of ether. The extract was washed twice with 25-mL portions of saturated $NaHSO_3$ and then with 30 mL of 5% $NaHCO_3$. After drying (Na_2SO_4) and removal of ether, there remained a residue which was distilled to yield 1.3 g of **2a**, which, except for $[\alpha]^{25}_D$ −32.34° (C_2H_5OH), had physical properties identical with those of an authentic sample of racemic 1,3-diol prepared by the reduction of ethyl β-hydroxy-β-phenylbutyrate[15a,b] with $LiAlH_4$:[15b] IR 3450–3600 (OH), 1070, 1050 (C–O), 760, 695 (Ph) cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 3 H, Me), 1.95 (t, 2 H, C–C**H**$_2$–CH_2OH), 3.20–4.0 (m, 2 H, C**H**$_2$OH), 4.33–4.56 (m, 2 H, 1- and 3-OH), 7.35 (m, 5 H, Ph).

(*R*)-(+)-3-Phenylbutane-1,3-diol (2b). By the procedure just described for **2a**, 6.5 g (0.039 mol) of the (+)-diol mixture from **1b** afforded 2.8 g of **2b**, with all properties identical with those of **2a** and the authentic preparation, except $[\alpha]^{25}_D$ +22.9°.

(+)- and (−)-3-Phenylbutane-1,3-diol Tosylates (3a, 3b). (−)-3-Phenylbutane-1,3-diol (**2a**; 1.14 g, 6.8 mmol) was washed into a 100-mL flask with 15 mL of anhydrous pyridine, and then 1.6 g (8.4 mmol) of *p*-toluenesulfonyl chloride was added in small portions with stirring and cooling. The stirring was continued overnight at room temperature, after which the mixture was cooled in ice, acidified with 10% HCl, and extracted three times with ether. The combined ether extracts were washed three times with saturated NaCl, dried (Na_2SO_4), and evaporated on a rotary evaporator. The viscous residue had $[\alpha]^{25}_D$ −7.22° (C_2H_5OH); IR 3500 (OH), 1330 and 1145 (sulfonate) cm^{-1}.

In the same way, **2b** (2.6 g, 15.8 mmol) was tosylated with 3.68 g (19.3 mmol) of tosyl chloride in 20 mL of anhydrous pyridine. The product **3b**, after workup, had the same IR spectrum as **3a**, but had $[\alpha]^{25}_D$ +9.92° ($CHCl_3$).

The signs of rotation of these tosylates agree with those of the preparations by Mitsui et al.[16] Both products were used directly for reduction to the enantiomeric 2-phenyl-2-butanols.

(*S*)-(−)-2-Phenyl-2-butanol (4a). To a stirred suspension of 0.57 g (15 mmol) of $LiAlH_4$ in 10 mL of dry tetrahydrofuran (THF) was added dropwise a solution of 1.8 g (6 mmol) of crude **3a**. The mixture was heated to gentle reflux and then stirred at room temperature for 12 h. Excess hydride was destroyed with ethyl acetate, followed by 15 mL of 1 N NaOH. The salts were filtered and washed with ether, and the aqueous layer was extracted three times with ether. The ether extracts were combined with the THF layer, washed once with water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure provided 750 mg (83%) of crude product: $[\alpha]^{25}_D$ −8.52° (C_2H_5OH); bp 59–60 °C (1 torr) [lit.[17] bp 90–91 °C (4 torr)]; IR (neat) 3550 and 1025 (OH), 760 and 695 (Ph) cm^{-1};[18] NMR ($CDCl_3$) δ 0.77 (s, 3 H, CH_2**C**H_3), 1.45 (s, 3 H, C-1 Me), 1.81 (q, 2 H, CH_2), 2.30 (s, 1 H, OH), 7.36 (m, 5 H, Ph).

(*R*)-(+)-2-Phenyl-2-butanol (4b). When 4.5 g (14.5 mmol) of crude **3b** was reduced by the method just described, 2 g (91%) of crude product was obtained, with $[\alpha]^{25}_D$ +6.7°. Microdistillation increased the rotation to $[\alpha]^{25}_D$ +9.50°, bp 53–54 °C (0.5 torr). IR and NMR spectra matched those of **4a**, as well as those of a sample of inactive 2-phenyl-2-butanol prepared from authentic 3-phenylbutane-1,3-diol.

(*S*)-(+)-2-Phenylpropanal (5b). The combined aqueous bisulfite extracts from the H_5IO_6 oxidation of the (+)-diol mixture (**2b**) were treated with excess saturated Na_2CO_3 solution, and the liberated

organic layer was extracted into ether. Workup provided 2.5 g of crude product with $[\alpha]^{25}_D$ +123.1°. Microdistillation at 62–63 °C (3.5 torr) [lit.[14] bp 90–93 °C (10 torr)] increased its rotation to $[\alpha]^{25}_D$ +130.7°. Spectral properties were identical with those of an authentic sample prepared by decarboxylation of β-methyl-β-phenylglycidic acid:[14] IR (neat) 3040, 2900, 2800 doubl (CHO), 1720 (C=O), 752, 695 cm^{-1}; NMR δ 1.42 (d, J = 7 Hz, 3 H, Me), 3.63 (m, J = 2 and 7 Hz, 1 H, PhCH), 7.30 (m, 5 H, Ph), 9.65 (d, J = 2 Hz, 1 H, CHO).

(*R*)-(−)-2-Phenylpropanal (5a). This substance was obtained in very low material and optical yield. A large quantity of ethanol was added to and allowed to stand for 2 days with the sodium bisulfite extract following oxidation of the (−)-diol mixture derived from **1a**, the purpose being to precipitate the bisulfite–aldehyde addition product. Workup of the precipitate led to a thick liquid, thought at first to be the aldehyde, but which had a very weak IR absorption at 1720 cm^{-1} and a very broad and strong absorption in the region 1100–1000 cm^{-1}, suggesting an acetal. Hydrolysis with dilute H_2SO_4 in H_2O–dioxane and workup led to approximately 400 mg of material with $[\alpha]^{25}_D$ −4.60° and an IR spectrum identical with authentic 2-phenylpropanal.

(*S*)-(+)-Hydratropic Acid (6b). To provide further proof of the structure of **5b** (and of **1b**), aldehyde **5b** was oxidized to (*S*)-(+)-hydratropic acid (**6b**). A solution of 1.5 g (9.4 mmol) of $KMnO_4$ and 1.13 g (9.4 mmol) of anhydrous $MgSO_4$[19] (to maintain neutrality) in 30 mL of H_2O was added dropwise to a vigorously stirred solution of 1.51 g (11.3 mmol) of **5b** in 20 mL of acetone, never allowing the temperature above 5 °C while the flask was immersed in an ice bath. The mixture then was warmed to room temperature and filtered, the ether was removed under reduced pressure, and 5 mL of 10% NaOH was added to the aqueous residue. After two ether extractions the aqueous residue was acidified with 6 N HCl and again extracted to remove the organic acid. Following drying and solvent removal, the residue was distilled to give 0.85 g (51%) of pure (*S*)-(+)-hydratropic acid: $[\alpha]^{25}_D$ +42.6°; bp 140 °C (10 torr) [lit.[20] bp 143 °C (12 torr)]; IR (neat) 2800–2400, 1710, 1215, 925, 755, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (d, J = 7 Hz, 3 H, Me), 3.67 (t, J = 7 Hz, 1 H, CH–), 7.25 (m, 5 H, Ph), 11.9 (broad, 1 H, COOH).

Registry No.—**1a,** 33530-46-0; (±)-**1a** acid, 68330-60-9; **1a** acid brucine salt, 68330-57-4; **1a** acid sodium salt, 59492-56-7; **1a** acid silver salt, 68330-58-5; **1b,** 59492-57-8; **1b** acid brucine salt, 68365-92-4; **1b** acid silver salt, 68365-93-5; **2a,** 770-88-7; **2b,** 68330-54-1; **3a,** 68258-23-1; **3b,** 68258-24-2; **4a,** 53777-08-5; **4b,** 1006-06-0; **5a,** 38235-74-4; **5b,** 33530-47-1; **6b,** 7782-24-3; (±)-**7,** 68330-59-6; **7a,** 68330-55-2; **7b,** 68330-56-3; 3-phenyl-1,2-butanediol, 68258-25-3.

References and Notes

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Pyridopyrimidines. 10. Nucleophilic Substitutions in the Pyrido[3,2-*d*]pyrimidine Series

Ananthachari Srinivasan and Arthur D. Broom*

Department of Medicinal Chemistry, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

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A new, simple approach to the synthesis of a wide variety of pyrido[3,2-*d*]pyrimidines is described. The approach involves Michael addition of 5-aminouracil to dimethyl acetylenedicarboxylate followed by thermal cyclization to give 6-(carbomethoxy)-2,4,8-trioxopyrido[3,2-*d*]pyrimidine. The latter compound is then converted to the trichloro derivative, which can undergo selective nucleophilic substitution in the order 4 > 2 > 8 to give the desired pattern of substituents.

Since an extensive review of the literature of pyridopyrimidines appeared in 1969,[1] little work has been reported describing synthetic approaches to the rather difficulty accessible pyrido[3,2-*d*]pyrimidines. Among the more important of these few studies from the point of view of biological activity was the extension of earlier work[2] by DeGraw et al.[3] to the synthesis of 8-deazafolic acid. This compound was found to be as potent as methotrexate in the inhibition of certain bacterial cell lines and was active against some methotrexate resistant strains.[3]

Two general approaches to the pyrido[3,2-*d*]pyrimidine ring system have been described. The first involved the cyclization of 3-aminopicolinic acid with various isocyanates or isothiocyanates to give 2,4-dioxo (or thio) derivatives.[4,5] This method suffers from the serious disadvantage that 3-aminopyridine-2-carboxylates bearing additional substituents in useful positions are very difficult to obtain. The alternative approach has been the cyclization of 5-aminouracils or 5-amino-2,4-dimethoxypyrimidine with β-dicarbonyl or α,β-unsaturated carbonyl compounds.[1,6] Of these cyclizations, the best from a synthetic point of view was the cyclization with diethyl ethoxymethylenemalonate to give 7-(carbethoxy)-8-oxopyrido[3,2-*d*]pyrimidines such as **1**.

In its quest for the synthesis of "multisubstrate analogue

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