Chiral Benzhydrol-2,3,4,5,6-d_5

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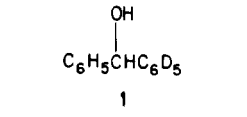
(−)-Benzhydrol-2,3,4,5,6-d_5, $C_6H_5C^*HOHC_6D_5$, $[\alpha]^{20}_D$ −0.85° (*c* 16, $CHCl_3$), has been prepared from resolved, enantiomerically pure (+)-4′-nitrobenzhydrol-2,3,4,5,6-d_5, by reduction, diazotization, and replacement of the diazonium group with hydrogen using hypophosphorous acid. The enantiomeric purity of this material was found to be 86% by use of a chiral NMR shift reagent. (−)-Benzhydrol-2,3,4,5,6-d_5 [(−)-1] was converted with thionyl chloride–lutidine into (−)-benzhydryl-2,3,4,5,6-d_5 chloride [(−)-8]. It was previously reported that (+)-1 gave (−)-8 using thionyl chloride–lutidine. Circular dichroism spectra of (−)-1 and (−)-8, which are chiral by virtue of deuterium substitution, are complex and rich in detail in the 240–300-nm region.

The separation of benzhydrol-2,3,4,5,6-d_5 (1) into enantiomers via fractional crystallization of the brucine salt of its acid phthalate was reported by Pocker[1] in 1961. To our knowledge this resolution by classical crystallization methods stands as the only undisputed report in which a compound that is diastereomeric by virtue of isotopic substitution has been reported to be separable by crystallization. In 1936 Clemo and McQuillen[2a] reported the classical resolution of benzhydrylamine-2,3,4,5,6-d_5 (2), but they expressed some reservations about their results.



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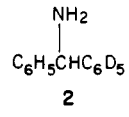

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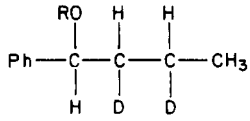

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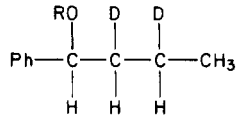

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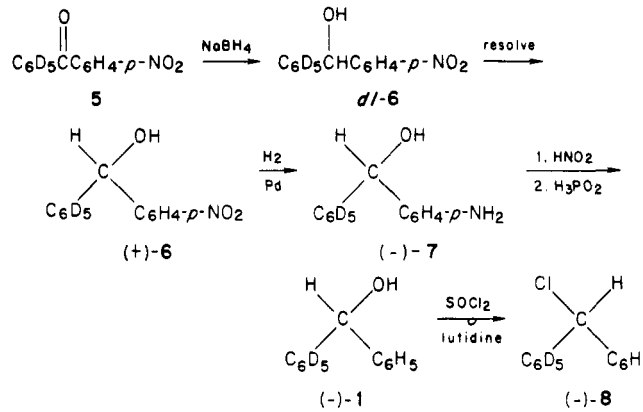
In 1938 Adams and Tarbell[3] were unsuccessful in trying to repeat this work. After Pocker's publication, Clemo and Raper[2b] suggested that the originally reported resolution of 2 may have been real. There the problem rests. Coppock et al.[4,5] were unable to achieve the separation of diastereomers 3 and 4 in very carefully designed and executed experiments. Finally, although the melting points of H_2O and D_2O differ by 3.8 °C, their crystalline structures are so similar that all attempts to separate the two by fractional crystallization have failed.[6] It seems reasonable to assume that the crystals of all organic compounds which differ only by isotopic substitution will be isomorphous and cannot be separated by fractional crystallization.[7]

Our interest in compounds that are chiral by virtue of deuterium substitution[8] led us to devise the unequivocal synthesis of chiral benzhydrol-2,3,4,5,6-d_5 (1), which is outlined in Scheme I.[9]

Scheme I



4′-Nitrobenzophenone-2,3,4,5,6-d_5 (5) was prepared by the reaction of 4-nitrobenzoyl chloride on hexadeuteriobenzene (99% deuteriated) by a procedure adapted from the synthesis of the nondeuteriated analogue[10] (CF_3SO_3H catalyst). The ketone was reduced ($NaBH_4$) to the *dl*-carbinol (6) which was resolved via the quinine salt of the acid phthalate ester according to the details reported for the nondeuteriated parent compound.[11,12] Resolved (+)-6 was reduced (H_2, Pd) to (−)-7, which was deaminated (HNO_2, H_3PO_2) to give (−)-benzhydrol-2,3,4,5,6-d_5, (1), $[\alpha]^{20.0}_D$ −0.85° (*c* 16, $CHCl_3$). The enantiomeric purity of 1 was determined to be 86 ± 3% by ^1H NMR using a chiral shift reagent. The signals for the ortho hydrogens on the C_6H_5 ring of *d*-1 and *l*-1 isomers had significantly different chemical shifts in the presence of the chiral shift reagent Eu(DCM)$_3$[13] (Figure 1). Attempts to determine the enantiomeric purity with the chiral MTPA ester[14] and with the MTPA ester in the presence of a chiral shift reagent[15] were unsuccessful. The rotation of enantiomerically and isotopically pure 1 must be $[\alpha]^{20}_D$ 1.00 ± 0.03° (*c* 16, $CHCl_3$). This compares with $[\alpha]^{20}_D$ +0.8° (C_6H_6) reported in ref 1.

(1) Pocker, Y. *Proc. Chem. Soc.* **1961**, 140.
(2) (a) Clemo, G. R.; McQuillen, A. *J. Chem. Soc.* **1936**, 808. (b) Clemo, G. R.; Raper, R. *Proc. Chem. Soc.* **1961**, 333.
(3) Adams, R.; Tarbell, S. *J. Am. Chem. Soc.* **1938**, *60*, 1260.
(4) Coppock, J. B. M.; Partridge, S. M. *Nature (London)* **1936**, 907.
(5) Coppock, J. B. M.; Kenyon, J.; Partridge, S. M. *J. Chem. Soc.* **1938**, 1069.
(6) Bruni (Bruni, G. *J. Am. Chem. Soc.* **1934**, *56*, 2013) reduced 4000 L of water by a nine-step fractional freezing to 280 mL without observing any concentration. Similarly La Mer and Baker reported[7] that they were unable to effect a perceptible separation of H_2O and D_2O by slow crystallization of a mixture containing 40% D_2O.
(7) La Mer, V. K.; Baker, W. N. *J. Am. Chem. Soc.* **1934**, *56*, 2641.
(8) (a) Reich, C. J.; Sullivan, G. R.; Mosher, H. S. *Tetrahedron Lett.* **1973**, 1505. (b) Mosher, H. S. *Tetrahedron* **1974**, *30*, 1733.
(9) A similar scheme was unsuccessful when $(Bu)_3SnH$ failed to dehalogenate *p*-chlorobenzhydrol which has been resolved [Green, G.; Kenyon, J. *J. Chem. Soc.* **1950**, 751]. The *p*-bromo analogue was successfully debrominated, but its resolution was unsatisfactory (cf. ref 17). We thank Debera B. LaVergne for these experiments.
(10) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 299.
(11) Puckowski, R. T.; Ross, W. A. *J. Chem. Soc.* **1959**, 3555.
(12) Rutherford, K. G.; Brien, J. F.; Mamer, O. A. *Tetrahedron* **1971**, *27*, 2627.
(13) McCreary, M. D.; Lewis, D. W.; Wernik, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038. Eu(DCM)$_3$ is tris[*d*,*d*-dicamphoylmethanato]europium(III).
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1973**, *95*, 512. MTPA stands for α-methoxy-α-(trifluoromethyl)phenylacetic acid.
(15) Yamaguchi, S. In "Asymmetric Synthesis"; Morrison, J., Ed.; Academic Press: London, 1983; Vol. 1, pp 125–152.

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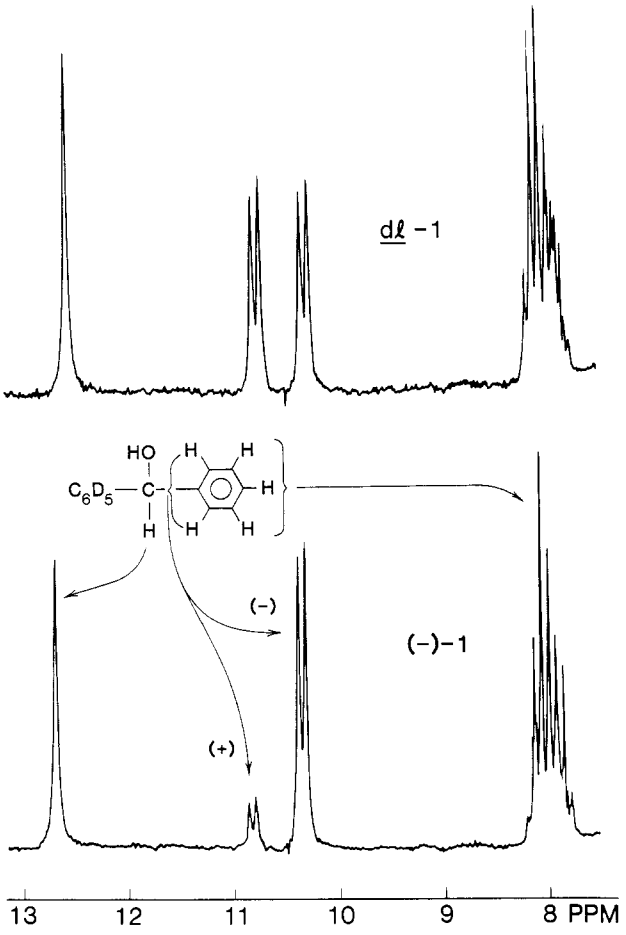

Figure 1. ^1H NMR (300 MHz) chiral shift reagent[13] study in $CDCl_3$ with $Eu(DCM)_3$ on (-)-benzhydrol-*2,3,4,5,6-d*$_5$ (**1**), $[\alpha]^{20}_D$ −0.85 ± 0.03° (*c* 16, $CHCl_3$).

The absolute configurations of the compounds in this series have been tentatively assigned using the Horeau method.[16] Treatment of (+)-**6** with excess *dl*-α-phenylbutyric anhydride gave recovered (+)-α-phenylbutyric acid, $[\alpha]^{20.0}_D$ +1.45 ± 0.03° (*c* 7, C_6H_6). Using the Horeau empirical model[16] as interpreted by the results of Capillon and Guettê,[17] we tentatively assign[18] the *S* configuration[19] to (+)-**6**. Since the chiral center is not disturbed in removal of the nitro group, (-)-**1** is tentatively assigned the *R* configuration.[19]

(-)-Benzhydrol-*2,3,4,5,6-d*$_5$ (**1**), $[\alpha]^{20.0}_D$ −0.85° (*c* 16, $CHCl_3$), was converted to (-)-benzhydryl-*2,3,4,5,6-d*$_5$ chloride (**8**), $[\alpha]^{20.0}_D$ −0.21° (*c* 14, $CHCl_3$), by use of thionyl chloride and excess 2,6-lutidine at −5 °C under conditions of an S_N2 inversion reaction.[12,20] We therefore conclude that (-)-**1** gives (-)-**8** and that benzhydrol **1** and benzhydryl chloride **8** with opposite configurations have the same sodium D line rotation. In contrast to these results it was previously reported[1] that (+)-**1**, $[\alpha]^{20}_D$ +0.8° (in C_6H_6), gave

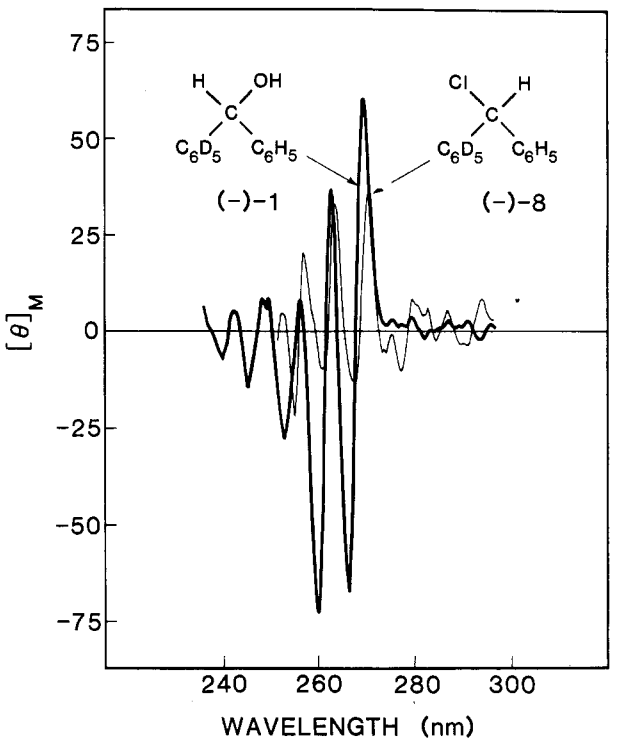

Figure 2. Circular dichroism spectra in cyclohexane solvent on JASCO J-5 CD spectrometer. Heavy line: (-)-benzhydrol-*2,3,4,5,6-d*$_5$ [(-)-**1**], $[\alpha]^{20.0}_D$ −0.85 ± 0.03° (*c* 16, $CHCl_3$), 86 ± 3% enantiomeric excess; major peaks ($[\theta]_M$ over 10), λ/$[\theta]_M$ 270/60, 267/−67, 263/38, 260/−73, 257/11, 253.5/−29, 249/11, 245.5/−12. Light line: (-)-benzhydryl-*2,3,4,5,6-d*$_5$ chloride [(-)-**8**], $[\alpha]^{20.0}_D$ −0.21° (*c* 14, $CDCl_3$), less than 86% enantiomeric excess; major peaks ($[\theta]_M$ over 10), λ/$[\theta]_M$ 278/−15, 272/37, 269/−16, 264.5/36, 262/−12, 257.5/20, 255.8/−20.

(-)-**8**, $[\alpha]^{20}_D$ −0.36°, "when treated with thionyl chloride in the presence of 2,6-lutidine at low temperature in the absence of solvent." The relative configurations of *p*-nitrobenzhydrol and *p*-nitrobenzhydryl chloride are known and the conditions for conversion via retention and inversion of configurations have been established.[12] We have verified that thionyl chloride and 2,6-lutidine, under several conditions, including the ones we employed, converted (+)-*p*-nitrobenzhydrol to (+)-*p*-nitrobenzhydryl chloride with inversion of configuration. Therefore it seems extremely improbable that the discrepancy between our results and those in the literature can be ascribed to differences in reaction conditions.

The CD spectra of (-)-$C_6H_5CHOHC_6D_5$ and (-)-$C_6H_5CHClC_6D_5$ which have opposite configurations are shown in Figure 2. Their complex CD spectra are rich in detail and similar in some regions but quite different in others. These spectra should be worthy of a theoretical study to further elucidate the effect of C–H vs. C–D bonds on the optical properties of aromatic systems.

Experimental Section

Optical rotations were taken on a Rudolph Research Autopol III and/or a Perkin-Elmer 141 electronic polarimeter, both of which read to 0.001° and are reproducible to ±0.002° with standard solutions. Measurements were made in 1-dcm, permanent-window cells thermostated at 20.0 °C or other appropriate temperature regulated to ±0.1 °C. Circular dichroism (CD) measurements were made on a JASCO CD–UV, J-5 spectrometer in cyclohexane solvent. Proton magnetic resonance spectra (^1H NMR) were taken at either 100 MHz (Varian XL-100) or 300 MHz (Nicolet, NMC) in Fourier transfer mode. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (Me_4Si) as internal standard in $CDCl_3$ solvent. Reactions were routinely followed by thin-layer chromatography (TLC) using

(16) Horeau, A. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 3, pp 51–94.
(17) Capillon, J.; Guettê, J.-P. *Tetrahedron* **1979**, *35*, 1801.
(18) We are now engaged in experiments to correlate by direct chemical means the configuration of **6** to mandelic acid and thus to verify this tentative assignment. Because of the tentative nature of the present assignment, we have not represented the formulas with absolute stereochemistry nor with *R* and *S* designations.
(19) Application of the *R–S* nomenclature scheme to **6**, **7**, and **1** may be confusing. We have assigned the para-substituted phenyl groups sequence priority over the perdeuteriophenyl group and the perdeuteriophenyl priority over phenyl. Thus, **6** and **7** will have opposite stereochemical designations to **1** even though they are configurationally related.
(20) Boozer, C. E.; Lewis, E. S. *J. Am. Chem. Soc.* **1953**, *75*, 3182.

Table I. Comparison of Optical Rotations of $C_6H_5CXHC_6D_5$ Compounds

specific rotation of 1[a]		specific rotation of 8[b]		specific rotation of 9[a]	
λ, nm	$[\alpha]^{20.0}$, deg (c, solv)	λ, nm	$[\alpha]^{20.0}$, deg (c, solv)	λ, nm	$[\alpha]^{20.0}$, deg (c, solv)
589	−0.85 ± 0.03 (16, $CHCl_3$)	589	−0.21 ± 0.02 (14, $CDCl_3$)	589	−0.53 ± 0.04 (3.6, $CDCl_3$)
546	−0.99 ± 0.03 (16, $CHCl_3$)	546	−0.26 ± 0.04 (14, $CDCl_3$)	546	−0.65 ± 0.04 (3.6, $CDCl_3$)
589	−0.85 ± 0.03 (12, C_6H_6)	589	−0.15 ± 0.02 (11, C_6H_6)	589	−0.33 ± 0.04 (7, CH_3OH)
546	−1.01 ± 0.03 (12, C_6H_6)	546	−0.19 ± 0.02 (11, C_6H_6)	546	−0.43 ± 0.02 (7, CH_3OH)
				589	−0.4 ± 0.4 (0.5, C_6H_6)[c]
			Pocker Data[1]		
589	+0.8 (C_6H_6)[d]	589	−0.36[d,e]	589	+1.4 (C_6H_6)[d,f]

[a] This sample was approximately 86% enantiomerically pure; thus the values for the pure isomer should be corrected accordingly. This is tentatively assigned the *R*-(−) configuration.[18,19] [b] The enantiomeric purity cannot be higher than 86% and may be lower. Note that this chloride has the opposite configuration from the alcohol with the same sign of rotation. [c] The solubility of this acid phthalate in benzene is approximately 0.66 g/100 mL, which is too low to allow a meaningful rotation.[24] [d] Concentration not specified. [e] Solvent not specified. [f] See ref 24.

Analtech PGBE silica gel GF plates (250 μm with ethyl acetate–hexane (3:2) as developing solvent. Melting points were determined between cover glasses on an aluminum block microscope hot stage. Infrared and ^1H NMR spectra were taken of each compound reported and found to be compatible with the structures proposed, including ^1H NMR integration indicating extent of deuteration.

4′-Nitrobenzophenone-2,3,4,5,6-d_5 (5). The reaction of *p*-nitrobenzoyl chloride (50 g), benzene-d_6 (150 mL, 99% deuteriated), and trifluoromethane sulfonic acid (10 mL) at 80 °C for 18 h by an adaptation of the method described for nondeuteriated analogues,[10] gave recovered benzene-d_6 (92.3 mL) and **5**, after crystallization from benzene, mp 137–138 °C (44.2 g, 71% yield based on *p*-nitrobenzoyl chloride or 28% based on benzene-d_6 consumed).

***dl*-4′-Nitrobenzhydrol-2,3,4,5,6-d_5 (6).** Treatment of **5** (44.2 g), suspended in anhydrous ethanol (220 mL) with sodium borohydride (3.6 g) for 17 h at 20 °C followed by the procedure for the nondeuteriated compound[12] gave a yellow oil, which crystallized, 39 g (85% yield), and after recrystallization ($CHCl_3$–hexane) showed mp 77–78 °C (lit.[11,12] mp of nondeuteriated compound 76–78, 71–73 °C).

(−)-4′-Nitrobenzhydrol-2,3,4,5,6-d_5 (6). The *dl* compound was converted to the acid phthalate (92% yield). This acid phthalate (58 g) was resolved according to the literature procedure for the nondeuteriated analogue[11,12] via crystallization of the quinine salt to give regenerated (+)-acid phthalate (12.7 g, 58% yield), mp 128–130 °C, $[\alpha]^{20}_D$ +32.69° (*c* 4, $CHCl_3$). From the validity of the maximum reported rotation[10] of the nondeuteriated material and the approximation that the rotations of deuteriated and nondeuteriated compounds are close to each other, this material is approximately 88% enantiomerically pure. This (+)-acid phthalate (7.64 g) was hydrolyzed with 0.2 N NaOH in 10% CH_3OH at 20 °C for 22 h to give 4.50 g (97% crude yield) of (+)-**6**, which was recrystallized from 1:1 benzene–hexane to give 3.39 g, mp 80–81 °C, $[\alpha]^{20}_D$ +77.4° (*c* 2, $CHCl_3$), which is 99% of the literature[11,12] maximum. Racemization takes place on hydrolysis at higher temperatures. The alternate pathway of reduction of the *p*-nitrobenzhydrol acid phthalate to the *p*-aminobenzhydrol acid phthalate followed by hydrolysis (or by deamination then hydrolysis) was abandoned because of unsolved complications[11] in the reduction step.

(−)-4′-Aminobenzhydrol-2,3,4,5,6-d_5 (7). (+)-4′-Nitrobenzhydrol-2,3,4,5,6-d_5 (**6**) (3.98 g), $[\alpha]^{20}_D$ +77.44° (*c* 2, $CHCl_3$), in CH_3OH (35 mL) was hydrogenated (1 atm, 25 °C) over 10% Pd/C (400 mg) to give 3.26 g of light brown solid, mp 116–120 °C. Several crystallizations from $CHCl_3$–hexane and $CHCl_3$ with minimum heating gave white crystals, mp 122–127 °C, $[\alpha]^{20}_D$ −30.4 ± 0.5° (*c* 0.5, $CHCl_3$); [lit. values for the nondeuteriated analogue,[10] mp 136–7 °C, $[\alpha]^{20}_D$ −30.3° (*c* 1.12, $CHCl_3$). Heating must be minimized during crystallization to avoid racemization.[11,21] In subsequent experiments with nondeuteriated material the hydrogenation was done at 0 °C with better results. 4-Aminodiphenylmethane was isolated as a byproduct in these reactions.

(−)-Benzhydrol-2,3,4,5,6-d_5 (1). The (−)-amine **7** (679 mg, 3.33 mmol) was suspended in 18% HCl (7 mL) precooled to −10 °C; a cooled solution of sodium nitrite (272 mg, 3.8 mmol) in H_2O (1 mL) was added dropwise with stirring. The resulting, almost colorless but slightly opaque, solution was stirred at −5 °C for 10 min; chilled 40% hypophosphorous acid (7.2 mL) was added dropwise, and the mixture was stirred for an additional 15 min at −5 °C. The reaction was stored at 5 °C for 48 h and then at room temperature for 24 h and finally worked up by extraction with ether, washing with 5% NaOH and then with water, drying ($MgSO_4$), and concentration to yield **1** (620 mg of light brown syrup), which crystallized. After extraction of these crystals with hot hexane (4 × 20 mL), 34 mg of insoluble oily residue remained. The extracts, on concentration and cooling, gave 440 mg (70%) of crystals, mp 66–69.5 °C. Several crystallizations from petroleum–ether (35–65 °C) gave needles, mp 69.5–70.5 °C, $[\alpha]^{20}_D$ −0.85° (*c* 16, $CHCl_3$) (cf. Table I for other optical rotations, Figure 1 for enantiomeric purity, and Figure 2 for the CD spectrum).

(−)-Benzhydrol-2,3,4,5,6-d_5 Acid Phthalate (9). The above benzhydrol **1** (195 mg) was converted to the acid phthalate according to the procedure for the nondeuteriated analogue.[22] The product, 180 mg, was dissolved in $CHCl_3$, passed through a small Nuchar column, and crystallized from $CHCl_3$–hexane to give white crystals, mp 161–162 °C (lit.[22,23] mp for nondeuteriated analogue 157–158, 164–165 °C), $[\alpha]^{20}_D$ −0.65 ± 0.04° (*c* 3.6, $CDCl_3$). The solubility in benzene was too slight to give a meaningful rotation;[24] cf. Table I for other values.

***dl*-Benzhydrol-2,3,4,5,6-d_5 (*dl*-1).** For use in model experiments and for the shift reagent and MTPA studies, *dl*-**1** was obtained by reaction of the Grignard reagent from perdeuteriated bromobenzene (Aldrich Chemical Co.) with benzaldehyde in a purified yield of 76%, mp 70–71 °C. The NMR spectrum of this sample in the presence of the chiral shift reagent $Eu(DCM)_3$[13] is shown in Figure 1.

Enantiomeric Purity of (−)-1. Figure 1 shows a portion of the 300-MHz ^1H NMR spectrum of a solution of 10 mg of (−)-**1**, $[\alpha]^{20}_D$ −0.85° (*c* 16, $CHCl_3$), and 50 mg of $Eu(DCM)_3$[13] in 0.5 mL of $CDCl_3$. Integration of the two doublets representing the ortho hydrogens in the enantiomers of **1** indicates 86 ± 3% enantiomeric excess (% ee) of the (−) isomer, corresponding to the 88% ee of precursor (+)-**6**.

Horeau Configurational Determination[16,17] on (+)-6. A mixture of (+)-*p*-nitrobenzhydrol (162 mg, 0.708 mmol), $[\alpha]^{20}_D$ +75.5° (*c* 5.6, $CHCl_3$), *dl*-2-phenylbutanoic anhydride (4.39 mg, 1.416 mmol), and pyridine (3.5 mL) was allowed to react at 20

(21) *p*-Aminobenzhydrol proved to be sensitive to acid and to heat and subject to racemization by alkyl–oxygen cleavage.[10] Reduction results were erratic. In subsequent experiments the hydrogenation was done at 0 °C with better results. The use of the meta isomer[11] in this series might have been a better choice.

(22) Balfe, M. A.; Doughty, M. A.; Kenyon, J. *J. Chem. Soc.* **1942**, 611.
(23) Fessler, W. A.; Shriner, R. *J. Am. Chem. Soc.* **1936**, *58*, 1385.
(24) We find that a saturated solution of the acid phthalate of **1** in benzene is about 0.006 g/mL, which is too low for a meaningful rotation in our electronic polarimeters. It is therefore impossible to check the rotation in benzene given in ref 1. Assuming the same specific rotation in benzene as in $CHCl_3$, the observed rotation of a saturated benzene solution at 20 °C in a 1-dcm tube would be $[\alpha]^{20}_D$ 0.004° (*c* 0.006, C_6H_6, *l* 1). This is at the limits of error of the electronic polarimeter and beyond the limits of error of visual polarimeters in common use at the time of ref 1, even if a 4-dcm tube were used.

°C for 20 h. Water (0.5 mL) was added; titration with 0.1 N NaOH after 45 min indicated quantitative esterification. The recovered 2-phenylbutanoic acid (333 mg), $[\alpha]^{20}_D$ +1.39 ± 0.03° (*c* 6.6, C_6H_6), corresponded to an "optical yield"[16] of 4.3%. An identical determination using (+)-*p*-nitrobenzhydrol-*2,3,4,5,6-d*$_5$ [(+)-**6**] (175 mg), $[\alpha]^{20}_D$ +78.2° (*c* 1.1, $CHCl_3$), gave (+)-2-phenylbutanoic acid (346 mg), $[\alpha]^{20}_D$ +1.45 ± 0.03° (*c* 7.6, C_6H_6), "optical yield" 4.5%. On the basis of the Horeau model,[16,17] as applied to benzhydrols,[17] the *S* configuration[19] is tentatively assigned.[18]

(−)-Benzhydryl-*2,3,4,5,6-d*$_5$ Chloride (8). To a solution of (−)-**1** (352 mg, 1.86 mmol) in 2,6-lutidine (0.84 mL, 7.31 mmol) at −5 °C was added with stirring thionyl chloride (0.16 mL, 2.23 mmol). After 24 h at 5 °C the reaction mixture was extracted with hexane (5 × 6 mL), and the extracts were washed (H_2O), dried ($MgSO_4$), and concentrated to give 368 mg of a light brown oil, which was diluted with $CHCl_3$, passed through a Nuchar column (6 × 30 mm), distilled, and redistilled to give (−)-**8** (174 mg), $[\alpha]^{20}_D$ −0.21 ± 0.02° (*c* 14, $CDCl_3$) (cf. Table I for other rotations and Figure 2 for CD curve).

(−)-*p*-Nitrobenzhydryl Chloride.[12] (+)-*p*-Nitrobenzhydrol[12] (200 mg, 0.8 mmol), $[\alpha]^{20}_D$ +79.5° (*c* 1.3, $CHCl_3$) was dissolved in 2,6-lutidine (0.097 mL, 1.05 mmol) and the mixture cooled to −70 °C. Thionyl chloride (0.080 mL, 1.1 mmol) was added and the glassy mixture allowed to warm with stirring first to −40 °C and then to −20 °C over 1 h. The mixture was diluted with water (1 mL), extracted with hexane, and dried ($MgSO_4$), and the concentrated extracts were purified by preparative thin-layer chromatography (1:4 EtOAC–hexane) to give the chloride [121 mg, α^{20}_D +0.180 ± 0.002° (*c* 1.90, $CHCl_3$, *l* 1), $[\alpha]^{20}_D$ +9.8 ± 0.1° (*c* 1.9, $CHCl_3$)]. Rechromatography did not change this rotation significantly.[25] This experiment was repeated under the conditions used for converting (−)-**1** to (−)-**8**, namely, excess lutidine at −5 °C. The rotation of the resulting *p*-nitrobenzhydryl chloride was $[\alpha]^{20.0}_D$ +7.6 ± 0.1° (*c* 0.8, $CHCl_3$). Thus, inversion took place in these experiments using either equivalent amounts or excess lutidine in the absence of solvent, as well as with pyridine in $CHCl_3$ solvent.[12]

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(25) We obtained (+)-nitrobenzhydryl chloride with higher rotation, $[\alpha]^{20}_D$ +9.8 ± 0.1° (*c* 1.9, $CHCl_3$), than the maximum that was reported,[12] $[\alpha]^{20}_D$ −5.8° (*c* 1.0, $CHCl_3$). Our material was purified by preparative thin-layer chromatography while that reported in the literature was subjected to high vacuum distillation and probably underwent some racemization.

Notes

The Intramolecular Opening of the Oxirane Ring in Butyl 4,5-Anhydro-3,6-dideoxyhexaldonate

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Recently we reported a simple synthesis of racemic allomuscarine (**1**) from butyl (*E*)-2-hydroxyhex-4-enoate (**2**).[1] The crucial step of the synthesis involved the Lewis acid catalyzed intramolecular opening of the epoxide ring in

butyl 4,5-anhydro-3,6-dideoxyhexaldonate. From a mixture of epimeric epoxides **3** and **4** the ester **5** was obtained as the only product.

This paper returns to the intramolecular opening of the epoxide ring in **3** and **4** with the intention to explain the steric course of the reaction.

Epoxidation of the double bond in **2** with *m*-chloroperoxybenzoic acid afforded a mixture of two stereoisomeric epoxides **3** and **4** in a ratio of about 2:3.[2] The mixture was separated into pure components using GLC (cf. Experimental Section). The configuration lyxo and xylo was assigned to **3** and **4**, respectively, via correlation of **4** with allomuscarine at the later step of the synthesis.

The careful examination of the acid-catalyzed rearrangement of epoxides **3** and **4** led to the isolation of **5** and a mixture of diastereomeric compounds **6** and **7** (about 7% yield) and of an unidentified polymeric product (Scheme I). On the basis of analytical and spectral data (cf. Experimental Section), a structure of bicyclic ortho esters was assigned to **6** and **7**. The formation of an ortho ester is to our knowledge the first example of the intramolecular opening of the epoxide ring with an ester carbonyl group.[3]

The mixture of diastereomeric **6** and **7** without separation was hydrolyzed with aqueous acetic acid to give known lactones **11** and **12** in proportion of about 6:5, respectively. In ref 2, the configuration arabino was erroneously ascribed to the ribo lactone, and vice versa, the configuration ribo was erroneously ascribed to the arabino one.[4]

The intramolecular opening of the oxirane ring in **3** and **4** was followed by ^1H NMR using pure epoxides. The reactions were performed in $CDCl_3$ solution at −40 °C. The epoxide **4** in 10 min after the addition of the catalyst displayed signals due to **5** (significant prevalence) and to an unidentified ortho ester. On the other hand the epoxide **3** was found to be less reactive. It reacted in 1 h. The ^1H NMR spectrum of the postreaction mixture exhibited absorptions in regions characteristic for ortho esters and lacked signals due to the ester **5**. Examination of these reactions using TLC is fully consistent with observations

(1) Chmielewski, M.; Guzik, P. *Heterocycles* **1984**, *22*, 7.
(2) Chmielewski, M. *Tetrahedron* **1980**, *36*, 2345.
(3) Meskens, F. A. J. *Synthesis* **1981**, 501. Bodenbenner, K. *Justus Liebigs Ann. Chem.* **1952**, *623*, 183.
(4) The correct assignment of configuration to all 3,6-dideoxyhexaldonolactones has been made by Lundt, I., Bock, K., and Pedersen, C., and will be published soon (personal communication).
(5) For the sake of simplicity all formulae in Scheme I refer to monosaccharide D series, although in fact they represent racemic compounds.

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