3.80 (s, CH_3O, 3), 3.10 (s, CH_3O, 3), 0.98 (s, $(CH_3)_3C$, 9).

Anal. ($C_{12}H_{18}O_4$) C, H.

A 2.05-g sample of this 4-*tert*-butyl-4,5-dimethoxy-2-hydroxy-2,5-cyclohexadien-1-one in chloroform was eluted onto 65 g of Brinkmann silica gel, packed in chloroform on a 4-cm-diameter column, and then allowed to stand at room temperature overnight. Slow elution gave 1.70 g of a 70:30 mixture of **5-*tert*-butyl-4-methoxy-1,2-benzoquinone (10)** and the cyclohexadienone. After repetition of the chromatographic process to eliminate methanol, a total of 1.52 g (representing a 71% yield) of bright red, solid *o*-benzoquinone **10** was obtained. Recrystallization from ether at −20 °C provided an analytical sample: mp 95.5–97 °C (large red plates); IR (thin solid film) 1690–1645, 1620 cm^{-1}; UV (methanol) λ_{max} 272.5 nm (ϵ 6540), 417.5 (1100); mass spectrum (CI, ammonia/methane), *m/e* 195 (MH^+); NMR ($CDCl_3$) δ 6.28 (s, CH=, 1), 5.77 (s, C=CO, 1), 3.90 (s, CH_3O, 3), 1.32 (s, $(CH_3)_3C$, 9); ^{13}C NMR ($CDCl_3$) δ 181.59 (s, C=O), 178.73 (s, C=O), 170.68 (s, =$COCH_3$), 159.04 (s, =$CC(CH_3)_3$), 125.72 and 103.41 (2 d, =CH), 56.48 (q, CH_3O), 36.32 (s, $C(CH_3)_3$), 29.66 (q, $(CH_3)_3C$).

Anal. ($C_{11}H_{14}O_3$) C, H.

Acknowledgment. We thank Messrs. Bruce Van Buskirk and John Rodler for their dedicated technical assistance in all phases of this work. We are also indebted to the staff of our Chemical Physics Department for their contributions.

Registry No. 1, 67857-70-9; 2, 61186-98-9; 3 (isomer 1), 61186-95-6; 3 (isomer 2), 61186-97-8; **4a**, 1947-24-6; **4b**, 74752-68-4; (*Z,Z*)-**5**, 74752-69-5; (*Z,E*)-**5**, 74752-70-8; **6a**, 74752-71-9; **7a**, 74752-72-0; **7b**, 74752-73-1; 8, 1020-31-1; **10**, 36122-03-9; methoxy(pyridine)copper(II) chloride, 28733-06-4; 4-*tert*-butylcatechol, 98-29-3; 4-*tert*-butyl-1,2-benzoquinone, 1129-21-1; 2-chlorophenol, 95-57-8; 3-chloro-2-hydroxybenzaldehyde, 1927-94-2; 4-*tert*-butyl-4,5-dimethoxy-2-hydroxy-2,5-cyclohexadien-1-one, 74752-74-2.

Direct Optical Resolution of *trans*-1,2-Diaminocyclohexane from an Amine Mixture

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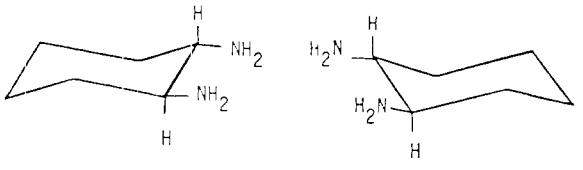
A direct one-step process for the separation and optical resolution of *trans*-1,2-diaminocyclohexane (*trans*-DACH, **1**) from an amine mixture has been developed.[1] *trans*-DACH is the key starting material for the preparation of a variety of optically active alkali metal chelates useful for asymmetric syntheses.[2,3] The process employs a partial molar quantity of natural *d*-tartaric (or *l*-tartaric) acid in combination with a second acid component in an amount sufficient to neutralize all remaining amino groups in the aqueous amine mixture. With *d*-tartaric acid and aqueous propanoic acid, an amine mixture containing 28% **1**, 31% 2-(aminomethyl)cyclopentylamine, and 41% 1,6-hexanediamine gave (*R,R*)-(−)-**1** in 97% optical purity and 99% chemical purity.

As part of a study of the effect of chelating agent structure on the stereoselectivity of the reaction of optically active alkali-metal chelates with prochiral substrates, a facile route to large quantities of (*R,R*)-(−)-**1** and (*S,S*)-(+)-**1** was desired. Racemic *trans*-1,2-cyclohexanediamine



(R,R)-(-)-trans-1 (S,S)-(+)-trans-1

(**1**) is a component in a byproduct amine stream generated during the purification of 1,6-hexanediamine (HDA) which is used in Nylon 66 manufacture. A sample of this byproduct amine stream[4] was N-permethylated[5] and subsequently analyzed by vapor-phase chromatography (VPC). The primary components of this mixture were 31% racemic **1**, 10% 2-(aminomethyl)cyclopentylamine (60% cis, 40% trans), and 51% HDA. The mixture also contained 8% of a fifth component whose structure was not determined. No *meso-cis*-**1** was detected in the mixture.

A variety of inorganic lithium and sodium salts were tried in an effort to effect selective chelate formation with the *trans*-**1** component of the amine mixture.[6] Of the salts tried, LiCl in benzene gave the most selective separation of *trans*-**1** upon recovery of the amine products from the chelate: 86% *trans*-**1** and 14% HDA. This purity was, however, below the 98+% desired, and attention was focused on the direct separation and optical resolution of (*R,R*)-(−)-**1** or (*S,S*)-(+)-**1** from the multicomponent amine mixture.

Optical resolution of *pure trans*-**1** to give (*R,R*)-(−)-**1** has previously been achieved with natural *d*-tartaric acid in aqueous medium.[7] One of the specific properties of *trans*-**1** is its existence as a racemic mixture.[8] Some of the salts of *trans*-**1** also form racemic mixtures. Racemic

(1) T. A. Whitney, U.S. Patent 4 085 138 (1978).
(2) T. A. Whitney and A. W. Langer, *Adv. Chem. Ser.*, **No. 130**, 270 (1974).
(3) T. A. Whitney and A. W. Langer, U.S. Patent 4 156 300 (1979).
(4) While the particular byproduct mixture containing **1** used in this investigation is no longer available, a similar commercial amine mixture (**1** content ~10–25%) is available from Monsanto Chemical Intermediates Co. Also more concentrated **1** of ~60–90% purity is available from Adams Chemical Co, Pfaltz and Bauer, Inc., and Sapon Laboratories. These amine mixtures containing more or less **1** would be treated as described above. The mole fraction of *trans*-**1** is determined, and 1 equiv of *d*- or *l*-tartaric acid is used together with a sufficient quantity of acetic acid, etc. to neutralize all other amino groups in the mixture.
(5) H. T. Clark, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
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(8) For a general reference on racemic modifications, see E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, Chapter 4.

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Table I. Effect of Second Acid Component on Resolution/Separation of (*R,R*)-(−)-1,2-Diaminocyclohexane [(*R,R*)-(−)-*trans*-1] from Amine Mixture

run	amt water, mL	amt amine mixture, g[a] (mmol of contained (*R,R*)-*trans*-1)	amt *d*-tartaric acid, mmol	second acid component, (g mmol)	wt recovd tartrate, g	recovd (*R,R*)-(−)-*trans*-1 chem purity, %[c] (wt, g)	recovd (*R,R*)-(−)-*trans*-1 optical purity, %[c]
1	177	59.0 (147)	147.7	acetic (44.1, 731)	11.2	94.4 (4.48)	85.6
2	68	23.4 (58.6)	58.6	formic (14.7, 293)	2.5	98.9 (0.9)	91.5
3	72	23.9 (60)	60.0	propanoic (22.2, 330)	4.55	98.9 (1.7)	97.0
4	67	22.46 (56.2)	56.2	butanoic (24.9, 283)	5.2	97.7 (2.1)	81.5
5	36	20.9 (52.4)	52.4	benzoic (31.9, 261)	2.0	97.5 (0.86)	96.3
6	29	22.46 (56.2)	56.2	HCl (24.2 mL, 281)	1.22	(0.59)	92.9
7	160	21.15 (53)	53	H_2SO_4 (7.5 mL, 135)	6.5	95.7 (2.74)	0
8	64	23.87 (59.8)	59.8	HNO_3 (18.7 mL of 70%, 299)			
9	same as run 1, but no second acid component; no tartrate salt separated						
10	169	22.92 (57.4)	57.4	oxalic (12.9, 143.4)	11.6	93.5 (3.72)	0
11	72	23.52 (58.9)	58.9	succinic (17.35, 147.1)	4.0	98.8 (1.56)	91.6
12	67	22.4 (56.3)	56.3	adipic (20.53, 140.4)	4.0	96.5 (1.62)	95.6
13	69	23.06 (57.7)	57.9[d]	acetic (17.2, 285)	4.4	96.4 (1.68)	91.8

[a] Composition: 28% *trans*-1, 31% 2-(aminomethyl)cyclopentylamine, and 40% 1,6-hexanediamine. [b] By VPC analysis. [c] Based on $[\alpha]^{25}_{589}$ −41.5° (*c* 5.23, benzene) for optically pure *trans*-1. [d] Unnatural *l*-tartaric acid used.

mixtures have the properties that each enantiomer is higher melting than the racemate and that each enantiomer has a lower solubility than the racemate. In the case of *trans*-1 the racemate is a liquid while either pure enantiomer is a solid having a melting point of 44 °C. Hence if only a moderate degree of optical resolution of *trans*-1 could be obtained directly from the amine mixture, the optically impure *trans*-1 product could be upgraded in optical purity by fractional crystallization from a melt or a hydrocarbon solvent. Such upgrading of optically impure *trans*-1 to 99+% purity had been previously demonstrated.[9,10]

The above facts suggested that optically active *trans*-1 might be obtained directly from the grossly chemically impure amine mixture by using a partial molar quantity of *d*-tartaric acid and a second acid with water as solvent. The quantity of the second acid employed would be such that neutralization of all of the amino groups of the remaining components in the amine mixture would occur. If (*R,R*)-(−)-1·*d*-tartrate were the least soluble of the many ammonium salts in solution, optical resolution and chemical purification could occur simultaneously. The second acid component could therefore be critical to the success of the direct chemical separation and optical resolution of *trans*-1 from an amine mixture due to the differing solubilities of the several salts present when two acids are combined with four amines.

The acid initially chosen as the second acid component was acetic acid, and the molecular weights of all components of the starting amine mixture were assumed to be the same as that of 1 (i.e., 114). The amount of *d*-tartaric acid employed was equal to the mole fraction of *trans*-1, and the amount of acetic acid corresponded to the remaining NH_2 groups. The total salt concentration in water was chosen to be the same as that used earlier for the optical resolution of pure *trans*-1 (1.46 M).[2] All components were brought into solution by heating the mixture to 80 °C, and the hot reaction mixture was allowed to cool slowly to room temperature in the presence of a seed crystal of (*R,R*)-(−)-1·*d*-tartrate. A crop of crystals separated which was recovered by filtration and added to excess aqueous NaOH, and this mixture was continuously extracted with benzene until all the amine product was recovered. The product was found to be 94.4% chemically pure *trans*-1 containing 5.6% HDA as an impurity. The (*R,R*)-(−)-*trans*-1 was 85.6% optically pure. Since the starting material was racemic and contained 28.5% *trans*-1, a chemical separation and optical resolution had been achieved simultaneously.

The initial success of the optical resolution process prompted the study of other readily available acids as the second acid component to determine the effect of the second acid component on optical yield and product chemical purity. The results are summarized in Table I.

Inspection of the data in Table I reveals that of the organic acids investigated propanoic acid gave the best results, affording (*R,R*)-(−)-*trans*-1 in 98.8% chemical purity and 97.0% optical purity with an optical yield of 52%.[12] Except for oxalic acid, which yielded racemic *trans*-1, the other carboxylic acids investigated gave results that were about the same or slightly inferior to propanoic acid. The mineral acids examined were all decidedly inferior to the carboxylic acids under similar reaction conditions. Sulfuric acid gave racemic *trans*-1 regardless of the mode of addition of the two acid components to the aqueous amine solution. Thus if oxalic or sulfuric acid is used with *d*-tartaric acid, racemic *trans*-DACH can be readily separated from the amine mixture. *l*-Tartaric acid separates (*S,S*)-(+)-*trans*-1 from the amine mixture. Thus both optical antipodes of *trans*-1 may be conveniently obtained by this process. It was also determined that no separation or resolution of *trans*-1 occurred when a partial molar quantity of *d*-tartaric acid was used without the presence of the second acid component. No attempt was made to further optimize conditions of temperature, salt concentration, or mole fraction of *d*-tartaric acid with any second acid component in order to maximize product chemical purity and optical yield.

In summation, a facile one-step chemical purification–optical resolution of *trans*-1 has been developed. The compound is the starting material for the synthesis of a variety of chiral *N,N,N′,N′*-tetraalkyl-substituted chelating

(9) Reference 2.

(10) Furthermore, optically and chemically impure (*R,R*)-(−)-*trans*-*N,N,N′,N′*-tetramethyl-1,2-cyclohexanediamine (*trans*-TMCHD) and LiBr form a chelate which is also a racemic mixture that upon fractional crystallization from benzene affords optically pure *trans*-TMCHD, leaving the chemical impurities in solution. The procedure used is the same as that for purifying racemic *trans*-TMCHD.[11]

(11) L. P. Klemann, T. A. Whitney, and A. W. Langer, Jr., *Adv. Chem. Ser.*, No. 130, 159 (1974).

(12) Optical yield refers to the amount of either enantiomer (which is half of the amount of the racemic component) obtained vs. 100 times the amount of that enantiomer present in the original amine mixture.

agents useful in asymmetric synthesis reactions employing organometallic reagents. The chemistry of these systems is under active investigation and will be reported on in due course.

Experimental Section

General Methods. VPC analyses were made on a Varian Aerograph Series 200 gas chromatograph equipped with a thermal-conductivity detector and a 3.3-m, 10% KOH–10% Carbowax 20M on 60/80-mesh Chromosorb W column. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter using a 1-dm jacketed cell. *d*- and *l*-tartaric acids were J. T. Baker reagent grade and were used as received. Amine product recovery by continuous extraction was conducted under a nitrogen atmosphere.

General Procedure for the Separation/Optical Resolution of *trans*-1,2-Diaminocyclohexane (*trans*-1; Run 1). A 59.0-g portion of an amine mixture having a composition of about 28% *trans*-1, 31% 2-(aminomethyl)cyclopentylamine, and 41% 1,6-hexanediamine by VPC analysis was dissolved in 177 mL of water. To stirred solution was added 22.2 g (147.7 mmol) of *d*-tartaric acid which corresponds to the amount of *trans*-1 present in the amine mixture. To the solution was then added 42 mL (731 mmol) of glacial acetic acid, and the temperature of the reaction mixture increased to 60 °C. A few crystals of (*R,R*)-(−)-*trans*-1·*d*-tartrate were added to the hot reaction mixture, and it was allowed to cool to ambient temperature over a 4-h period. A crop of white crystals separated which was recovered by filtration and dried (11.2 g). The crystals were transferred to a liquid–liquid extractor, excess 20% NaOH solution was added to liberate *trans*-1 from the tartrate salt, and the mixture was continuously extracted with benzene for 5 h. The benzene extract was evaporated under vacuum, leaving a solid crude product which was optically active (*R,R*)-(−)-*trans*-1. The crude product displayed $[\alpha]^{25}_{589}$ −36.0° (*c* 5.0, benzene) which corresponds to 86% optical purity. The weight of the crude product (4.48 g) corresponds to a 46% optical yield based on the amount of (*R,R*)-(−)-*trans*-1 isomer contained in the starting amine mixture and with correction of the product optical purity to 100%.

Runs 2–13 were done in the same manner with the following exceptions. The reaction mixture in run 2 was cooled to 2 °C. Run 6 deposited no tartrate salt upon cooling of the mixture to 2 °C. Therefore, it was concentrated on a vacuum rotary evaporator until solid deposited, this was heated to 80 °C, and enough H_2O was added to redissolve all solids while hot (total solution weight 9.17 g) and the mixture was finally allowed to cool to ambient temperature. Run 13 employed *l*-tartaric acid. Table I records the quantities of all reagents used in the various experiments.

Acknowledgment. The author thanks Mr. William J. Mykytka for his excellent technical assistance and Dr. Arthur W. Langer, Jr., for stimulating discussions on some aspects of this work.

Registry No. (±)-*trans*-1, 41013-43-8; (*R,R*)-(−)-*trans*-1, 20439-47-8; (*R,R*)-(−)-*trans*-1 *d*-tartaric acid salt, 39961-95-0; (*S,S*)-(+)-*trans*-1, 21436-03-3; (*S,S*)-(+)-*trans*-1 *l*-tartaric acid salt, 67333-70-4; *d*-tartaric acid, 8769-4; *l*-tartaric acid, 147-71-7; *cis*-2-(aminomethyl)cyclopentylamine, 74684-84-7; *trans*-2-(aminomethyl)cyclopentylamine, 74684-85-8; 1,6-hexanediamine, 124-09-4.

Synthesis and Properties of Unsymmetrical Aryl Glucosyl Disulfides: Models for a New Class of Cleavable Nonionic Detergents

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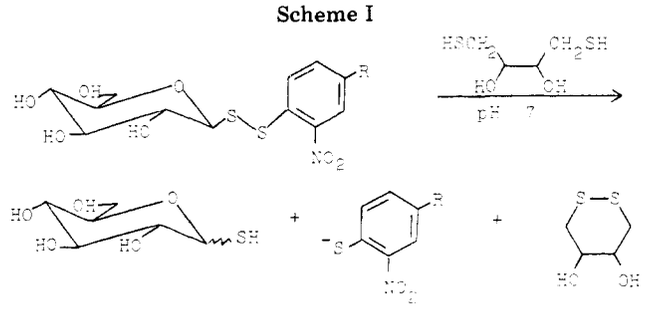
The purpose of this study was the synthesis and evaluation of the first members of a new series of unsymmetrical aryl glucosyl disulfides. Such cleavable molecules are potentially useful as solubilizing agents for membrane proteins. Unsymmetrical disulfides **6a–d** were prepared as follows. The corresponding phenol was converted into the *N,N*-dimethylcarbamothioic acid ester (e.g., **2a**) which was rearranged thermally to the thioester (e.g., **3a**). Hydrolysis gave the corresponding thiophenol (e.g., **4a**) which was then converted into the sulfenyl chloride (e.g., **5a**) by treatment with SO_2Cl_2. The key step was reaction of the sulfenyl chloride with β-D-thioglucose sodium salt in dry acetonitrile in the presence of 15-crown-5 to give the desired unsymmetrical disulfides (e.g., **6a**). Cleavage of **6c** at 25 °C (pH 7–9) with dithioerythritol was rapid and quantitative, as determined by UV–visible spectroscopy. However, these particular unsymmetrical disulfides have the limitation of low water solubility. Other unsymmetrical disulfides with larger polar headgroups should improve the water solubility, and these are under investigation.

The isolation, purification, characterization, and reconstitution of integral membrane proteins[1] such as cytochrome oxidase[2,3] and Na,K-ATPase[4,5] is currently an area of intensive biochemical investigation. Detergents[5-7] are necessarily used in the isolation and purification of membrane proteins. Reconstitution of the purified proteins into a controlled lipid environment involves the replacement of the solubilizing detergent molecules by phospholipids, for example.[8] Sometimes it is very difficult to remove the

Scheme I



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