Table II. Comparison of Calculated ΔG° and Literature E_a

amino acid	ΔG°	E_a (kcal mol^{-1}) Bada[a]	Dungworth[b]	Smith et al.[c]
alanine	31.1	30.9	29.4	28.5
valine	32.0		29.1	28.6
isoleucine	31.9	31.4	28.9	27.9
leucine	31.5		29.3	27.7
phenylalanine	30.6	28.6		24.0
D-phenylglycine	28.1			

[a] Bada, J. L. *Adv. Chem. Ser.* **1971**, *No. 106*, 309. [b] Dungworth, G.; Vincken, N. J.; Schwartz, A. W. In Tissot, B.; Bienner, F. *Adv. Inorg. Chem.* **1973**, 689. [c] Smith, G. G.; Williams, K. M.; Wonnacott, D. M. *J. Org. Chem.* **1978**, *43*, 1.

k_d and pK_a values for a variety of amino acids are reported in Table I. Generally, k_{rac} values are determined at elevated temperatures due to the relatively slow rate of racemization at room temperature. These values are readily available in the literature for a variety of amino acids and reaction conditions.[1] It must be noted that racemization at basic pH is general base catalyzed, thus necessitating accurate knowledge of pH and buffer concentration when determining or comparing pK_a values.[1]

The k_d value is dependent upon both the temperature at which the k_{rac} was determined and the viscosity of the solvent, according to eq 2,[4] where η is viscosity. Viscosity

$$k_d = 8RT/2000\eta \quad (2)$$

is inversely proportional to the solution temperature and can be calculated at a specific temperature from empirical relationships derived from viscosity measurements.[5] It is assumed that pressures greater than 1 atm do not have a significant effect upon the k_d calculation.

An assessment of the validity of the assumption that the reprotonation is predominantly diffusion controlled can be made by calculating ΔG° from the pK_a values obtained using k_d (Table I) via the equation $\Delta G^\circ = 2.303RTpK_a$. ΔG° should be equal to the energy of activation (E_a) since we assumed no energy barriers in the reprotonation step. Table II shows ΔG° calculated from the pK_a values in comparison to literature E_a values. The close agreement of these values indicates that this simple calculation (eq 1), from existing racemization data, provides a good estimate of the α-hydrogen pK_a and E_a for amino acids and further substantiates the Smith–Sivakua mechanism for amino acid racemization.

Experimental Section

An HP5830A gas chromatograph, equipped with an FID detector, was used to determine the D/L configuration of the amino acids. The isotope-exchange studies employed an LKB 2091 gas chromatograph–mass spectrometer interfaced to a PDP 11-03 data system.

Racemization (Figure 1) and Derivatization Procedure. L-Alanine-*2-H* and L-alanine-*2-d* (MSD Isotopes, 98 atom % D) were dissolved in 0.05 M NaH_2PO_4 buffer to give a 0.02 M solution of pH 8.7. Aliquots (1.0 mL) were sealed in glass tubes and heated at 121.7 °C for six time periods ranging from 0 to 20 days. Samples were evaporated to dryness under a stream of N_2. 2-Propanol–4 N HCl (1.5 mL) was added. The tubes were sealed and heated at 110 °C for 2 h to effect esterification. The excess 2-propanol was evaporated as above, and 1.5 mL of 30% trifluoroacetic anhydride–methylene chloride was added. The solution remained at room temperature for 45 min, after which the excess reagent was evaporated to produce the *N*-(trifluoroacetyl)amino acid isopropyl ester derivative.

Exchange Experiment (Figure 2). L-Alanine-*2-H* was dissolved in D_2O to produce a 0.02 M solution. A control of L-alanine-*2-H* in H_2O was identically prepared. Both were heated and derivatized as described above.

Sample Analysis. Gas Chromatography. The derivatized samples were dissolved in 0.5 mL of CH_2Cl_2 and 1.0-μL aliquots were analyzed for D/L by GC. A stainless steel capillary column (150 ft × 0.02 in.) coated with a 1/1 mixture of *N*-octadecanoyl-L-valyl-L-valylcyclohexyl ester and *n*-docosanoyl-L-valyl-*tert*-butylamide was used. Base-line resolution of the D and L isomers was obtained in all analyses.

Mass Spectroscopy. The L-alanine-*2-d* and L-alanine-*2-H* (in D_2O) samples were analyzed for exchange. With use of the same column described above, the samples were resolved to their D and L isomers, and the mass spectrum of each was recorded. Exchange was calculated as a ratio of the absolute intensity of ions 140 to 141 in the L isomer. These values were corrected by an unracemized L-alanine-*2-d* control (in the racemization experiment of Figure 1) and by an unracemized L-alanine-*2-H* control (in the exchange experiment of Figure 2). A derivation of the amino acid racemization equation used in plotting Figures 1 and 2 may be found in ref 7.

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Registry No. L-Alanine, 56-41-7; L-valine, 72-18-4; L-isoleucine, 73-32-5; L-leucine, 61-90-5; L-phenylalanine, 63-91-2; D-phenylglycine, 875-74-1; L-alanine-*2-d*, 21386-65-2.

(4) Murov, S. L. "Handbook of Photochemistry"; Marcel Dekker: New York, 1973; p 55.
(5) "Handbook of Chemistry and Physics", 62nd ed.; CRC Press: Boca Raton, FL, 1981; p F-42.
(6) Wonnacott, D. M. Ph.D. Thesis, Utah State University, Logan, UT, 1979.
(7) Williams, K. M.; Smith, G. G. *Origins Life* **1977**, *8*, 91.

Asymmetric Strecker Synthesis: Isolation of Pure Enantiomers and Mechanistic Implications

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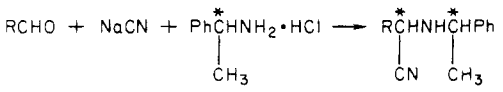
The current direction in organic synthesis toward biologically active asymmetric compounds has been stimulated by advances in asymmetric syntheses. Though recently developed reagents for asymmetric induction have resulted in increasingly higher optical yields, few reactions have afforded pure enantiomers,[1] the ultimate goal of an asymmetric synthesis. We herein report results of our research on the Strecker reaction whereby aliphatic and aromatic aldehydes are isolated as pure chiral amino nitriles of either absolute configuration in acceptable synthetic yields. The ease of synthesis and isolation of these highly functionalized compounds makes them attractive starting materials for the synthesis of more complex molecules of biological interest. In addition, the asymmetric center provides information as to the mechanism of the Strecker reaction.

The asymmetric Strecker synthesis has been known for nearly 2 decades,[2] though it has been utilized primarily in the synthesis of chiral amino acids. The isolation of chiral

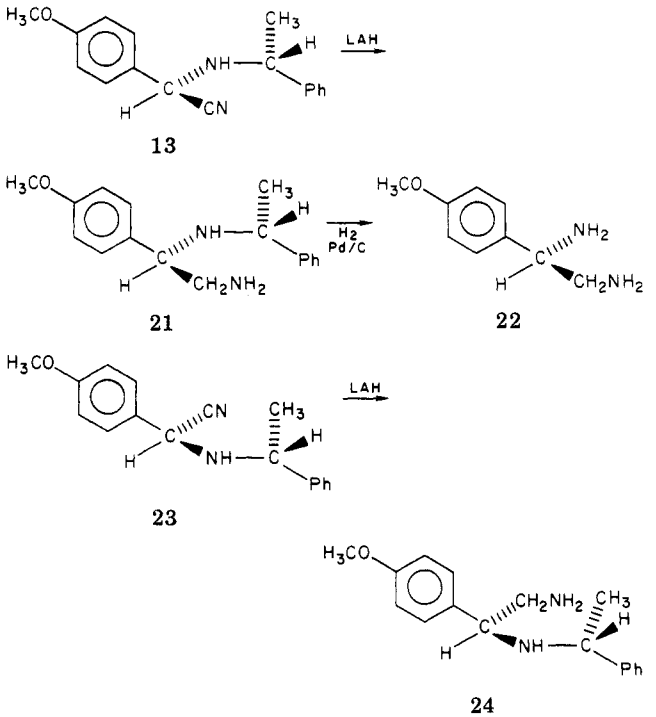
(1) For a review of recent advances in asymmetric synthesis see: Ap-Simon, J.; Seguin, R. *Tetrahedron*, **1979**, *35*, 2797.
(2) Harada, K. *Nature (London)* **1963**, *200*, 1201.

0022-3263/83/1948-5369$01.50/0

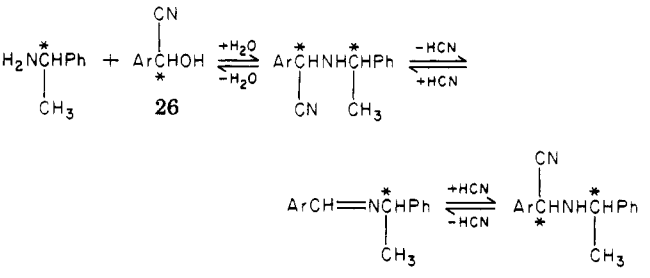
Scheme I



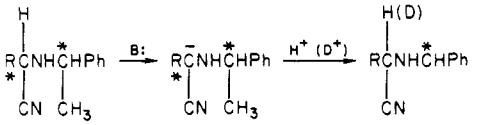
Scheme II



Scheme III



Scheme IV



amino nitriles has been limited to those prepared from methyl ketones.[3] Our need for chiral amino nitriles of both absolute configurations derived from aldehydes prompted us to explore the asymmetric Strecker synthesis. We chose α-methylbenzylamine as the chiral inducing agent because of the ready availability of (*R*)- and (*S*)-α-methylbenzylamine and because it has been demonstrated that the reagent could induce asymmetry in a Strecker reaction.[2,3a,4]

The reaction (Scheme I) with both aryl and alkyl aldehydes in every case afforded mixtures of diastereomers, with one diastereomer predominating (see Table I). Generally, one to two crystallizations of the HCl salts afforded the major diastereomers, which were pure by ^{1}H NMR spectroscopy (vide infra) and which had optical rotations that did not change with repeated recrystallizations.

The absolute stereochemistry of the products was determined by ^{1}H NMR spectroscopy (see Table II). Harada[5] found that the major product from the reaction of acetaldehyde, (*S*)-(−)-α-methylbenzylamine, and sodium cyanide, when hydroylzed and hydrogenolyzed, was (*S*)-(+)-alanine. When we ran the identical condensation reaction, the ^{1}H NMR of the crude amino nitriles showed two quartets, one at 3.10 ppm and the other at 3.58 ppm, in the ratio of 3.3:1. Each quartet is derived from the proton attached to the carbon bearing the nitrile. Thus, on the basis of Harada's findings,[5] the upfield (major) quartet is from the *S* chiral center of the amino nitrile portion of the molecule and the downfield (minor) quartet is from the *R* chiral center. Identical results were observed with all amino nitriles, indicating that in all cases in this Strecker reaction (*S*)-(−)-α-methylbenzylamine affords *S* amino nitriles and (*R*)-(+)-α-methylbenzylamine leads to the *R* amino nitriles.

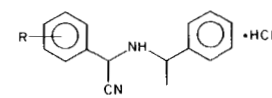
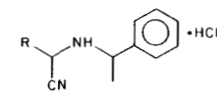
As an example of the stability of the chiral center of the amino nitriles to chemical manipulation, the *R,R* diastereomer **13** was reduced with lithium aluminum hydride (LAH) to the *R,R* diastereomeric diamine **21** (Scheme II). Similarly, pure *S,R* diastereomer **23**, the minor product obtained in the synthesis of **13**, when reduced with LAH, afforded the *S,R* diasteromeric diamine **24**. The two products could be distinguished by ^{1}H NMR spectroscopy. The proton on the chiral carbon (the carbon originally bearing the nitrile in each of the starting materials) was identified by decoupling the protons on the methylene amine of the products, which appeared as broad doublets at ca. 3.2 ppm. Thus, the proton on the methine carbon of **21** appeared at 4.2 ppm, while that of **24** appeared at 3.63 ppm. In neither case was there any of the opposite diastereomer, indicating that the integrity of the chiral center was maintained during the reduction. Finally, compound **21** was smoothly debenzylated to the *R* enantiomeric diamine **22**.

The formation of amino nitriles with methyl ketones has been found to occur under kinetic control, though over 24 h an equilibrium was established between the diastereomers of the chiral dioxane product.[3c] In order to determine whether the ratio of amino nitriles formed from aldehydes was under kinetic or thermodynamic control, we observed the fate over time of the free base of the pure minor diastereomer of **13**, **23** (the *S,R* diastereomer), by ^{1}H NMR spectroscopy in CD_3OD. The singlet for the proton on the carbon bearing the nitrile for the minor diastereomer decreased while that for the major diastereomer increased until the equilibrium mixture was reached in ca. 0.5 h.

Rate constants for the equilibrium of each diastereomer were calculated from a linear regression analysis of the peak intensities of the proton singlets for the major diastereomer.[6] With a correlation of −0.996 and an equilibrium constant of 0.33 the rate for the isomerization of the minor diastereomer was found to be 9.3×10^{-2} s^{-1} and that for the major diastereomer was 3.1×10^{-2} s^{-1} at 36 °C (probe temperature). Thus, unlike the case with methyl ketones, the formation of amino nitriles from aldehydes is under thermodynamic control.

(3) (a) Weinges, K.; Gries, K.:, Stemmle, B.; Schrank, W. *Chem. Ber.* **1977**, *110*, 2098. (b) Weinges, K.; Stemmle, B. *Ibid.* **1973**, *106*, 2291. (c) Weinges, K.; Graab, G.; Nagel, D.; Stemmle, B. *Ibid.* **1971**, *104*, 3594.
(4) Matier, W. L.; Comer, W. T., U.S. Patent 3914249, 1975.
(5) Harada, K.; Fox, S. *Naturwissenschaften* **1964**, *51*, 106.
(6) Capellos, C.; Bielski, B. H. J. "Kinetic Systems"; Wiley-Interscience: New York, 1972; p 35.

Table I. Synthesis of Pure Diastereomeric Amino Nitriles

R	no.	ratio of diastereomers[a]	isolated yield of diastereomer, %	isolated yield of pure diastereomer,[b] %	[α], deg	absolute configuration at amino nitrile[c]	absolute configuration of benzylamine	mp, °C
								
R	1	3.2:1	93	33	+67.9	*R*	*R*	148–155
	2	3.2:1	97	26	−70.6	*S*	*S*	153–160
2-Cl	3	6.0:1	96	78	+119.1	*R*	*R*	153–156
	4	4.5:1	96	19	−118.9	*S*	*S*	152–154
3-Cl	5	2.1:1	96	14	+57.7	*R*	*R*	158–170
	6	2.7:1	89	29	−52.7	*S*	*S*	154–166
4-Cl	7	3.3:1	93	39	+44.4	*R*	*R*	143–151
	8	3.2:1	85	21	−44.2	*S*	*S*	145–149
2-CH_3O	9	2.5:1	97	8	+89.9	*R*	*R*	135–145
	10	2.3:1	97	5	−88.1	*S*	*S*	133–145
3-CH_3O	11	2.4:1	90	8	+58.2	*R*	*R*	130–135
	12	2.5:1	94	3	−57.0	*S*	*S*	130–135
4-CH_3O	13	3.0:1	97	48	+44.5	*R*	*R*	127–128
	14	3.0:1	97	46	−43.8	*S*	*S*	127–128
4-CH_3	15	3.0:1	87	45	+56.6	*R*	*R*	143–149
	16	3.0:1	80	54	−56.0	*S*	*S*	140–143
								
CH_3	17	3.0:1	99	12	+103.8	*R*	*R*	145–149
	18	3.3:1	92	25	−108.7	*S*	*S*	139–142
CH_2CH_3	19	3.6:1	99	13	+98.9	*R*	*R*	138–147
	20	3.6:1	96	9	−97.0	*S*	*S*	143–152

[a] Based on integration of the NMR proton signal on the amino nitrile carbon. [b] All products afforded combustion analyses within ±0.4% of theoretical values. [c] See text for the elucidation of the absolute configuration.

Table II. ^{1}H NMR Spectral Data

compd	CD_3OD
1	1.88 (d, J = 6 Hz, 3 H), 4.60 (q, J = 6 Hz, 1 H), 5.25 (s, 1 H), 7.37 (s) and 7.40 (s, total = 10 H)
2	1.78 (d, J = 6 Hz, 3 H), 4.65 (q, J = 6 Hz, 1 H), 5.33 (s, 1 H), 7.55 (s) and 7.57 (s, total = 10 H)
3	1.88 (d, J = 6 Hz, 3 H), 4.67 (q, J = 6 Hz, 1 H), 5.28 (s, 1 H), 7.2-7.6 (m, 8 H), 7.7-8.1 (m, 1 H)
4	1.90 (d, J = 6 Hz, 3 H), 4.72 (q, J = 6 Hz, 1 H), 5.35 (s, 1 H), 7.2-7.6 (m, 8 H), 7.7-7.9 (m, 1 H)
5	1.75 (d, J = 6 Hz, 3 H), 4.65 (q, J = 6 Hz, 1 H), 5.33 (s, 1 H), 7.3-7.7 (m, 9 H)
6	1.77 (d, J = 6 Hz, 3 H), 4.67 (q, J = 6 Hz, 1 H), 5.35 (s, 1 H), 7.5-7.7 (m, 9 H)
7	1.77 (d, J = 6 Hz, 3 H), 4.65 (q, J = 6 Hz, 1 H), 5.33 (s, 1 H), 7.4-7.6 (m, 9 H)
8	1.80 (d, J = 6 Hz, 3 H), 4.67 (q, J = 6 Hz, 1 H), 5.37 (s, 1 H), 7.4-7.6 (m, 9 H)
9	1.85 (d, J = 6 Hz, 3 H), 3.75 (s, 3 H), 4.57 (q, J = 6 Hz, 1 H), 5.28 (s, 1 H), 6.7-7.1 (m, 2 H), 7.2-7.6 (m, 7 H)
10	1.85 (d, J = 6 Hz, 3 H), 3.75 (s, 3 H), 4.57 (q, J = 6 Hz, 1 H), 5.28 (s, 1 H), 6.7-7.1 (m, 2 H), 7.2-7.6 (m, 7 H)
11	1.87 (d, J = 6 Hz, 3 H), 3.80 (s, 3 H), 4.58 (q, J = 6 Hz, 1 H), 5.20 (s, 1 H), 6.8-7.2 (m, 3 H), 7.2-7.5 (m, 6 H)
12	1.85 (d, J = 6 Hz, 3 H), 3.83 (s, 3 H), 4.58 (q, J = 6 Hz, 1 H), 5.23 (s, 1 H), 6.8-7.2 (m, 3 H), 7.2-7.5 (m, 6 H)
13	1.78 (d, J = 6 Hz, 3 H), 3.80 (s, 3 H), 4.60 (q, J = 6 Hz, 1 H), 5.25 (s, 1 H), 7.03 (d, J = 8 Hz, 2 H), 7.50 (s, 5 H), 7.53 (d, J = 8 Hz, 2 H)
14	1.75 (d, J = 6 Hz, 3 H), 3.85 (s, 3 H), 4.62 (q, J = 6 Hz, 1 H), 5.28 (s, 1 H), 7.08 (d, J = 8 Hz, 2 H), 7.55 (s, 5 H), 7.57 (d, J = 8 Hz, 2 H)
15	1.77 (d, J = 6 Hz, 3 H), 2.38 (s, 3 H), 4.60 (q, J = 6 Hz, 1 H), 5.25 (s, 1 H), 7.3-7.7 (m, 9 H)
16	1.76 (d, J = 6 Hz, 3 H), 2.40 (s, 3 H), 4.60 (q, J = 6 Hz, 1 H), 5.25 (s, 1 H), 7.3-7.7 (m, 9 H)
17	1.95 (d, J = 7 Hz) and 1.99 (d, J = 7 Hz, total = 6 H), 3.50 (q, J = 7 Hz, 1 H), 4.65 (q, J = 7 Hz, 1 H), 7.3-7.9 (m, 5 H)
18	1.79 (d, J = 7 Hz) and 1.81 (d, J = 7 Hz, total = 6 H), 3.65 (q, J = 7 Hz, 1 H), 4.55 (q, J = 7 Hz, 1 H), 7.4-7.9 (m, 5 H)
19	1.05 (t, J = 7 Hz, 3 H), 1.93 (d, J = 6 Hz, 3 H), 2.0-2.7 (m, 2 H), 3.1-3.5 (m, 1 H), 4.45 (q, J = 6 Hz, 1 H), 7.0-7.5 (m, 5 H)
20	1.05 (t, J = 7 Hz, 3 H), 1.93 (d, J = 6 Hz, 3 H), 2.0-2.7 (m, 2 H), 3.1-3.5 (m, 1 H), 4.48 (q, J = 6 Hz, 1 H), 7.0-7.5 (m, 5 H)

There has been some debate as to the mechanism of the amino nitrile formation in the Strecker synthesis. Evidence for cyanohydrin **25**[7] (Scheme III) and imine **26**[3a,8-10] intermediates exists. In our NMR study of the equilibration of the minor (*S,R*) diastereomer **23** in $CDCl_3$, cyanohydrin **25** must not be an intermediate in the reaction since no source of water was present during the equilibration. The equilibration could also conceivably occur via the abstraction of the chiral proton by the amine (Scheme IV). This was ruled out by carrying out the equilibration in CD_3OD. In this system such an abstraction should result in the diminution of the proton singlet as it is exchanged with deuterium, but no such reduction was observed. Thus, imine **26** must be the intermediate involved in the equilibration of the minor diastereomer and, by the principle of microscopic reversibility, the Strecker synthesis in this case must proceed via imine **26**.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter at a concentration of 0.02 g in 2 mL of methanol. ^{1}H NMR spectra were recorded on a Varian T-60A spectrometer in $CDCl_3$ or CD_3OD with tetramethylsilane as a standard. Reaction kinetics were obtained on an IBM NR/80 FT NMR in the ^{1}H mode using an automated stack-plot sequence. Elemental analyses were performed by our analytical chemistry group or by Galbraith Laboratories, Knoxville, TN.

The following procedure is typical for the asymmetric Strecker reactions unless otherwise noted.

(*R*,*R*)-(+)-α-[(1-Phenylethyl)amino]-α-(4-methoxyphenyl)acetonitrile (13). The procedure is a modification of that described by Matier et. al.[11] To a stirred solution of 9.80 g (0.200 mol) of sodium cyanide and 31.5 g (0.200 mol) of (*R*)-(+)-α-methylbenzylamine hydrochloride in 140 mL of water was added a solution of 27.2 g (0.200 mol) of *p*-anisaldehyde in 140 mL of methanol. The mixture was stirred at room temperature for 18 h, after which 500 mL of water was added. The oil that formed was extracted with CH_2Cl_2, the combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated under reduced pressure. The resulting oil (51.7 g, 97.2% yield) was assigned a diastereomer ratio by integrating the ^{1}H NMR singlets for the protons on the carbons bearing the nitriles. The oil was dissolved in ether, and methanolic HCl was added until the solution was ca. pH 1. The white solid that formed was collected by filtration and was identified as a mixture of diastereomers by ^{1}H NMR. The solid was repeatedly recrystallized from methanol/ether, with optical rotations measured after each recrystallization, until no change in optical rotation was observed and no minor diastereomer was observed by ^{1}H NMR. The yield of white crystalline salt was 29.4 g (48.5%): mp 127–128 °C; $[\alpha]^{22}$ +44.5°; NMR (CD_3OD) δ 1.78 (d, J = 6 Hz, 3 H), 3.80 (s, 3 H), 4.60 (qt, J = 6 Hz, 1 H), 5.25 (s, 1 H), 7.03 (d, J = 8 Hz, 2 H), 7.50 (s, 5 H), 7.53 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{17}H_{18}N_2O\cdot HCl$: C, 67.43; H, 6.33; N, 9.25. Found: C, 67.30; H, 6.45; N, 9.39.

Compounds **17–20** were prepared in a manner similar to the previous cases except that the reaction flask was sealed with a rubber septum and a methanol solution of the aldehydes was added with a syringe. Recrystallizations were carried out with ethyl acetate/ether.

(*R*,*R*)-(+)-β-[(1-Phenylethyl)amino]-4-methoxyphenethylamine (21). The free base of **13** (neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2) (3.0 g, 0.011 mol) in 100 mL of ethyl ether was added dropwise to a mechanically stirred suspension of 2.0 g (0.053 mol) of lithium aluminum hydride (LAH) in 400 mL of ethyl ether that was maintained between −10 and 0 °C under a nitrogen atmosphere. After 0.5 h the reaction mixture was allowed to slowly warm to room temperature and stirring was continued for 18 h.

The excess LAH was destroyed by sequential and cautious addition of 2 mL of H_2O, 2 mL of 15% aqueous NaOH, and 6 mL of H_2O. The resulting precipitate was removed by filtration, the filtrate was dried ($MgSO_4$) and concentrated, and the remaining oil was dissolved in ethyl acetate. Dry hydrogen chloride gas was slowly bubbled into the solution, affording a white insoluble solid. Recrystallization from methanol/ethyl ether yielded

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1.72 g (49%) of the monohydrochloride salt (the dihydrochloride salt was found to be a noncrystallizable, hygroscopic, amorphous solid): mp 203–204 °C; $[\alpha]^{22}$ +5.7°; NMR ($CDCl_3$) δ 1.38 (d, J = 6 Hz, 3 H), 3.09 (d, J = 7 Hz, 2 H), 3.5–3.8 (m) and 3.73 (s) (total = 4 H), 4.0–4.3 (m, 1 H), 6.40 (b s, 4 H), 6.7–6.9 (m, 2 H), 7.0–7.4 (m, 7 H).

Anal. Calcd for $C_{17}H_{22}N_2O$·HCl: C 66.55; H, 7.56; N, 9.13. Found: C, 66.74; H, 7.51; N, 9.18.

(*R*,*S*)-(+)-β-[(1-Phenylethyl)amino]-4-methoxyphenethylamine (24). The compound was prepared in the same manner as **21**: mp 222–224 °C; $[\alpha]^{22}$ +165.7°; NMR ($CDCl_3$) δ 1.43 (d, J = 6 Hz, 3 H), 3.20 (d, J = 7 Hz, 2 H), 3.4–3.9 (m) and 3.80 (s) (total = 5 H), 5.90 (b s, 5 H), 6.7–7.0 (m, 2 H), 7.1–7.4 (m, 7 H).

Anal. Calcd for $C_{17}H_{22}N_2O$·HCl·0.5H_2O: C, 64.44; H, 7.95; N, 8.84. Found: C, 64.47; H, 7.81; N, 8.78.

(*R*)-(+)-2-Amino-2-(4-methoxyphenyl)ethylamine (22). A solution of 25 g (0.082 mol) of **21**·2HCl in 800 mL of methanol was added to a suspension of 5.0 g of 10% Pd/C in 400 mL of methanol at 0 °C. The mixture was then shaken under an atmosphere of hydrogen at 50 psi and 45 °C for 48 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. Crystallization from methanol/ethyl ether afforded 18 g (94%) of white crystals: mp 158–159 °C; $[\alpha]^{22}$ +35.6°; NMR (CD_3OD) δ 3.6–3.8 (m, 3 H), 3.88 (s, 3 H), 7.13 (d, J = 9 Hz, 2 H), 7.67 (d, J = 9 Hz, 2 H).

Anal. Calcd for $C_9H_{14}N_2O$·2HCl: C, 45.20; H, 6.74; N, 11.71. Found: C, 44.82; H., 6.76; N, 11.55.

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Registry No. **1**, 87712-72-9; **2**, 87712-73-0; **3**, 87712-74-1; **4**, 87712-75-2; **5**, 87712-76-3; **6**, 87712-77-4; **7**, 87712-78-5; **8**, 87712-79-6; **9**, 87712-80-9; **10**, 87712-81-0; **11**, 87712-82-1; **12**, 87712-83-2; **13**, 87712-84-3; **13** free base, 87712-85-4; **14**, 87712-86-5; **15**, 87712-87-6; **16**, 87712-88-7; **17**, 87712-89-8; **18**, 87712-90-1; **19**, 87712-91-2; **20**, 87712-92-3; **21**·HCl, 87712-93-4; **21**·2HCl, 87712-94-5; **22**·2HCl, 87712-95-6; **24**·HCl, 87712-96-7; NaCN, 143-33-9; (*R*)-(+)-α-methylbenzylamine hydrochloride, 10277-86-8; *p*-anisaldehyde, 123-11-5.

Polycyclic Hydroxyquinones. 13.[1] A Novel Synthesis of Islandicin and Digitopurpone

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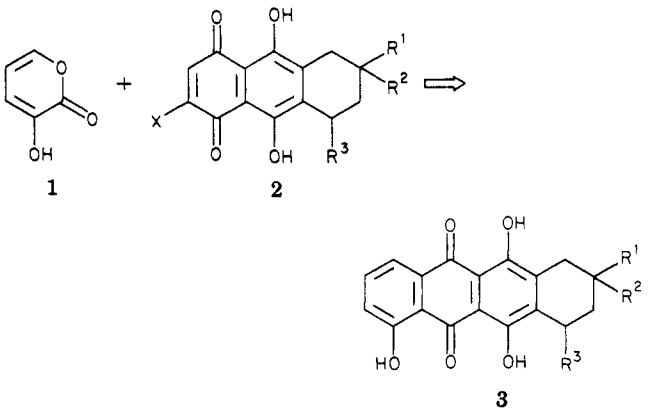
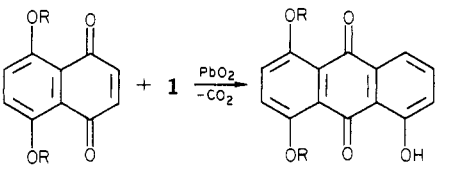
Recent interest in anthracyclines[2] is due to the useful antitumor activity which they possess and has stimulated the development of new routes to related systems and regiospecific synthesis of unsymmetrically substituted anthraquinones, which could be used as intermediates or synthetic models for anthracyclinones.

The use of 3-hydroxy-2-pyrone (1) as a diene in the Diels–Alder reaction, reported by Corey et al.,[3] could be of potential utility for the construction of the OH-substituted ring D of anthracyclinones. Thus, in view of the fact that the regiochemistry of the Diels–Alder reaction of 1 is controlled by the 3-OH group,[3] it seemed likely that the cycloaddition to an appropriate synthon of type 2 would afford tetracyclic precursors of anthracyclinones 3 in a simple and regiospecific way (Scheme I).

Scheme I



Scheme II



4, R = H
5, R = Ac

6, R = H
8, R = Ac

In the present paper we report on the Diels–Alder reaction of 3-hydroxy-2-pyrone (1) with naphthazarin (4), its diacetate (5), and adequately substituted derivatives, in order to gain more information on the reactivity of diene 1. We have also carried out a novel synthesis of the unsymmetrically substituted anthraquinones islandicin (15)[4] and digitopurpone (16)[5] which have served as models for the eventual construction of anthracyclinones.[6]

In a preliminary experiment, naphthazarin (4) and the diene 1 were refluxed in acetonitrile, affording in poor yields the known 1,4,5-trihydroxy-9,10-anthraquinone (6)[7] and 5,8-dihydroxy-2,3-dihydro-1,4-naphthoquinone (7).[8] The formation of 6 may be rationalized as a Diels–Alder reaction followed by extrusion of carbon dioxide and aromatization in the presence of the starting naphthazarin, which, in turn, is reduced to 7. In order to enhance the yield of the cyclization and to avoid the consumption of naphthazarin as an oxidant, we have conducted the reac-

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