Synthesis of Optically Active 2,3-Epoxycyclohexanone and the Determination of Its Absolute Configuration

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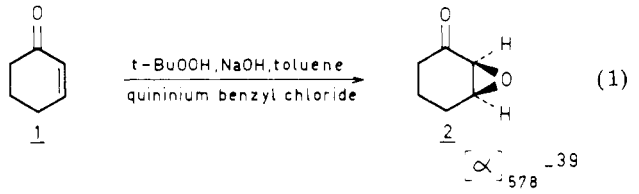
2,3-Epoxycyclohexanone (**2a**) has been obtained in optically active form by epoxidation of cyclohexenone in the presence of quininium benzyl chloride. The absolute configuration of the epoxy ketone has been established, and the transformation to (*R*)-(+)-cyclohex-2-en-1-ol (**3**) has been carried out without loss of optical activity.

The preparation of optically active epoxy ketones via asymmetric catalysis under phase-transfer conditions has been reported.[1] Enantiomeric yields up to 55% have been achieved.[2] The chiral epoxy ketone function is increasingly being recognized as an important functionality in its own right: as a metabolic intermediate,[3] as part of a growing list of physiologically active natural products,[4-10] and as a chiral synthon.[11] We therefore turned our attention to the epoxidation of cycloalkenones using a chiral catalyst. This paper describes the transformation of cyclohex-2-en-1-ones to the corresponding optically active epoxycyclohexanones.[12] Early attempts to epoxidize cyclohexenone, using our phase-transfer system, failed. The new successful epoxidation procedure involved the use of *tert*-butyl hydroperoxide in toluene to which catalytic quantities of solid sodium hydroxide and the chiral catalyst quininium benzyl chloride were added. It appeared essential to avoid the strongly basic aqueous layer in the chiral epoxidation of cyclohexenones.

When this heterogeneous mixture was allowed to react with cyclohexenone, a 60% chemical yield of optically active 2,3-epoxycyclohexanone,[13] with $[\alpha]_{578}$ −39°, was obtained. The enantiomeric excess (ee) determined by NMR using $Eu(tfc)_3$ as the chiral shift reagent was found to be 20 ± 3%.

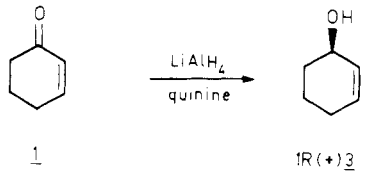
To our knowledge, optically active 2,3-epoxycyclohexanone has not been made previously. The new technique of asymmetric epoxidation, viz., toluene, quininium benzyl chloride, solid sodium hydroxide, and *tert*-butyl hydroperoxide, could be used to epoxidize a number of α,β-unsaturated ketones not amenable to asymmetric epoxidation via the hydrogen peroxide method. Cyclohexenones substituted at C-5[14] and C-6[15] with *gem*-dimethyl groups could easily be epoxidized but *gem*-dimethyl groups at C-4, and methyl groups at C-2 or C-3 gave no epoxidation, possibly due to steric hindrance.[16] The results of the epoxidation and the inductions are summarized in Table I.



(1)

Absolute Configuration

Both from the point of view of the reaction mechanism as well as for the interpretation of the CD spectra the knowledge of the absolute configuration of 2,3-epoxycyclohexanone is essential. Optically active (*R*)-(+)-cyclohex-2-en-1-ol[17] (**3**) was prepared by reduction of cyclohexenone following the method of Cervinka,[18] using $LiAlH_4$ in the presence of quinine (eq 2). The ee of



(2)

(*R*)-(+)-**3** with $[\alpha]^{RT}_{578}$ +21° (CH_2Cl_2) proved to be ca. 13%. Epoxidation of (*R*)-(+)-**3**, using MCPBA, which is known to proceed via cis epoxidation for >95%,[19a,20b] furnished nearly chemically pure (+)-2,3-epoxycyclohexan-1-ol[19b] (**4**) ($[\alpha]^{RT}_{578}$ +6.4° (CH_2Cl_2)) with an excess of the enantiomer with the 1*R*,2*R*,3*S* configuration. Further oxidation of (+)-**4** with pyridinium chlorochromate[20]

(1) (a) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; and Wynberg, H. *Tetrahedron Lett.* **1976**, 1831. (b) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, 1089. (c) Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.

(2) Wynberg, H.; Greydanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427.

(3) See, for example: Suttie, J. W.; Larson, A. E.; Canfield, L. M.; Carlisle, T. L., *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*, 2605 for the metabolic role of vitamin K epoxide.

(4) Bacilysin and similar epoxides: Walker, J. E.; Abraham, E. P. *Biochem. J.* **1970**, *118*, 563. Neuss, N.; Molloy, B. B.; Shah, R.; Dela Higuera, N. *Ibid.* **1970**, *118*, 571.

(5) Quinone epoxides: Sheehan, J. C.; Lawson, W. B.; Gaul, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 5536. Miller, M. W. *Tetrahedron* **1968**, *24*, 4839. Rashid, A.; Read, G. *J. Chem. Soc. C* **1969**, 2053. Read, G.; Rashid, A.; Vining, L. C. *J. Chem. Soc. C* **1969**, 2059. Lillie, T. J.; Musgrave, O. C.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 463.

(6) Crotepoxide: Kupchan, S. M.; Hemingway, R. J.; Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 2982. Demuth, M. R.; Garrett, P. E.; White, J. D. *Ibid.* **1976**, *98*, 634.

(7) Methylenomycin A: Scarborough, R. M., Jr.; Smith, III, A. B. *J. Am. Chem. Soc.* **1977**, *99*, 7085.

(8) Pimaricin: Patrick, J. B.; Williams, K. P.; Webb, J. S. *J. Am. Chem. Soc.* **1958**, *80*, 6689.

(9) 1,2-Epoxypulegone: Reitsema, R. H. *J. Am. Chem. Soc.* **1956**, *78*, 5022.

(10) Limonin: Arnott, S.; Davie, A. W.; Robertson, J. M.; Sim, G. A.; Watson, D. G. *Experientia* **1960**, *16*, 49.

(11) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.

(12) Further publications will describe our successful attempts with cyclopentenones and other cycloalkenones.

(13) (a) Nazarov, I. N.; Akhrem, A. A. *Tzvest. Akad. Nauk SSSR, Otd. Khim. Nauk Akad. Nauk SSSR, Gos. Opt. Inst. Sb. Statei* **1956**, 1383. *Chem. Abstr.* **1957**, *51*, 8021. (b) Felix, D.; Winter, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 52.

(14) Frank, R. L.; Hall, H. K., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 1645. Dauben, W. G.; Shaffer, G. W.; Vietmeyer, N. D. *J. Org. Chem.* **1968**, *33*, 4060.

(15) Freppel, C.; Poirier, M. A.; Richer, J. C.; Maroni, Y.; Manuel, G. *Can. J. Chem.* **1974**, *52*, 4133.

(16) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

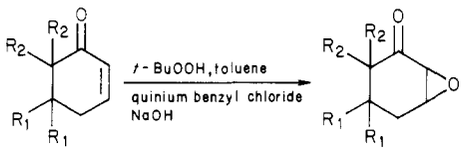
(17) (a) Otzek, L.; Pascual, J.; Sistaré, J. *An. R. Soc. Esp. Fis. Quim., Ser. B* **1966**, *62*, 965. (b) Hill, R. K.; Morgan, J. W. *J. Org. Chem.* **1968**, *33*, 927. (c) Yamada, S.; Takamura, N.; Mizoguchi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2539.

(18) Cervinka, O.; Kriz, O. *Collect. Czech. Chem. Commun.* **1973**, *38*, 294.

(19) (a) Chamberlain, P.; Roberts, M. L.; Whitman, G. H. *J. Chem. Soc. B*, **1970**, 1374. (b) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

0022-3263/80/1945-0158$01.00/0

Table I

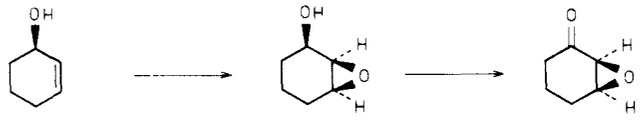


1 2

	yield,[a] %	$[\alpha]^{rt}_{578}$,[b] deg	ee,[c] %	reaction temp, °C
1a → 2a, $R_1 = R_2 = H$	54	−39	20	0-20
1b → 2b, $R_1 = CH_3$; $R_2 = H$	59	+9	16	−35 to +20
1c → 2c, $R_1 = H$; $R_2 = CH_3$	60	−15	15	20

[a] Yield after distillation of the product. [b] All rotations are measured in CH_2Cl_2 (concentration 1). [c] Determined by NMR with Eu(tfc)$_3$.

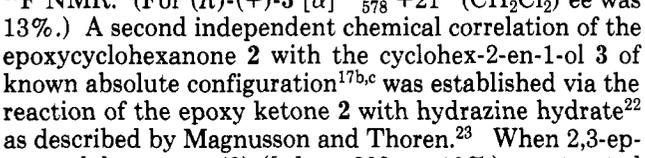
gave the desired optically active 2,3-epoxycyclohexanone (eq 3).



1R(+)3 1R,2R,3S(+)4 2S,3S(−)2

(3)

The rotation of the epoxy ketone thus obtained was $[\alpha]^{RT}_{578}$ −19° (CH_2Cl_2). If we assume the ee of this material to be identical with the ee of the starting chiral alcohol (+)-3, which was 13%, and compare this with the ee of 20% determined for the epoxy ketone with $[\alpha]_{578}$ −39° prepared by asymmetric catalysis, the values correspond within the experimental errors. Furthermore, 1*R*,2*R*,3*S* epoxy alcohol (+)-4 has furnished an epoxy ketone having a negative rotation. Thus the absolute configuration of (−)-epoxycyclohexanone is 2*S*,3*S*. The determination of the ee of (*R*)-(+)-3, although not essential to the establishment of the absolute configuration (the sign suffices), was nevertheless carried out. Attempted determination of the ee of the (*R*)-(+) alcohol 3 or of its acetate, using chiral Eu(tfc)$_3$ and NMR, failed. However, when (*R*)-(+)-3 was treated with optically pure α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, Mosher's reagent,[21] the two diastereomeric esters could be clearly distinguished, using ^{19}F NMR. (For (*R*)-(+)-3 $[\alpha]^{RT}_{578}$ +21° (CH_2Cl_2) ee was 13%.) A second independent chemical correlation of the epoxycyclohexanone 2 with the cyclohex-2-en-1-ol 3 of known absolute configuration[17b,c] was established via the reaction of the epoxy ketone 2 with hydrazine hydrate[22] as described by Magnusson and Thoren.[23] When 2,3-epoxycyclohexanone (2) ($[\alpha]_{578}$ −20°; ee 10%) was treated with hydrazine hydrate and a few drops of acetic acid in methanol at 0 °C for 0.5 h a 48% yield of chemically pure (*S*)-(−)-2-cyclohexenol, $[\alpha]_{578}$ −15° (ee 9%), was obtained. The reaction probably proceeds as in eq 4.



2S,3S(−)2 1S(−)3

(4)

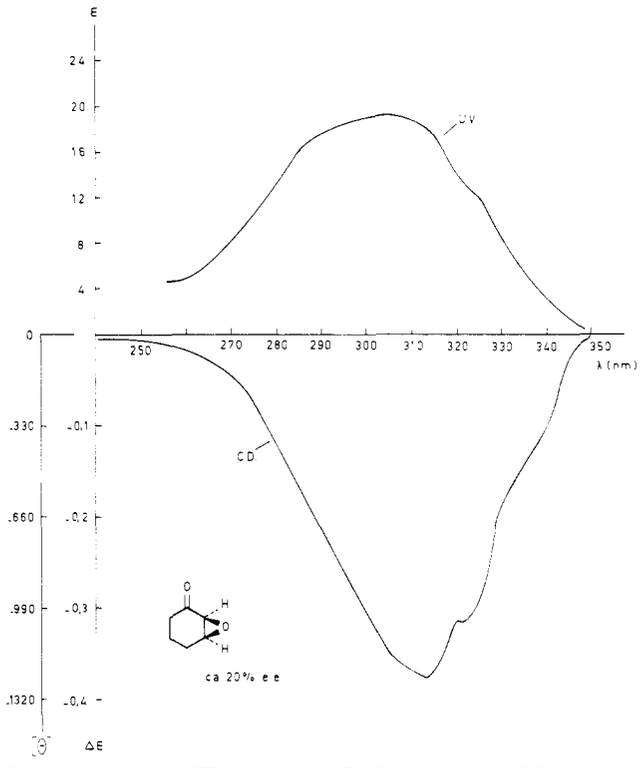
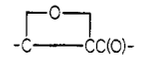


Figure 1. UV and CD spectra of (2*S*,3*S*)-(−)-epoxycyclohexanone, ee 20% in *n*-hexane.

The stereochemical integrity at C_3 of the epoxy ketone which becomes C_1 of the cycloalcohol is maintained during the reaction. Thus, again the absolute configuration of (−)-epoxycyclohexanone is *S* at C_3 and consequently *S* at C_2. The absolute configuration of this basic chromophore



is further supported nicely by the CD spectrum shown in Figures 1-3. The antioctant effect of the epoxide function upon the n–π* transition has been documented previously.[24] The oxygen of the epoxide function is in the left hand upper rear octant (see Figure 4), a (+) octant. Antioctant behavior then predicts a negative contribution to the sign of the cotton effect at the n–π* transition in accord with the spectrum (Figures 1-3).

The CD spectrum of 2,3-epoxycyclohexanone (ee 20%) (Figure 1) shows an extremum at λ 313 nm with Δε −0.376. In the same way, 5,5-dimethyl-2,3-epoxycyclohexanone (ee 11%) has an extremum at λ 305 nm with Δε −0.028 (Figure 2), and 6,6-dimethyl-2,3-epoxycyclohexanone (ee ca. 15%)

(20) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (b) Roberts, M. R.; Parsons, W. H.; Schlessinger, R. H. *J. Org. Chem.* **1978**, *43*, 3970.
(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(22) (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Coffen, D. L.; Korzan, D. G. *Ibid.* **1971**, *36*, 390.
(23) Magnusson, G.; Thoren, S. *J. Org. Chem.* **1973**, *38*, 1380.
(24) Djerassi, C.; Klyne, W.; Norin, T.; Ohloff, G.; Klein, E. *Tetrahedron* **1965**, *21*, 163.

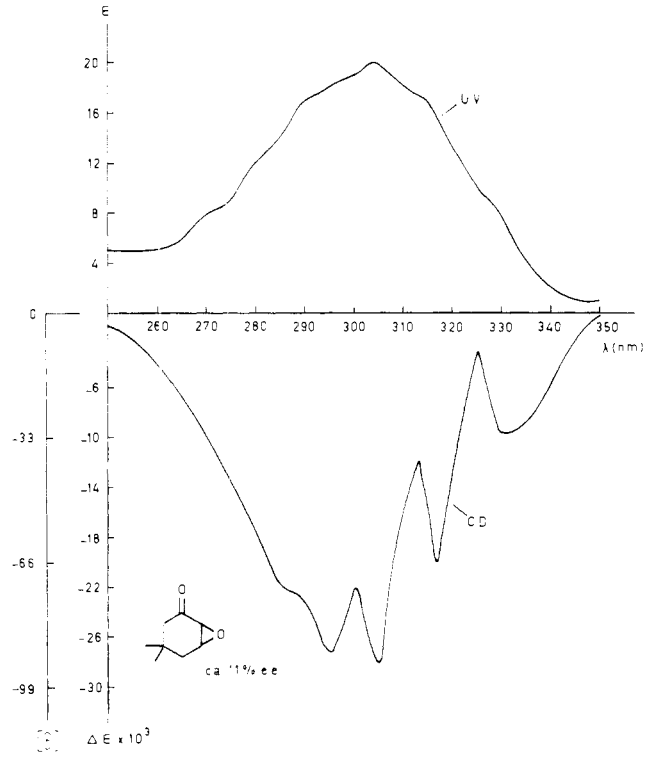


Figure 2. UV and CD spectra of (+)-*5,5*-dimethyl-2,3-epoxycyclohexanone, ee 11% in *n*-hexane.

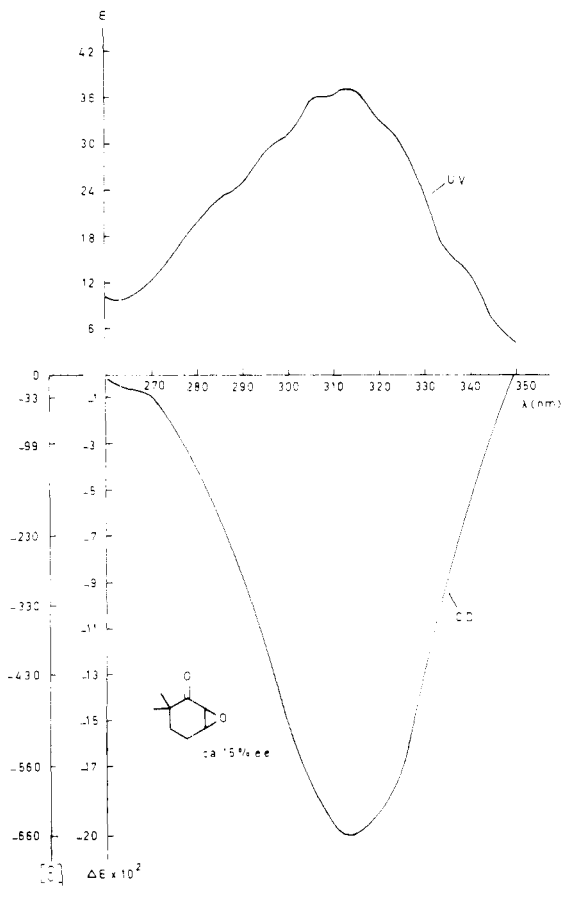


Figure 3. UV and CD spectra of (−)-6,6-dimethyl-2,3-epoxycyclohexanone in *n*-hexane.

has an extremum at λ 313 nm with Δε −0.201 (Figure 3).

Discussion

The synthesis, absolute configuration determination, and CD spectrum of the basic chiral chromophore (2*S*,3*S*)-(−)-epoxycyclohexanone (**2**) gives additional support to the numerous configurational assignments of chiral epoxy ketones[24,25] as well as to the semiempirical rules of Snatzke.[26]

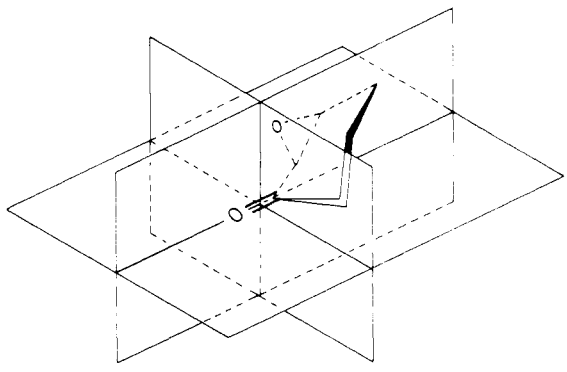


Figure 4.

Attempts were made to increase the asymmetric induction in the epoxidation by studying variations in structure of the cyclohexenone, solvent, base, and structure of the chiral catalyst. Of the four bases tried (NaOH, KO-*t*-Bu, LiOH, and Ag_2O), sodium hydroxide proved to be the best. Solvent variation (ether, CH_2Cl_2, CH_3OH, toluene) resulted in toluene as the solvent of choice, in full accord with previous[2] solvent studies. Salts of quinine[27] and salts of ephedrine[28,29] were used as chiral catalysts. Optimum results (ee 23%) were obtained using benzylmethyl ephedrinium bromide[29] in toluene, using sodium hydroxide and cyclohexenone for 4 h at room temperature. For 5,5-dimethylcyclohexenone, a lower reaction temperature resulted in a higher optical yield. Obviously, the asymmetric induction is still too low to speculate on a detailed mechanism. Nevertheless the method has been useful in preparing hitherto inaccessible chiral epoxides. Large gaps remain in our understanding of the process involved in these chiral asymmetric syntheses.

Experimental Section

(2*S*,3*S*)-(−)-Epoxycyclohexanone (2a). To a mixture of 9.8 g of cyclohexenone (100 mmol), 50 mL of toluene, 0.5 g of quininium benzyl chloride, and 100 mg of powdered NaOH was added at 0 °C 15 mL of a *t*-BuOOH solution (80%). After the solution was stirred for 4 h, ether was added, and the solution was extracted with 4 × 100 mL of H_2O. The organic layer was dried ($MgSO_4$) and evaporated, yielding 9.8 g of crude product. After Kugelrohr distillation, 6.17 g of pure product was obtained: yield 54%; $[\alpha]_{578}$ −38° (*c* 0.82, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.5 (m, 1 H), 3.1 (d, 1 H, ^3J = 4 Hz), 2.7–1.3 (m, 6 H).

5,5-Dimethyl-2,3-epoxycyclohexanone[30] (2b). To a mixture of 1.85 g of 5,5-dimethylcyclohexenone (15 mmol), 10 mL of toluene, 0.5 g of quininium benzyl chloride, and 100 mg of powdered NaOH was added at room temperature 10 mL of a *t*-BuOOH solution (80%). After the solution was stirred for 5 h, ether was added, and the solution was extracted with 4 × 50 mL of H_2O. The organic layer was dried ($MgSO_4$) and evaporated, yielding 1.75 g of crude product. After Kugelrohr distillation, 1.23 g of pure product was obtained: yield 59%; $[\alpha]^{578}$ +5.9° (*c* 0.64, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.5 (m, 1 H), δ 3.2 (d, 1 H), 2.8–1.6 (m, 4 H), 1.0 (s, 3 H), 0.9 (s, 3 H).

6,6-Dimethyl-2,3-epoxycyclohexanone (2c) was obtained in the same way: yield after Kugelrohr distillation of the product

(25) Scopes, P. M. In "Progress in the Chemistry of Organic Natural Products", Zechmeister, L.; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York: 1975; Vol. 32, p 185.
(26) Snatzke, G. *Angew. Chem.* **1979**, *91*, 363.
(27) Jacobs, W. A.; Heidelberger, H. *J. Am. Chem. Soc.* **1919**, *41*, 2090.
(28) Eberhard, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1915**, *253*, 65.
(29) Horner, L.; Brich, W. *Justus Liebigs. Ann. Chem.* **1978**, 710.
(30) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 4777.

60%; $[\alpha]_{578}$ -15° (c 0.68, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.6 (m, 1 H), 3.2 (d, 1 H), 2.3–1.3 (m, 4 H), 1.1 (s, 3 H), 1.0 (s, 3 H). Anal. Calcd: C, 68.54; H, 8.63. Found: C, 67.79; H, 8.65.

(*R*)-(+)-2-Cyclohexenol (3). $LiAlH_4$ (1.69 g, 44 mmol) was suspended in ca. 300 mL of dry ether. Quinine (44 mmol, 14.24 g) was added, and the suspension was refluxed for 15 min. After the mixture was cooled to 0 °C, 3.84 g of cyclohexenone (40 mmol) dissolved in 10 mL of ether was added, and stirring was maintained for 1 h at 0 °C. Water was added (ca. 5 mL) followed by 10% H_2SO_4 until all of the solid had disappeared. The water layer was extracted with ether (3 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated, yielding 2.6 g of cyclohexenol (58%), $[\alpha]_{578}$ +21.7° (c 1.95, CH_2Cl_2).

***cis*-2,3-Epoxycyclohexanol [(+)-4].** Cyclohexenol (1.5 g) ($[\alpha]_{578}$ +21.8) and 3.1 g of *m*-chloroperbenzoic acid (85% purity) were dissolved in CH_2Cl_2 at 0 °C. After the mixture was sitrred for 16 h, it was filtered and the organic layer extracted with dilute NaOH solution and H_2O. The organic layer was dried ($MgSO_4$) and evaporated, yielding 0.85 g of epoxide: $[\alpha]_{578}$ +6.4° (c 2.05, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.0 (m, 1 H), 3.3 (s, 2 H), 2.8 (s, OH), 2.0–1.0 (m, 6 H).

(*S*,*S*)-(-)-2,3-Epoxycyclohexanone. *cis*-2,3-Epoxycyclohexanol (0.85 g) ($[\alpha]_{578}$ +6.4), 1.44 g of sodium acetate, and 3.55 g of pyridinium chlorochromate were suspended in CH_2Cl_2, and the solution was stirred for 6 h. Ether was added, and the mixture was filtered over florisil. The organic layer was extracted with $NaHCO_3$ solution and with H_2O. After the solution was dried and evaporated, the product was obtained: yield 0.3 g; $[\alpha]_{578}$ -19° (c 1.54, CH_2Cl_2).

(*S*)-(-)-2-Cyclohexenol. To a solution of 2.2 g of (*S*,*S*)-(-)-2,3-epoxycyclohexanone in 25 mL of MeOH at 0 °C were added a few drops of acetic acid and 2.5 mL of hydrazine hydrate, and after the solution had been stirred for 0.5 h, it was evaporated. Water was added and extracted with ether. After drying ($MgSO_4$) and evaporating the organic layer, crude product was obtained. Distillation gave 0.93 g of pure (*S*)-(-)-2-cyclohexenol: yield 48%; $[\alpha]_{578}$ -15° (c 1.28, CH_2Cl_2).

Determination of the Enantiomeric Excess of Alcohol 3. Following the procedure described by Mosher,[21] the ester of the alcohol 3 ($[\alpha]_{578}$ +21°) was prepared, and its ^1H and ^{19}F NMR were determined: ^1H NMR ($CDCl_3$) δ 7.6–7.4 (m), 6.0–5.5 (m), 3.6 (s), 2.1–1.6 (m); ^{19}F NMR ($CFCl_3$) δ 72.1 (two signals).

Registry No. 1a, 930-68-7; **1b**, 4694-17-1; **1c**, 6553-64-6; **2a**, 72029-30-2; **2b**, 72003-85-1; **2c**, 72003-86-2; (*R*)-**3**, 3413-44-3; (*S*)-**3**, 6426-26-2; **4**, 72029-31-3.

Notes

Application of *N*-Phenyltrifluoromethanesulfonamides to the Synthesis of Pyrazines

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Introduction

The pyrazines have long been of interest to medicinal chemists. These compounds, many of which are natural products, have proven to be useful as antibiotics,[2] tuberculostatics,[3] diuretics,[4] organoleptics,[5] and antitumor agents.[6]

The two most common routes to these heterocycles involve either the self-condensation of α-amino ketones[7] or the condensation of 1,2-dicarbonyl compounds with 1,2-diamines,[8] followed by oxidation of the resulting dihydropyrazines to the corresponding pyrazines.[9] As with most synthetic methods, the utility of the sequence is limited by the accessibility of the starting materials. Unfortunately, none of the above starting materials is easily synthesized in high yield, and at least one group of them, the α-amino ketones, has the added problem of instability.

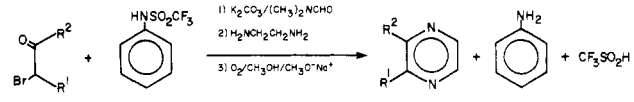
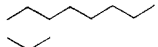


Figure 1. Reaction scheme for the synthesis of the pyrazines from the corresponding α-imino ketones.

Table I

R^1	R^2	yield, %
	CH_3	70
	CH_3	65
	CH_3	60
	CH_3	64

Results and Discussion

This investigation is directed at improving the diamine sequence described above. Our scheme emphasizes the synthesis of a reactive imino ketone intermediate which can be condensed with the appropriate diamine and the resulting dihydropyrazine oxidized to the corresponding pyrazine. The sequence proceeds in good yield and does not require the isolation of intermediates.

In an earlier investigation we determined that *N*-phenyltrifluoromethanesulfonamides could be alkylated

(1) This work was done in partial fulfillment of the requirements for a Doctorate in Chemistry at the University of Maryland.
(2) J. Briggs, *J. Chem. Soc.*, 2995 (1965).
(3) I. M. Weiner and J. P. Tinker, *J. Pharmacol. Exp. Ther.*, **180**, 411 (1972).
(4) Kenneth L. Shepard, Wasyl Halczenko, and Edward J. Cragoe, Jr., *J. Heterocycl. Chem.*, **13**, 1219 (1976).
(5) J. A. Maga and C. E. Sizer, "Pyrazines in Food", T. E. Furia and N. Bellanca, Eds., CRC Press, Inc., Cleveland, OH, 1975, p 47.
(6) Andre Rosowsky, Katherine K. N. Chem, and Nickolas Papathanasopoulos, *J. Heterocycl. Chem.*, **13**, 727 (1976).
(7) H. Iida, K. Hayashida, M. Yamada, K. Takahashi, and K. Yamada, *Synth. Commun.*, **3**, 225 (1973).
(8) N. Sato, *J. Heterocycl. Chem.*, **15**, 665 (1978).
(9) T. Akiyama, Y. Enomoto, and T. Shibamoto, *J. Agric. Food Chem.*, **26**, 1176 (1978).

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