2 Hz), 2.20 (1 H, dd, J = 12 and 6 Hz), 2.8 (1 H, m), 3.47 (1 H, m), 4.13 (1 H, distorted t, J = 2 Hz), 5.65 (1 H, ddd, J = 6, 3, and 2 Hz), 5.80–6.30 (3 H, overlapping multiplets), 6.80–7.25 (2 H, m).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.04. Found: C, 78.15; H, 6.04.

Compound **9** was obtained as colorless crystals: mp 105–106 °C, after recrystallization from cyclohexane; IR (Nujol) 1670, 1625, 1605, 1420, 1330, 1305, 1255, 1240, 1185, 1095, 1020, 955, 970, 930, 890, 865, 845, 820, 805 cm^{-1}; NMR (CCl_4) δ 1.40 (3 H, br s), 1.68 (2 H, s), 2.29 (2 H, narrow m), 4.31 (1 H, unresolved dd, J = 3 and 1 Hz), 5.87 (1 H, dd, J = 10 and 2 Hz), 6.01 (1 H, dd, J = 10 and 2 Hz), 6.57 (1 H, dd, J = 10 and 3 Hz), 6.90 (1 H, dd, J = 10 and 3 Hz).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.04. Found: C, 78.16; H, 6.05.

NMR analysis of the earlier eluted chromatographic fractions containing compound **9** revealed the presence of another component, which we were unable to isolate in pure form. The NMR spectrum of this compound, to which we have assigned structure **10**, was determined by subtracting the contribution made by **9** to the NMR spectrum of the mixture of **9** and **10**: NMR (CCl_4) δ 1.0 (1 H, d, J = 9 Hz), 1.7 (1 H, d, J = 9 Hz), 2.85 (1 H, t, J = 5 Hz), 2.9–3.2 (2 H, overlapping multiplets), 5.21 (1 H, t, J = 5 Hz), 5.7–6.0 (2 H, m), 6.1–6.5 (2 H, m), 6.8–7.3 (2 H, m).

Photocycloaddition of *p*-Benzoquinone to Quadricyclane. A solution of 2.0 g of *p*-benzoquinone and 35 mL of quadricyclane in 35 mL of benzene was irradiated for 7 h at room temperature. Removal of the solvent and unreacted quadricyclane under vacuum on a rotary evaporator provided 3.9 g of viscous yellow syrup, a small portion of which was dissolved in CCl_4 and re-evaporated several times. NMR analysis of the residue showed that it consisted almost entirely of the adducts **7** and **8** in a ratio of approximately 56:44. Only traces of **9** and **10** could be detected in the NMR spectrum of this mixture. Chromatographic separation of the crude product mixture by the procedure described above provided samples of pure **7** and **8** which were identical (melting point, IR, NMR) with the corresponding compounds obtained in the *p*-benzoquinone–norbornadiene reaction.

Catalytic Hydrogenation of 7. A solution of **7** (91 mg) in 95% ethanol (10 mL) was hydrogenated at 45 psig of hydrogen in the presence of 10% palladium/charcoal (20 mg) for 1 h. After removal of the catalyst and solvent, the crude product was dissolved in 10 mL of 5% NaOH, and the solution was extracted with ether (2 × 5 mL) and acidified with dilute HCl. Extraction of the resultant mixture with ether (3 × 5 mL), followed by washing of the combined ether extracts with saturated NaCl, drying over Na_2SO_4, and evaporation, provided the phenol **11** (37 mg) as a microcrystalline white powder: mp 152–154 °C, after recrystallization from benzene;[23] IR (Nujol) 3350 (br), 1615, 1600, 1510, 1240, 1180, 1150, 1110, 1065, 1035, 840, 810, 789, 776, 724 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 1.0–2.5 (8 H, m), 2.80 (1 H, d, J = 6 Hz, CHAr, endo), 3.85 (1 H, d, J = 6 Hz, CHOH, endo), 4.76 (2 H, br s, OH), 6.70 (2 H, d, J = 8 Hz, *o*-H in ArOH), 7.00 (2 H, d, J = 8 Hz, *m*-H in ArOH).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.22; H, 7.83.

Catalytic Hydrogenation of 8. A solution of **8** (210 mg) in 95% ethanol (20 mL) was hydrogenated at 45 psig of hydrogen in the presence of 10% palladium/charcoal (50 mg) for 1 h. The reaction mixture was worked up as described above, and the crude product was recrystallized from benzene to give the phenol **13** (132 mg) as colorless needles: mp 160–161 °C; IR (Nujol) 3300 (br), 1610, 1595, 1515, 1245, 1180, 1150, 1105, 1075, 840, 827, 722 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 1.0–2.4 (8 H, m), 2.74 (1 H, d, J = 6 Hz, CHAr, endo), 3.97 (1 H, br s, CHOH), 5.36 (2 H, br s, OH), 6.70 (2 H, d, J = 8 Hz, *o*-H in ArOH), 7.17 (2 H, d, J = 8 Hz, *m*-H in ArOH).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.38; H, 7.68.

Photocycloaddition of *p*-Benzoquinone to Norbornene. A solution of 2.0 g of *p*-benzoquinone and 5.0 g of norbornene in 50 mL of benzene was irradiated under nitrogen for 5 h at room temperature. Solvent and unreacted norbornene were removed by rotary evaporation under vacuum to give 3.5 g of brown syrup. A portion (1.7 g) of this material was chromatographed once on a 2.5 × 55 cm column of silica gel with C_6H_6–EtOAc (95:5) to provide 0.59 g of the crude oxetane **12** as a yellow oil,[24] which was used in the following experiment without further purification.

Catalytic Hydrogenation of 12. A portion (156 mg) of the product obtained in the preceding experiment was dissolved in 95% ethanol (15 mL) and hydrogenated at 45 psig of hydrogen in the presence of 10% palladium/charcoal (50 mg) for 1 h. The reaction mixture was worked up as before, and the crude product (91 mg), mp 148–151 °C, was recrystallized from benzene to give a microcrystalline white powder, mp 151–153 °C, the IR and NMR spectra of which were identical with those of the product (**11**) obtained in the hydrogenation of **7**.

Registry No. **1**, 121-46-0; **6**, 278-06-8; **7**, 72300-91-5; **8**, 72275-63-9; **9**, 72275-64-0; **10**, 72300-92-6; **11**, 72275-65-1; **12**, 72283-21-7; **13**, 72275-66-2; *p*-benzoquinone, 106-51-4.

(23) The earlier workers[2] gave a melting point of 119–120 °C for the reduction product of their photoadduct.

(24) NMR analysis of this product indicated that it was a mixture of the exo and endo isomers in a ratio of ~4:1.

Asymmetric Reductions of α,β-Acetylenic Ketones and Acetophenone Using Lithium Aluminum Hydride Complexed with Optically Active 1,3-Amino Alcohols

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Asymmetric reduction of the α,β-acetylenic ketones **9a–f** using the freshly prepared complex derived from $LiAlH_4$ and (2*S*,3*R*)-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol (Darvon alcohol; **10**) at −70 °C gives mainly the (*R*)-carbinols **1a–f** in yields of 62–99% and enantiomeric excesses of 34–90%. Similar treatment of **9e** with the complex formed from $LiAlH_4$ and **11**, the enantiomer of **10**, affords **2e**, a useful intermediate for the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E), in 96% yield and 90% ee. The optically pure 1,3-amino alcohol ligands **12–16**, which are structurally related to **10**, were prepared by starting from the known (*S*)-ether sulfonate **23** and its enantiomer. Reduction of **9a** and acetophenone using the $LiAlH_4$–**12** complex gives an excess of the corresponding (*S*)-carbinols **2a** (36% ee) and **27** (60% ee), respectively.

The optically active acetylenic carbinols **1a,b,d,e** and **2a,b,d,e** (Scheme I, Table I) are key intermediates in certain recently developed approaches to the total synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E) and related

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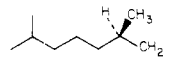
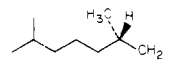
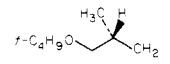
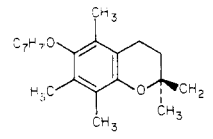
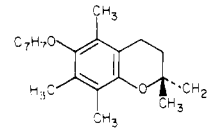
Table I. α,β-Acetylenic Ketones

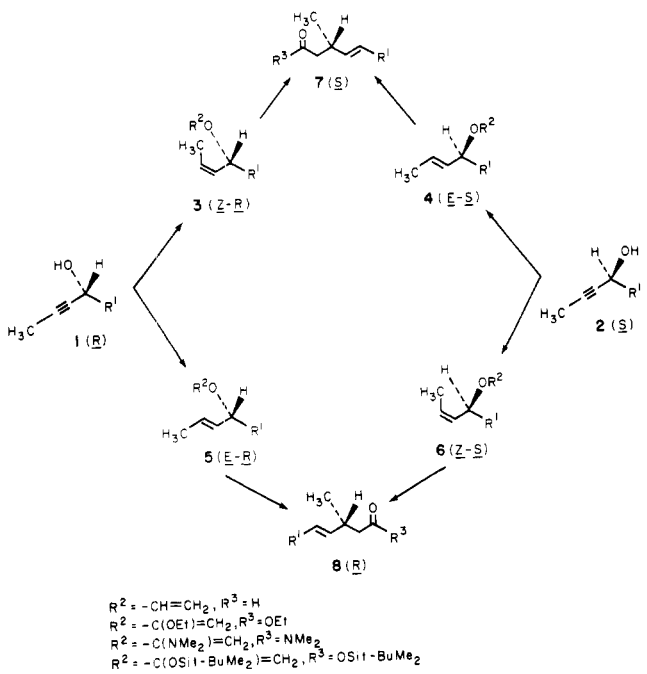
$R^1C(O)C{\equiv}CCH_3$

9

compd[a]	R^1	abs config	$[\alpha]^{25}_D$,[b] deg	bp, °C (mm)[c]	method[d]	yield, %[e]	formula
9a[k]	$(CH_3)_2CHCH_2$			98-101 (15)	A	80	$C_8H_{12}O$[f]
9b[g]		*R*	+14.62	73-76 (0.1)	B	90	$C_{13}H_{22}O$[f]
9c[h]		*S*	-15.87	69-72 (0.1)	B	63	$C_{13}H_{22}O$[f]
9d[h]		*R*	-2.70	75-78 (0.1)	B	77	$C_{12}H_{20}O_2$[f]
9e[i,j]		*S*	+5.30		A	85	$C_{25}H_{28}O_3$[f]
9f[i,j]		*R*	-5.59		A	94	$C_{25}H_{28}O_3$

[a] All compounds gave compatible IR, ^1H NMR, and mass spectra. [b] *c* 5, $CHCl_3$. [c] Bath temperature. [d] A = Jones oxidation,[10] B = modified Collins oxidation[11] of corresponding carbinol or mixture of epimeric carbinols. [e] Refers to chromatographically pure material. [f] This compound was analyzed for C and H and gave microanalytical values within 0.3% of theory. [g] Ca. 96% optically pure. [h] ≥99% optically pure. [i] Assumed to be ≥99% optically pure. [j] Viscous oil not distilled. [k] Turbanova, E. S.; Porfir'eva, Y. I.; Petrov, A. A. *Zh. Org. Khim.* **1966**, *2*, 772-7.

Scheme I



isoprenoids.[1] Crucial transformations in these schemes involve the "self-immolative",[2] asymmetric synthesis of intermediates such as **7** and **8**, in high enantiomeric purity, via [3,3] sigmatropic (Claisen[3,4]) rearrangements of the isomeric allylic alcohol derivatives **3–6**. Whereas (*Z*)-(*R*)-**3** and (*E*)-(*S*)-**4** both lead to (*S*)-**7**,[1a] the isomers possessing the alternative combinations of geometry and absolute configuration, namely, (*E*)-(*R*)-**5** and (*Z*)-(*S*)-**6**, generate the antipodal γ,δ-unsaturated carbonyl product (*R*)-**8**.[1b,c] In this manner, it is possible to construct naturally occurring isoprenoids by utilizing either a "right-to-left"[1a] or a "left-to-right"[1b,c] strategy. The required *Z* or *E* allylic alcohols (**3–6**, R^2 = H) are obtainable from the enantiomeric or epimeric acetylenic carbinols **1** and **2** by well-known selective reduction processes.[1,5]

Inherent in such approaches is the economic advantage that both antipodes or epimers of the chiral acetylenic alcohol, generated by standard, nonstereospecific means, may be employed for synthesis of the target molecule. On the other hand, the mandatory separation of (*R*)- and (*S*)-carbinols by classical resolution of a racemate[1a] or chromatographic fractionation of epimers[1a-c] is frequently tedious and labor intensive. Thus the stereospecific introduction of the carbinol center in **1** and **2** via asymmetric reduction[6] of the corresponding α,β-acetylenic ketones **9** (Table I) appeared to be a potentially valuable modifica-

(1) (a) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–505. (b) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1976**, *41*, 3512–5. (c) Chan, K.-K.; Specian, A. C., Jr.; Saucy, G. *Ibid.* **1978**, *43*, 3435–40; (d) Chan, K.-K.; Saucy, G. *Ibid.* **1977**, *42*, 3828–32.

(2) This rather dramatic but highly descriptive term has been employed to characterize certain examples of intramolecular chirality transfer via [2,3] sigmatropic rearrangements wherein the original chiral center is sacrificed in the process of forming a new chiral center. Cf.: (a) Moriwaki, M.; Yamamoto, Y.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1976**, *41*, 300–3. (b) Yamamoto, Y.; Oda, J.; Inouye, Y. *Ibid.* **1976**, *41*, 303–6.

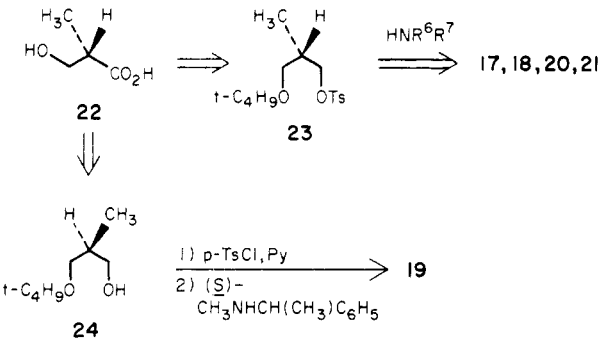
(3) For recent reviews of the Claisen rearrangement, see: (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1–252. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227–32. (c) Bennett, G. B. *Synthesis* **1977**, 589–606.

(4) For other examples of intramolecular chirality transfer in Claisen rearrangements, see: (a) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737–40. (b) Sucrow, W.; Schubert, B.; Richter, W.; Slopianka, M. *Chem. Ber.* **1971**, *104*, 3689–703. (c) Sucrow, W.; Caldeira, P.; Slopianka, M. *Ibid.* **1973**, *106*, 2236–45. (d) Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272–3.

(5) Reucroft, J.; Sammes, P. G. *Q. Rev., Chem. Soc.* **1971**, *25*, 135–69.

(6) For recent advances in the asymmetric reduction of ketones, see: (a) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329–56 and references cited therein. (b) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869–73. (c) Asami, M.; Mukaiyama, T. *Heterocycles* **1979**, *12*, 499–502. (d) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352–5. (e) Noyori, R.; Tomino, I.; Tanimoto, Y. *Ibid.* **1979**, *101*, 3129–31. (f) Hirao, H.; Mochizuki, H.; Nakahama, S.; Yamazaki, N. *J. Org. Chem.* **1979**, *44*, 1720–2.

Scheme II



tion of the existing synthetic schemes.[7]

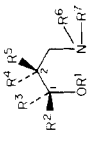
During the course of our studies on vitamin E, we became aware of the results obtained by a Stanford group,[8] involving the highly enantioselective asymmetric reduction of certain α,β-acetylenic ketones using the Mosher–Yamaguchi $LiAlH_4$–Darvon alcohol (**10**, Table II) complex.[9] The successful application of this procedure in an approach to steroids via biomimetic polyene cyclizations culminated in the development of an elegant asymmetric total synthesis of 11α-hydroxyprogesterone.[8c] Herein we wish to present our own results involving asymmetric reduction of propynyl ketones **9a–f**, utilizing the Mosher–Yamaguchi complex as well as related reagents derived from interaction of $LiAlH_4$ with certain new, optically active 1,3-amino alcohols.

Results

Preparation of Ketone Substrates. The α,β-acetylenic ketone substrates **9** were prepared in a straightforward manner, as shown in Table I, by Jones[10] or modified Collins[11] oxidation of the corresponding carbinol or epimeric carbinol mixture.[12] The chiral ketones **9b–f** possessed enantiomeric purities in the range of 95–100%.[16]

Preparation of New Optically Active 1,3-Amino Alcohol Ligands. In our previous synthetic studies involving the side chain of vitamin E, we had prepared the

Table II. Optically Active Amino Alcohols and Ethers



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	abs config	$[\alpha]^{25}_D$, deg	bp, °C (mm)[j]	method[a]	yield, %[b]	formula
10[c]	H	$C_6H_5CH_2$	C_6H_5	CH_3	H	CH_3	CH_3	*1S,2R*	+8.23[d]				$C_{19}H_{25}NO$
11[e]	H	C_6H_5	$C_6H_5CH_2$	H	CH_3	CH_3	CH_3	*1R,2S*	−7.64[d]				$C_{19}H_{25}NO$
12[m]	H	H	H	CH_3	H	CH_3	CH_3	*R*	−41.74[f]	70–73 (22)	C	88	$C_6H_{15}NO$[g,h]
13	H	H	H	CH_3	H	CH_3	(*S*)-$CH(CH_3)C_6H_5$	*R*	−62.47[f]	88–91 (0.025)	C	90	$C_{13}H_{21}NO$[g,h]
14	H	H	H	H	CH_3	CH_3	(*S*)-$CH(CH_3)C_6H_5$	*S*	+20.23[f]	88–91 (0.025)	C	90	$C_{13}H_{21}NO$[g,i]
15	H	H	H	CH_3	H	$C_6H_5CH_2$	$C_6H_5CH_2$	*R*	−102.51[f]	106–110 (0.025)	C	84	$C_{18}H_{23}NO$[g,i]
16[n]	H	H	H	CH_3	H	$-(CH_2)_4-$		*R*	−39.43[f]	95–98 (10)	C	82	$C_8H_{17}NO$[g,h]
17	*t*-C_4H_9	H	H	CH_3	H	CH_3	CH_3	*R*	−1.50[f]	72–74 (20)	A	90	$C_{10}H_{23}NO$[g,h]
18	*t*-C_4H_9	H	H	CH_3	H	CH_3	(*S*)-$CH(CH_3)C_6H_5$	*R*	−21.28[f]	81–84 (0.15)	B	73	$C_{17}H_{29}NO$[g,i]
19	*t*-C_4H_9	H	H	H	CH_3	CH_3	(*S*)-$CH(CH_3)C_6H_5$	*S*	−26.93[f]	81–84 (0.15)	B	73	$C_{17}H_{29}NO$[g,i]
20	*t*-C_4H_9	H	H	CH_3	H	$C_6H_5CH_2$	$C_6H_5CH_2$	*R*	+22.82[f]	100 (0.0075)[l]	B	41	$C_{22}H_{31}NO$[g,k]
21	*t*-C_4H_9	H	H	CH_3	H	$-(CH_2)_4-$		*R*	−6.12[f]	85–90 (10)	B	50	$C_{12}H_{25}NO$[g,i]

[a] See Experimental Section. [b] Data refer to pure products isolated by column chromatography and/or evaporative distillation. [c] (2*S*,3*R*)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol (*d*-propoxyphene carbinol base; Darvon alcohol), supplied by Eli Lilly Co. [d] *c* 6, C_2H_5OH. [e] Enantiomer of Darvon alcohol, supplied by Eli Lilly Co. [f] *c* 5, $CHCl_3$. [g] This compound furnished compatible IR, ^1H NMR, and mass spectra. [h] A satisfactory C, H, and N microanalysis (±0.4%) could not be obtained for this compound. [i] This compound was analyzed for C, H, and N and gave values within 0.3% of theory. [j] Bath temperature (evaporative distillation). [k] This compound was analyzed for C and H and gave values within 0.3% theory. [l] This compound crystallized on standing giving a solid, mp 29–31 °C. [m] The racemic modification of this compound is known: Traynelis, V. J.; Dadura, J. G. *J. Org. Chem.* **1961**, *26*, 686–691. Reported boiling point 62 °C (20 mm). [n] The racemic modification of this compound is known: Moffett, R. B. *J. Org. Chem.* **1949**, *14*, 862–867. Reported boiling point 91 °C (12 mm).

(7) The enantiomeric carbinols **1a** and **2a** have recently been obtained (although not in optically pure form) by microbial asymmetric hydrolysis of the corresponding racemic acetate: Mori, K.; Hiroko, A. *Tetrahedron Lett.* **1978**, 4127–30.

(8) (a) Johnson, W. S. Centennial Meeting of the American Chemical Society, New York, Apr 1976; American Chemical Society: Washington, DC; Abstr. ORGN 20. (b) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339–41. (c) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *Ibid.* **1977**, *99*, 8341–3. We are grateful to Professor Johnson and Dr. Brinkmeyer for providing us with details of their work prior to publication.

(9) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870–7.

(10) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45. See also: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley-Interscience: New York, 1976; Vol. I, p 142.

(11) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–1.

(12) The preparations of **1a**,[1a] **2a**,[1a] **1b**,[1a] **2b**,[1a] **1d**,[1b] **2d**,[1b] **1e**,[1c] and **2e**,[1c] all of which are useful for the production of (2*R*,4′*R*,8′*R*)-α-tocopherol, have been reported. The mixture of carbinols **1c** and **2c** was prepared by starting from **24**,[13] via (*S*)-(−)-dihydrocitronellal, as described for the **b** series.[1a,13] The mixture of carbinols **1f** and **2f** was prepared by starting from (*R*)-(+)-6-(benzyloxy)-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-acetic acid[14] as described for the **e** series.[1c,15]

(13) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505–11.

(14) Cohen, N.; Scott, J. W.; Bizzarro, F. T.; Lopresti, R. J.; Eichel, W. F.; Saucy, G.; Mayer, H. *Helv. Chim. Acta* **1978**, *61*, 837–43.

(15) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–306.

(16) The chromanyl ketones **9e,f** are susceptible to racemization via a β-elimination process. While we were unable to rigorously exclude the possibility of racemization during the preparation of these compounds, such an occurrence would seem highly unlikely under the mild conditions of the Jones oxidation procedure.[10] The enantiomeric purities of precursors to **9b–d** have been established previously.[1a,b]

Table III. Asymmetric $LiAlH_4$ Reductions of α,β-Acetylenic Ketones[a]

entry	substrate	chiral ligand	bp of prod, °C (mm)[b]	$[\alpha]^{25}_D$ of prod,[c] deg	% 1 (R)[d]	% 2 (S)[d]	% ee[d]	yield, %[e]
1	9a	10	98-101 (16)	+12.16[f]	91	9	82[g]	99
2	9a	12		-5.17[f,h]	32	68	36[g]	82
3	9a	13	83-92 (20)	*i*	49	51	2[g]	84
4	9a	14	84-90 (20)	*i*	47	53	6[g]	91
5	9a	15		-1.48[f,h]	45	55	10[g]	79
6	9a	16		-4.59[f,h]	33	67	34[g]	70
7	9b	10	78-80 (0.075)[j]	+7.97[j]	82	18	64[g]	78
8	9c	10	78-80 (0.075)	*i*	84	16	68[g]	62
9	9c	none	78-80 (0.075)	*i*	55	45	10[g]	84
10	9d	10	95-97 (0.02)	*i*	93	7	86[k]	94
11	9e	10		-25.62[l,m]	67	33	34[n]	87
12	9e	11		-37.23[l,m,o]	5	95	90[n]	96
13	9e	12		-35.33[l,m]	14	86	72[n]	60
14	9f	10		+35.38[l]	95	5	90[n]	93
15	9f	12		+21.82[l]	33	67	34[n]	75
16	9f	none		+31.10[l]	60	40	20[n]	83
17	9e,f[p]	10		+7.07[l]	80	20	60[n]	93

[a] All reductions performed at -70 °C[8] as described in the Experimental Section. [b] Bath temperatures (evaporative distillation). [c] *c* 5, $CHCl_3$. [d] Data refer only to carbinol center. [e] Data refer to pure products obtained by column chromatography and, in series a-d, evaporative distillation as well. [f] Lit.[1a] bp 58-59 °C (1 mm), $[\alpha]^{25}_D$ +13.48° (*c* 4.9, $CHCl_3$) for **1a**; bp 54-55 °C (0.3 mm), $[\alpha]^{25}_D$ -13.02° (*c* 5.0, $CHCl_3$) for **2a**. [g] Determined by GC analysis of the (*R*)-MTPA ester derivative; see ref 1a. [h] Chromatographed product not distilled. [i] Rotation not determined. [j] Lit.[1a] bp 87 °C (0.2 mm) (bath temperature), $[\alpha]^{25}_D$ +10.52° (*c* 3.3, $CHCl_3$) for **1b**; bp 87 °C (0.15 mm) (bath temperature), $[\alpha]^{25}_D$ -10.08° (*c* 2.9, $CHCl_3$) for **2b**. [k] Determined by direct GC analysis of carbinol epimers; see ref 1b. [l] Chromatographed product was a viscous oil. [m] Lit.[1c] mp 89-91 °C, $[\alpha]^{25}_D$ -16.2° (*c* 5, $CHCl_3$) for **1e**; mp 74-76 °C, $[\alpha]^{25}_D$ -42.0° (*c* 5, $CHCl_3$) for **2e**. [n] Estimated by direct ^1H NMR spectroscopy ($CDCl_3$, 100 MHz) using ratio of diastereomeric CH_3 singlets at δ 1.29 (*S,R* or *R,S*) and 1.34 (*S,S* or *R,R*); see ref 1c. [o] One recrystallization from CCl_4-hexane gave a colorless solid: mp 68-73.5 °C; $[\alpha]^{25}_D$ -41.77° (*c* 3, $CHCl_3$). [p] Racemic substrate.

bifunctional, four-carbon synthons **23** and **24** (Scheme II) starting from the microbiologically derived (*S*)-(+)-hydroxy acid **22**.[13] The ready availability of these intermediates encouraged us to synthesize several simple analogues of **10** as described in Table II. Our objectives were twofold. First, we sought optically pure ligands whose accessibility and efficacy in inducing high enantiomeric excesses (ee's) in the reduction of a variety of structurally diverse ketones were superior to those of **10**. Second, because of theoretical as well as practical considerations, we were interested in determining the relative importance of the two chiral centers in **10**. By studying analogues such as **12**, which lack the chiral tertiary carbinol center, we hoped to gain some insight regarding the structural factors in the ligand required for achieving high optical yields.

The new amino alcohols were prepared in a standard manner. Thus, condensation of (*S*)-(+)-ether tosylate **23** with various secondary amines provided the amino ethers **17**, **18**, **20**, and **21** which, in turn, gave the desired (*R*)-1,3-hydroxy amines **12**, **13**, **15**, and **16**, respectively, upon exposure to trifluoroacetic acid. In a similar manner, the antipodal tosylate (derived from **24**) yielded (*S*)-amino ether **19**, and ultimately, **14**. Since the starting synthons are known to be 99–100% optically pure[13] and because the simple transformations employed to produce the amino alcohols would not be expected to induce racemization, we assume that the new ligands described in Table II are also essentially enantiomerically homogeneous.

Asymmetric Hydride Reductions. Our results involving asymmetric hydride reductions of the α,β-acetylenic ketone substrates **9** are summarized in Table III. All experiments were carried out at -70 °C[8b] with insoluble, freshly prepared complexes in an effort to achieve maximum stereoselectivity.[8b,9] Chemical yields were in the range of 60–99%. Analysis of carbinol composition was carried out in entries 1–9 by GC of the (*R*)-MTPA ester derivatives,[1a,17] by direct GC in entry 10, and by direct ^1H NMR spectroscopic observation of the epimers in entries 11–17.

As Brinkmeyer and Kapoor had observed,[8b] all reductions utilizing the Mosher–Yamaguchi complex led to products in which the (*R*)-carbinol configuration predominates (entries 1, 7, 8, 10, 11, 14, 17). With the exception of entry 11, the ee's[18] are substantial (64–90%). The first entry, involving prochiral ketone **9a**, presents a result essentially identical with that reported by Brinkmeyer and Kapoor.[8b] The remaining substrates (**9b–f**) all possess a chiral center in a β position relative to the ketone moiety. Thus the possibility of double asymmetric induction exists in these examples. For reference purposes, two of the chiral substrates (**9c,f**) were reduced, at -70 °C, with uncomplexed $LiAlH_4$ (entries 9, 16), giving carbinol products having small but significant enantiomeric excesses.

In the aliphatic series, both the isobutyl (**9a**) and *tert*-butoxyisobutyl (**9d**) substrates give high (>80%) ee's (entries 1, 10). When the carbon skeleton in R^1 is extended to 2,6-dimethylheptyl as in **9b,c**, the ee drops to 60–70% (entries 7, 8). In this latter series, reversal of the substrate methyl stereochemistry has little effect on the course of reduction. We were most surprised, however, to find that the (*S*)-chroman substrate **9e**, when reduced with the $LiAlH_4$–Darvon alcohol complex, gives **1e** in relatively low ee (34%, entry 11). In contrast, the antipodal (*R*)-ketone **9f**, under identical conditions, reduces with high stereoselectivity, affording an approximately 19:1 mixture of carbinols in which the (*R,R*)-epimer **1f** is preponderant (entry 14).[19] Similar treatment of the racemic modification (**9e,f**) gives a carbinol ratio which is in agreement with

(17) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–9. (b) Hub, L.; Mosher, H. S. *Ibid.* **1970**, *35*, 3691–4.

(18) For convenience, the ratio of reduction products is described, in the present discussion, in terms of enantiomeric excess at the newly introduced carbinol center even though the products in series **b–f** are epimers and not enantiomers. Enantiomeric excess is defined as the percent excess of one enantiomer over the racemate.[9]

(19) We have been informed that reduction of **9f** with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (derived from (+)-α-pinene) gives, in 77% yield, an 85:15 mixture of carbinols **1f** and **2f**, respectively (70% ee) (personal communication from Professor M. Mark Midland).

that expected on the basis of the results obtained with the individual enantiomers (entry 17).

It should be noted that the chromanyl propynyl ketones are potentially capable of racemization via base-catalyzed β elimination during reduction; however, the substantially different stereochemical results noted with the enantiomeric substrates strongly suggest that such racemization does not occur. Furthermore, oxidation[10] of the carbinol mixture derived from treatment of **9f** with the Mosher–Yamaguchi complex regenerates **9f** having essentially unchanged optical rotation.

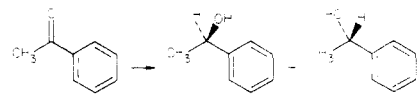
Returning to the application of these asymmetric reductions in vitamin E synthesis, our observations indicated that treatment of the "natural" (*S*)-chromanyl ketone **9e** with the complex derived from $LiAlH_4$ and the enantiomer of Darvon alcohol (**11**) would yield a result very useful for the production of (2*R*,4′*R*,8′*R*)-α-tocopherol (i.e., the highly stereoselective synthesis of **2e**). This goal was achieved as shown in entry 12. Thus it was possible to obtain, in 96% yield from **9e**, a 19:1 mixture of **2e** and **1e**, respectively, one recrystallization of which furnished essentially pure **2e**.[20]

Our results from utilization of the new ligands **12–16** were highly intriguing and modestly rewarding. Reduction of the prochiral ketone **9a** with the complex of $LiAlH_4$ and amino alcohol **12** gives mainly the (*S*)-enantiomer **2a** (entry 2). While the ee (36%) is smaller than that observed with **10**, *the predominant carbinol antipode now possesses the opposite absolute configuration.* This trend in direction of asymmetric induction holds for the chroman substrates. Thus both **9e** and **9f** yield an excess of the (*S*)-carbinol epimers when reduced with $LiAlH_4$–**12** (entries 13, 15). In comparing these two latter experiments, it is interesting to note that, as with the complex of **10**, substantially different ee's are observed, starting from the two enantiomeric substrates; however, now **9e**, rather than **9f**, is reduced with the greater stereoselectivity (cf. entries 11, 14).

Of the remaining ligands, only the pyrrolidino analogue **16** shows promise as a chiral adjunct in hydride reductions such as these. Using this amine to effect asymmetric reduction of **9a**, we obtained a result very similar to that noted with **12** (entry 6). Disappointingly, compounds **13** and **14**, which contain an additional chiral center attached to the N atom, give only very low ee's when applied to the reduction of **9a** (entries 3, 4). Similarly, the *N*,*N*-dibenzyl analogue **15** provides only a 10% ee when applied to the same substrate (entry 5).

In order to determine whether any of the new ligands might possess utility for the asymmetric reduction of other types of ketones, we applied three of them to the reduction of acetophenone. The results are summarized in Table IV. Using the $LiAlH_4$–**12** complex, we obtained an 83% yield of (*S*)-(−)-methylphenylcarbinol (**27**), having an ee of 60%. This optical yield is comparable to that reported by Mosher and Yamaguchi[9] for reduction of **25** with the insoluble, unaged $LiAlH_4$–**10** complex; however, as with the propynyl ketones **9a,e,f**, the *opposite carbinol enantiomer is now predominant.*[21] The complex of $LiAlH_4$ and **16** when employed for the reduction of **25** also produced mainly **27** but in somewhat lower ee relative to the result obtained with **12**. On the other hand, $LiAlH_4$–**15** afforded a very small excess of the (*R*)-carbinol **26**.

Table IV. Asymmetric $LiAlH_4$ Reductions of Acetophenone[a]



25 26 27

chiral ligand	bp of prod, °C (mm)[b]	$[\alpha]^{25}_D$ of prod,[c] deg	% 26 (*R*)[d]	% 27 (*S*)[d]	% ee[d]	yield, %[e]
12	85–90 (11)	−24.96	20	80	60 (58)	83
15	88–90 (11)	+1.15	51	49	2 (3)	84
16		−20.10	26	74	48 (47)	86[f]

[a] All reductions performed at −70 °C on 1.3–1.5 mmol of **25** as described in the Experimental Section. [b] Bath temperature (evaporative distillation). [c] *c* 7–8, cyclopentane. [d] Determined by GC analysis of the (*R*)-MTPA ester derivative.[17] See the Experimental Section for conditions. The ee values in parentheses are derived from the observed optical rotations by using $[\alpha]^{25}_D$ +43.1° (*c* 7, cyclopentane) as the reference value for enantiomerically pure **26**; see ref 9. [e] Data refer to pure products obtained by column chromatography and distillation in the first two entries. [f] Chromatographed product not distilled.

Discussion

From the foregoing results, several generalizations can be made. (1) In agreement with Brinkmeyer and Kapoor,[8b] we have found that α,β-acetylenic ketones can be reduced with the Mosher–Yamaguchi complex in generally good chemical and optical yields, giving product mixtures in which the (*R*)-carbinol configuration predominates. (2) The enantiomeric ratios appear to be determined by a subtle combination of structural factors present in the substrate as well as the chiral ligand. In certain of the chiral substrates, a double asymmetric induction effect can be observed, leading to either increased or diminished stereoselectivity. (3) The complexes derived from $LiAlH_4$ and the simple Darvon alcohol analogues **12** and **16** are reducing species which can effect substantial asymmetric induction when applied to α,β-acetylenic ketones or acetophenone but which, for reasons that are not at all obvious, induce a preponderance of the carbinol chirality opposite to that observed by using **10**. From these observations it becomes apparent that the chiral secondary methyl center in **10**, although relatively distant from the site of complexation with aluminum, is, alone, capable of exerting a substantial effect on the asymmetric induction. (4) The utility of these processes for the synthesis of natural vitamin E has been demonstrated and is best exemplified by the reduction of the (*S*)-chromanyl ketone **9e** with the complex of $LiAlH_4$–**11**, yielding **2e**[1c] in 96% yield and 90% ee.

We had hoped that data accumulated by altering various structural parameters in both substrate and ligand would shed some light on the factors responsible for the relatively high ee's which we and others[8,9] have noted in studying these reductions. While definite trends are seen, we have been unable to elucidate transition states whose stereochemical consequences readily accommodate the observed results. Such considerations are complicated by a lack of knowledge regarding the precise structure of the reducing species involved and by the finding that these complexes

(20) In contrast, the addition of propynylmagnesium bromide to (*S*)-(+)-6-(benzyloxy)-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-acetaldehyde, while also diastereoselective, affords a (2–2.5):1 ratio of **1e** to **2e**.[1c] This mixture requires recrystallization of the 3,5-dinitrobenzoate derivatives followed by further recrystallization of the regenerated carbinols in order to obtain the pure epimers for transformation to vitamin E.[1c]

(21) It has been reported that acetophenone can be reduced with the complex of $LiAlH_4$ and (*S*)-2-(anilinomethyl)pyrrolidine, at −78 °C, to give **27** in 84% yield and 84% ee.[6b]

(at least those derived from **10**) contain *two* molecules of the chiral ligand.[9] Furthermore, the unusually high ee's noted in the reductions of aryl and acetylenic ketones relative to saturated aliphatic substrates[8] suggest that electronic as well as steric factors must be taken into account. It would appear that, at this point, substantially more work will be required before a full understanding of these transformations is forthcoming, and we offer no unfounded mechanistic speculations herein.

From a practical point of view, the synthetic utility of asymmetric ketone reductions using the complex of $LiAlH_4$ and Darvon alcohol should now be well established. It is hoped that the complexes derived from the new, readily available, optically pure ligands **12** and **16** described above will become useful additions to the rapidly expanding armamentarium of reagents[6] capable of effecting asymmetric carbonyl reductions.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of argon. Column chromatography was performed by using EM silica gel 60 (0.063–0.2 mm). Reactions were monitored by thin-layer chromatography using EM silica gel 60 F-254 precoated plates with either 1:1 hexane–ether or 1:1 toluene–ethyl acetate as the mobile phase. Spots were detected with UV light and phosphomolybdic acid spray followed by heating. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. ^1H NMR spectra were obtained in $CDCl_3$ solution. Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were obtained in $CHCl_3$ solution. GC analyses of the (*R*)-MTPA ester derivatives[1a,17] were carried out by using a Hewlett-Packard 5710A instrument with a 3 m × 4 mm (i.d.) column of 10% OV-225 on GCQ 100/120, isothermally at 180 °C, with a carrier-gas flow rate of 30 mL/min. Base-line separation was observed. The (*R*)-carbinol derivatives were always eluted first. The "usual workup" involves three to six extractions with the specified solvent. Organic solutions were then washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator under water-aspirator pressure. MTPA derivatives[1a,17] were prepared by stirring the carbinol mixture with 1.5 equiv of optically pure acid chloride[17] ($[\alpha]^{25}_D$ +134.5° (*c* 2.5, CCl_4)) derived from (*R*)-(+)-MTPA[17] ($[\alpha]^{25}_D$ +73° (*c* 1.5, CH_3OH)) in anhydrous pyridine at room temperature until TLC analysis indicated complete esterification (usually overnight).

Preparation of α,β-Acetylenic Ketones. Procedure A. Jones Oxidation.[10] The preparation of (*S*)-(+)-1-[6-(benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-1-benzopyran-2-yl]-3-pentyn-2-one (**9e**) is representative. A solution of 150 mg (0.397 mmol) of (*S,S*)-carbinol **2e**[1c] in 3 mL of acetone was stirred with ice-bath cooling while 0.13 mL (0.52 millimolar equiv) of standard Jones reagent[10] was added dropwise over a 5-min period. The resulting mixture was stirred for 0.5 h and then decomposed by the addition of 12% aqueous $NaHSO_3$ solution. Workup with ether in the usual manner (the ether extracts were additionally washed with saturated aqueous $NaHCO_3$) gave a yellow oil which was chromatographed on 40 g of silica gel. Elution with 9:1 and 4:1 benzene–ethyl acetate afforded 126 mg (85%) of **9e** as a viscous oil (see Table I): IR 2220 (C≡C), 1665 cm^{-1} (conjugated ketone C=O); NMR δ 7.42 (m, 5, C_6H_5), 4.75 (s, 2, OCH_2), 2.96 (s, 2, $CH_2C{=}O$), 2.72 (t, 2, $ArCH_2$), 2.31, 2.26, 2.20 (3 s, 9, $ArCH_3$), 2.05 (s, 3, $CH_3C{\equiv}C$), 2.02 (t, 2, CH_2), 1.52 (s, 3, C-2 CH_3); mass spectrum, *m/z* 386 (M^+). Virtually identical results were obtained by starting from a mixture[1c] of **1e** and **2e**.

Procedure B. Modified Collins Oxidation.[11] The preparation of (*R*)-(−)-1-*tert*-butoxy-2-methylhept-5-yn-4-one (**9d**) is representative. To a solution of 2.37 g (30 mmol) of purified[11] pyridine in 30 mL of purified[11] CH_2Cl_2 was added 1.20 g (12 mmol) of chromium trioxide. After being stirred at room temperature for 15 min, the mixture was treated dropwise with a solution of 396 mg (2 mmol) of an approximately 1:1 mixture of carbinols **1d** and **2d**[1b] in 6 mL of purified CH_2Cl_2 over a 10-min period. The reaction mixture was stirred for 30 min after the addition was complete. The CH_2Cl_2 solution was decanted from the tarry precipitate and washed with 1 N aqueous NaOH, water, and brine. Completion of the usual workup gave 441 mg of a brown liquid which was chromatographed on 40 g of silica gel. Elution with 9:1 and 4:1 hexane–ether followed by evaporative distillation afforded 300 mg (77%) of pure **9d** (see Table I): IR 2220 (C≡C), 1665 cm^{-1} (conjugated ketone C=O); NMR δ 3.16 (m, 2, OCH_2), 2.46 (m, 2, $CH_2C{=}O$), 2.30 (m, 1, CH), 2.00 (s, 3, $CH_3C{\equiv}C$), 1.16 (s, 9, $(CH_3)_3C$), 0.94 (d, 3, *J* = 6 Hz, CH_3CH).

Preparation of Amino Alcohols. Procedure A. Synthesis of (*R*)-(−)-(3-*tert*-Butoxy-2-methyl-1-propyl)dimethylamine (17). A solution of 5.70 g (19 mmol) of (*S*)-ether tosylate **23**[13] in 60 mL of tetrahydrofuran was cooled in a dry ice–acetone bath and treated with ca. 10 mL of liquefied dimethylamine. The resulting mixture was stirred and heated at 100 °C in a pressure bottle for 4.5 h (42 lb/in^2). The reaction mixture was cooled in an ice bath and poured onto 0.5 N aqueous NaOH. Workup with ether in the usual manner gave 3.9 g of a pale yellow liquid. Evaporative distillation afforded 2.95 g (90%) of amino ether **17** as a colorless liquid (see Table II): NMR δ 3.27, 2.99 (2 m, 2, CH_2O), 2.10 (s, $N(CH_3)_2$), 1.08 (s, 9, $(CH_3)_3C$), 0.84 (d, 3, *J* = 6.5 Hz, CH_3CH). Various samples of this compound consistently gave low C, H, and N microanalytical values despite evidence of high purity provided by spectral and GC analyses.

Procedure B. The preparation of (*S,S*)-(−)-α,*N*-dimethyl-*N*-[2-methyl-3-[(1,1-dimethylethyl)oxy]propyl]benzenemethanamine (**19**) is typical. A solution of 6.0 g (20 mmol) of the *R* tosylate derived from (*S*)-hydroxy ether **24**[13] and 6.85 g (50 mmol) of (*S*)-(−)-*N*,α-dimethylbenzylamine in 60 mL of *N,N*-dimethylformamide was stirred and heated at 100 °C for 6 h. The resulting solution was cooled to room temperature and poured onto 0.5 N aqueous NaOH. Workup with ether in the usual manner gave 8.1 g of a yellow oil which was chromatographed on 200 g of silica gel. Elution with toluene–ethyl acetate mixtures (9:1 to 1:2) followed by evaporative distillation afforded 3.85 g (73%) of pure **19** as a colorless liquid (see Table II): NMR δ 7.28 (m, 5, C_6H_5), 3.55 (q, 1, *J* = 6.5 Hz, $NCHCH_3$), 3.26, 2.99 (2 m, 2, OCH_2), 2.13 (s, NCH_3), 1.86 (m, 1, $CHCH_3$), 1.32 (d, 3, *J* = 6.5 Hz, $NCHCH_3$), 1.14 (s, 9, $(CH_3)_3C$), 0.89 (d, 3, *J* = 6.5 Hz, $CHCH_3$).

Procedure C. The preparation of (*R*)-(−)-3-(dimethylamino)-2-methyl-1-propanol (**12**) is representative. A 4.39-g (25.4 mmol) sample of amino ether **17** was stirred with ice-bath cooling while 40 mL of trifluoroacetic acid was added dropwise. The resulting solution was stirred at room temperature for 20 h and then concentrated under water-aspirator pressure. The residue was treated with excess 20% aqueous NaOH, and the alkaline mixture was stirred for several minutes before being diluted with saturated brine. Workup with ether in the usual manner gave a yellow liquid residue which was evaporatively distilled. There was obtained 2.6 g (88%) of amino alcohol **12** as a colorless liquid (see Table II): IR 3200 cm^{-1} (OH); NMR δ 5.82 (br m, 1, OH), 3.51 (m, 2, OCH_2), 2.24 (s, m, 9, $N(CH_3)_2$, NCH_2, $CHCH_3$), 0.73 (d, 3, *J* = 6.5 Hz, CH_3CH); mass spectrum, *m/z* 117 (M^+). Various samples of this compound gave consistently low C, H, and N microanalytical values despite evidence of high purity provided by GC and spectral analyses. The higher molecular weight compounds required longer saponification times and the addition of methanol in order to assure complete cleavage of trifluoroacetate intermediates.

General Procedure for Asymmetric $LiAlH_4$ Reductions. A solution of 4.1 mmol of the optically active amino alcohol ligand in 7.5 mL of anhydrous ether (freshly distilled from $LiAlH_4$) was added dropwise to a stirred mixture of 1.8 mmol of $LiAlH_4$ in 45 mL of anhydrous ether, at 0 °C, over a period of ca. 2 min. After the addition was complete, the mixture was stirred for 2 min and then cooled to −72 °C (dry ice–acetone bath) whereupon a solution of 1.5 mmol of the ketone in 7.5 mL of anhydrous ether was added dropwise over a 10-min period. The resulting mixture was stirred at −72 °C for 7 h, then allowed to warm to room temperature over a 14-h period, and finally decomposed by the addition of water. The ether layer was washed several times with 1 N aqueous HCl to remove the amino alcohol and then processed in the usual manner. The residue was chromatographed on silica gel. The pure carbinol products were eluted with hexane–ether mixtures and evaporatively distilled or dried to constant weight under high vacuum (see Tables III and IV). Basification of the combined aqueous acidic extracts followed by saturation with NaCl and ether

extraction allowed recovery of the amino alcohol ligand.

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Registry No. **1a**, 60018-69-1; **1b**, 59983-84-5; **1c**, 72443-71-1; **1d**, 59983-28-7; **1e**, 64704-95-6; **1f**, 72443-72-2; **2a**, 60018-72-6; **2b**, 59983-36-7; **2c**, 72443-73-3; **2d**, 59983-27-6; **2e**, 64765-29-3; **2f**, 72443-74-4; **9a**, 13046-02-1; **9b**, 72443-75-5; **9c**, 72443-76-6; **9d**, 72443-77-7; **9e**, 72443-78-8; **9f**, 72443-79-9; **10**, 38345-66-3; **11**, 72541-03-8; **12**, 72443-80-2; **13**, 72453-30-6; **14**, 72443-81-3; **15**, 72443-82-4; **16**, 72496-14-1; **17**, 72443-83-5; **18**, 72443-84-6; **19**, 72443-85-7; **20**, 72443-86-8; **21**, 72443-87-9; **23**, 59965-12-7; **24**, 59965-11-6; **25**, 98-86-2; **26**, 1517-69-7; **27**, 1445-91-6; dimethylamine, 124-40-3; (*S*)-(−)-*N*,α-dimethylbenzylamine, 19131-99-8.

Synthesis of Biologically Active Metabolites of Dibenz[*a*,*h*]anthracene

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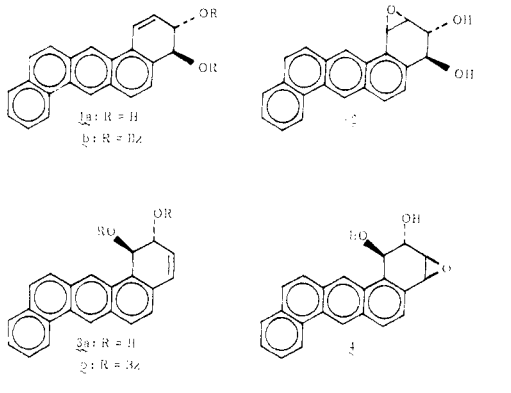
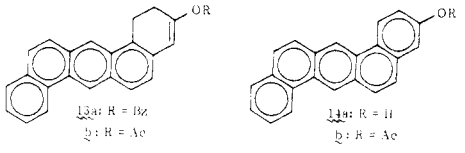
Syntheses are described of the trans 1,2- and 3,4-dihydro diol metabolites (**3a** and **1a**) of dibenz[*a*,*h*]anthracene (DBA) and the corresponding diol epoxide derivatives **4** and **2**, implicated as the ultimate carcinogenic metabolites of DBA. The syntheses of **1a** and **3a** are accomplished from DBA via lithium–ammonia reduction to 1,4,7,8,11,14-hexahydrodibenz[*a*,*h*]anthracene, base-catalyzed isomerization, Prévost reaction, dehydrogenation, and basic methanolysis. This approach involves considerably fewer steps and affords superior overall yields than obtainable by more conventional methods entailing multistep ring construction. Epoxidation of **1a** affords stereospecifically the anti diol epoxide isomer **2**, whereas similar reaction of **3a** furnishes a mixture of the corresponding syn and anti diol epoxide isomers in 3:1 ratio. Biological evidence implicates **1a** and **2** as proximate and ultimate carcinogenic forms, respectively, of DBA. Synthesis of 3-hydroxydibenz[*a*,*h*]anthracene, also known to be a metabolite of DBA, is also described.

Dibenz[*a*,*h*]anthracene (DBA) was the first pure polycyclic aromatic hydrocarbon demonstrated to be carcinogenic.[1] Subsequently, it has been the subject of intensive investigation and has been identified as a widespread environmental contaminant present in the atmosphere, soil, automobile exhaust, cigarette smoke, and foods.[2] Recent evidence indicates that polycyclic aromatic hydrocarbons undergo metabolic activation to highly mutagenic trans dihydro diols which may undergo further metabolic transformation to reactive diol epoxides capable of binding covalently to nucleic acids and inducing tumor formation.[3,4] In the case of DBA, there is evidence for the in vitro metabolic formation of significant amounts of all three possible dihydro diols,[5] and the 3,4-dihydro diol (**1a**) has been demonstrated[6] to undergo cytochrome P-450 catalyzed activation to a mutagenic metabolite presumed to be the corresponding anti diol epoxide derivative (**2**).[7]





Syntheses of the dihydro diols **1a** and **3a** from the corresponding ketonic intermediate 4-oxo- and 1-oxo-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracenes (**5** and **6**) in six steps each (in overall yields of 8% and 17%, respectively) are reported in a recent communication by Karle et al.[8] Compounds **5** and **6** were themselves synthesized from

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(2) International Agency for Research on Cancer: "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds"; World Health Organization: Geneva, Switzerland, 1973; Vol. 3.
(3) Reviews: (a) Harvey, R. G. In "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens: The Chemist's Viewpoint"; Walters, D. B., Ed.; Ann Arbor Science Publishers, Inc.: Ann Arbor, Mich., in press. (b) Harvey, R. G.; Fu, P. P. In "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism"; Gelboin, H. V., T'so, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 1, Chapter 6, p 133. (c) Yang, S. K.; Deutsch, J.; Gelboin, H. V., ref 3b, Chapter 10, p 205. (d) Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H., ref 3b, Chapter 9, p 189.
(4) Sukumaran, K. B.; Harvey, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 1353.
(5) Boyland, E.; Sims, P. *Biochem. J.* **1965**, *97*, 7. Sims, P. *Biochem. Pharmacol.* **1970**, *19*, 795.
(6) Wood, A. W.; Levin, W.; Thomas, P. E.; Ryan, D.; Karle, J. M.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 1967.
(7) Depicted is the anti isomer in which the epoxide oxygen atom and the benzylic hydroxyl group in the 4-position are on opposite faces of the ring; the syn isomer has these groups on the same face of the molecule.
(8) Karle, J. M.; Mah, H. D.; Jerina, D. M.; Yagi, H. *Tetrahedron Lett.* **1977**, 4021.

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