# Asymmetric Phenol Oxidation. Stereospecific and Stereoselective Oxidative Coupling of a Chiral Tetrahydronaphthol[1]

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The study of the factors which determine the intermolecular asymmetric phenol oxidation shows the importance of the stereochemical control exerted by asymmetry in the substrate. The oxidative coupling of (*S*)-(+)-2-hydroxy-3,4,8-trimethyl-5,6,7,8-tetrahydronaphthalene ((*S*)-(+)-1) resulted in the completely stereoselective formation of the optically active dinaphthol (*S*,*S*)-(+)-*trans*-**2a**. The results argue against the necessity of an asymmetric oxidant in intermolecular phenol coupling reactions. The synthesis of enantiomerically pure (*S*)-(+)-1 was completed by a six-step route from racemic 7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoic acid ((*R*,*S*)-**16**), which was resolved via its (+)-dehydroabietylamine salts. The chiroptical data of the tetrahydronaphthols **1**, **10**, **16**, and **23**–**25** and of dinaphthol **2a** are presented. Diastereomeric charge-transfer interactions, which resulted in long-range asymmetric influences, were observed in amides **27** and **29**.

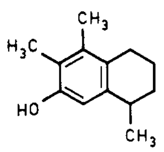
During the elucidation of key steps in natural phenol oxidation processes, a great deal of effort was focussed on the stereochemistry of the oxidation products especially in relationship with enzyme stereospecificity in the coupling step.[2] The early suggestions that the "in vivo" asymmetric phenol oxidation, in which the enzyme is the chiral agent, is probably common to several biosynthetic coupling pathways could not clearly be confirmed experimentally. Lack of stereospecificity in "in vivo" oxidations was attributed to a coupling reaction outside the active side of the enzyme.[2,3] These interpretations were mainly based on a free-radical mechanism of phenol coupling.

Numerous examples of natural phenol oxidation products are known in which the elements of chirality are introduced during the coupling step.

Stereochemical control could also be exerted by the asymmetric centers present in the substrate. The stereospecific chemical oxidation of reticuline to salutaridine is an example of the stereochemical control found in the intramolecular oxidative conversions of chiral 1-benzylisoquinolines.[2,4] Bobbitt and co-workers, in an elegant study of the intermolecular oxidative coupling of isoquinolines, reported the stereospecific and stereoselective chemical and electrochemical dimerization of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline.[5]

This paper reports the details of the synthesis and the stereospecific and stereoselective intermolecular oxidative coupling of a chiral tetrahydronaphthol.

The following requirements had to be met with respect to the choice of the substrate 3,4,8-trimethyl-5,6,7,8-tetrahydro-2-naphthol (1): (i) C–C coupling must be possible; (ii) there must not be a diversity of coupling modes; (iii) the new chirality must be created during the coupling step; (iv) no epimerization must take place at any of the chiral centers in the product under the reaction

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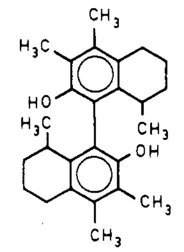


2

conditions. Model studies indicate that steric hindrance in **2** is large enough to prevent fast rotation around the $C_1C_1'$ biaryl bond and to create a barrier for rotation comparable to the one in 2,2′-dihydroxy-1,1′-dinaphthyl.

## Results and Discussion

**Synthesis of *dl*-3,4,8-Trimethyl-5,6,7,8-tetrahydro-2-naphthol (1).** The synthesis of *dl*-1 is pictured in Scheme I. The first four steps were performed in analogy to the routes as described by Lars and co-workers[6] and Fieser and Hersberg.[7]

The acid **6** was cyclized with polyphosphoric acid to 5,6-dimethyl-7-methoxy-α-tetralone (**7**). A Grignard reaction using methyl iodide yielded carbinol **8**, which was readily dehydrated with iodine to the dihydronaphthalene **9**.

During the dehydration small amounts of naphthalene derivative **12** were formed. Catalytic hydrogenation with $H_2$ and 5% Pd/C afforded *dl*-**10**, which was converted into *dl*-1 by means of hydroiodic acid in acetic acid. Analytically pure *dl*-1 was obtained by chromatography followed by crystallization. The structures of the compounds are based on the synthetic route and are consistent with analytical and spectroscopic data. The IR spectrum of *dl*-1 (mp 88.5–89.5 °C) showed the characteristic hydroxyl absorption at 3300 cm$^{-1}$. In the $^1$H NMR spectrum, a doublet was present for the $C_8$ methyl protons (δ 1.12), a multiplet for the cyclohexane H's (δ 1.5–2.8), two singlets for the $C_3$ and $C_4$ methyl H's (δ 2.07, 2.09), and singlets for the OH (δ 5.25) and aromatic protons (δ 6.3) in agreement with structure 1.

**Synthesis of (*S*)-(+)-3,4,8-Trimethyl-5,6,7,8-tetrahydro-2-naphthol ((*S*)-(+)-1). Attempted Resolution of *dl*-1 via Diastereomeric Derivatives.** For the resolution of *dl*-1 a route was chosen in which *dl*-1 was con-

(1) Partially published in a preliminary communication: B. Feringa and H. Wynberg, *J. Am. Chem. Soc.*, 98, 3372 (1976).
(2) (a) W. I. Taylor and A. R. Battersby, Eds., "Oxidative Coupling of Phenols", Marcel Dekker, New York, 1967; (b) H. Erdtman and C. A. Wachtmeister, "Festschift A Stoll", Birkhauser Verlag, Basle, Switzerland, 1957, p 144; (c) D. H. R. Barton and T. Cohen, *ibid.*, p 117; (d) A. I. Scott, *Q. Rev., Chem. Soc.*, 19, 1 (1965).
(3) Asymmetric phenol oxidation with a chiral oxidant has recently been achieved: B. Feringa and H. Wynberg, *Bioorg. Chem.*, 7, 397 (1978).
(4) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972).
(5) J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, 35, 2884 (1970); M. Tomita, Y. Masaki, and K. Fujitani, *Chem. Phar. Bull.*, 16, 257 (1968); J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Am. Chem. Soc.*, 93, 3551 (1971); J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Org. Chem.*, 41, 845 (1976); G. G. Lyle, *ibid.*, 41, 850 (1976).
(6) J. Lars, G. Nilsson, H. Selander, H. Sievertsson, and J. Skanberg, *Acta Chem. Scand.*, 24, 580 (1970).
(7) L. F. Fieser and E. B. Hersberg, *J. Am. Chem. Soc.*, 58, 2314 (1936).

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Scheme I. Synthesis of Racemic Trimethyl-5,6,7,8-tetrahydro-2-naphthol

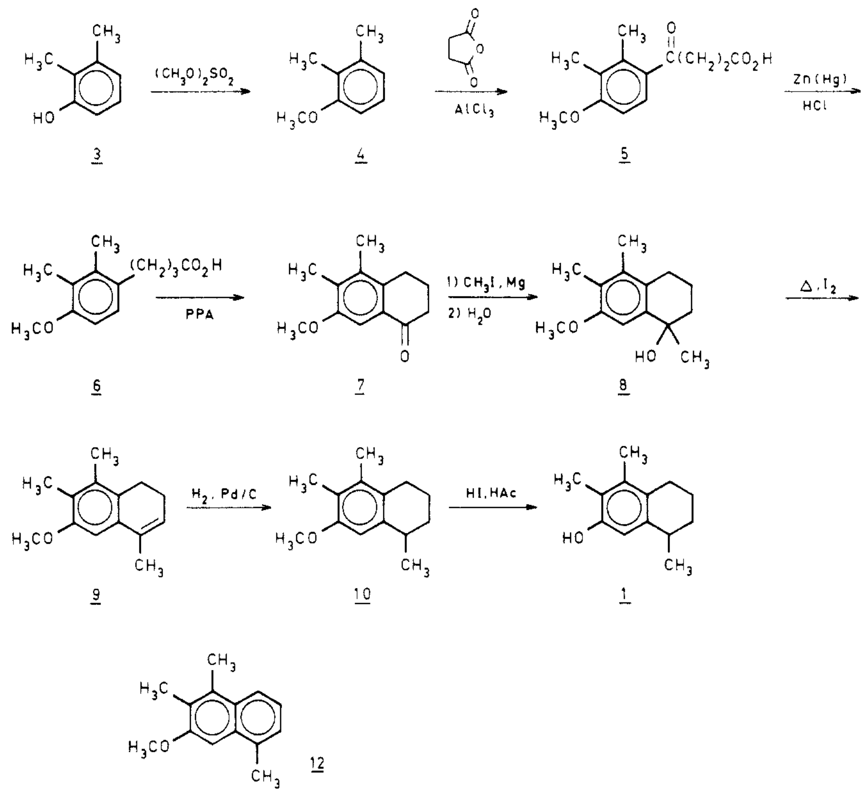
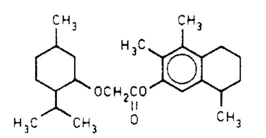
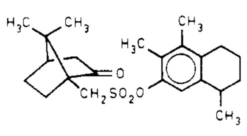
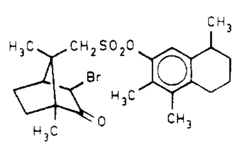


Table I. Chiral Derivatives of (*R*,*S*)-1 (Mixture of Diastereoisomers)

| no. | compd | mp, °C | $[\alpha]^{22}_{578}$ |
|---|---|---|---|
| 13 |  | — (oil) | 61.0° (c 0.54, $CH_3OH$) |
| 14 |  | 3-5 | 67.1° (c 0.37, $C_2H_5OH$) |
| 15 |  | 120-126 | 64.7° (c 0.26, $C_2H_5OH$) |

verted into a mixture of diastereomeric esters, followed by separation of the esters into diastereoisomers and hydrolysis to *d*-1 and *l*-1. The esters 13–15 (Table I) were prepared from the corresponding enantiomeric pure acid chlorides and *dl*-1. The 1-menthoxyacetic acid ester of *dl*-1 was an oil that failed to crystallize. The *d*-camphor-10-sulfonic acid ester of *dl*-1 was an oil at 20 °C, and although at 0 °C a solid was obtained, no separation into the diastereoisomers by means of crystallization could be achieved.

The ester **15** was a crystalline compound. Several crystallizations from ethanol showed only small changes in the rotation of **15**, and hydrolysis of **15** after three crystallizations yielded **1** which had a small optical activity ($[\alpha]_{578}$ −0.4°, ethanol). These results indicate that resolution of *dl*-1 via diastereomeric derivatives **13**, **14**, or **15** is not promising since enantiomerically pure **1** is necessary in studying the oxidation of **1**. Chromatographic separation of the diastereoisomers of **13–15** was not successful.

**Synthesis of *dl*-5,6-Dimethyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthoic Acid (*dl*-16).** Compound **16** was chosen as a target molecule for the synthesis of enantiomeric pure **1**.

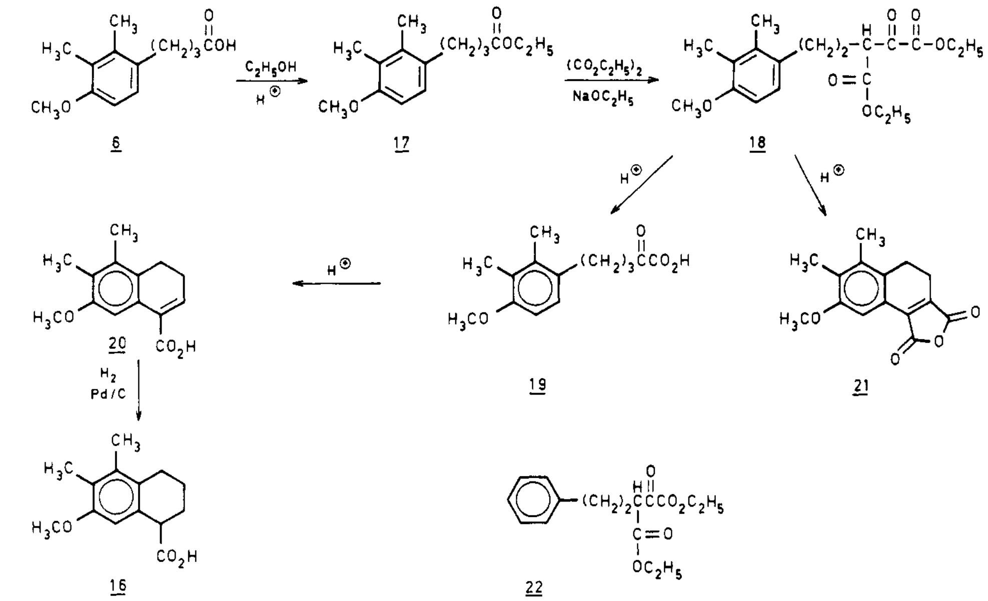
The synthesis of *dl*-**16** is pictured in Scheme II. The acid **6** was almost quantitatively converted into the ethyl ester **17**. Condensation of **17** with diethyl oxalate by using sodium ethoxide furnished **18**. Hydrolysis and subsequent decarboxylation of **18** with 5% $H_2SO_4$ yielded $\alpha$-keto acid **19**, which was converted into **20** by prolonged heating with 5% $H_2SO_4$ solution or by cyclization with 65% $H_2SO_4$. A complication during the hydrolysis and decarboxylation steps of **18** was the cyclization to anhydride **21**. When 15% $H_2SO_4$ or more concentrated $H_2SO_4$ solutions were used, as for the decarboxylation of **22**,[8] the cyclization to **21** was the main reaction (80% of **21** formed).

Compound **20** (mp 189–190 °C) showed in the $^1H$ NMR spectrum singlets for the aromatic H ($\delta$ 7.24), the carboxylic H ($\delta$ 10.5), and the methoxy H's ($\delta$ 3.74) and, furthermore, a triplet for the olefinic proton ($\delta$ 7.21). Hydrogenation of **20** using $H_2$ and 5% Pd/C yielded *dl*-**16**, mp 161–162.5 °C. The $^1H$ NMR spectrum of *dl*-**16** showed singlets for the $OCH_3$ protons ($\delta$ 3.73), the aromatic H ($\delta$ 6.58), and the carboxylic H ($\delta$ 10.2). All compounds described had spectral data in agreement with the assigned structures.

**(*S*)-(−)-5,6-Dimethyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthoic Acid ((*S*)-(−)-16).** The tetrahydronaphthoic acid *dl*-**16** was resolved via its diastereomeric (+)-dehydroabietylamine salts (DHAA salts) by fractional crystallization. Hydrolysis of the salt ($[\alpha]^{20}_{578}$ +23.05°) with 50% acetic acid solution afforded the (−)-acid **16**

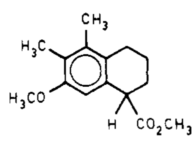
(8) L. F. Fieser and H. L. Holmes, *J. Am. Chem. Soc.*, **58**, 2319 (1936).

Scheme II. Synthesis of Racemic 5,6-Dimethyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthoic Acid



($[\alpha]^{22}_{578}$ −16.8°) in an overall yield of 6.1% from *dl*-16.

The enantiomeric excess (ee) of 16 could not be determined by means of $^1$H NMR of the (+)-DHAA salts. $^1$H NMR of 23 with the chiral europium shift reagent Eu(*d*-tfacCam)$_3$[9] did not give an accuracy better than 15% ee in the determination.



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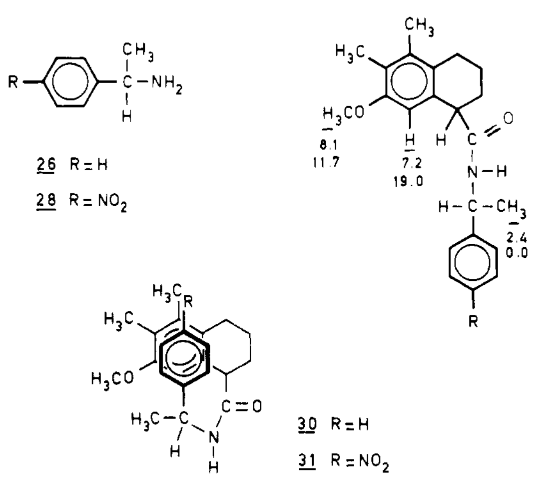
The accurate enantiomeric excess was determined by means of $^1$H NMR of amides 27. *dl*-16 and *l*-16 were converted quantitatively into the amide 27 with 1-phenylethylamine (26). Literature reports[10] on the use



26 R = H

28 R = NO$_2$

27 R = H

29 R = NO$_2$

30 R = H

31 R = NO$_2$

of 26 in determinations of the enantiomeric excess of carboxylic acids via diastereomeric amides indicate that usually separation of amine methyl proton absorptions occurs. Similar observations were made in the 100-MHz $^1$H NMR spectra of 27 prepared from *dl*-16; two well-separated doublets ($\Delta\delta$ = 2.4 Hz) were observed. In the amide 27 prepared from *l*-16 only one of the doublets was present. Accurate analysis of the spectrum indicated a >97.5% ee.

**Comments on the NMR Spectra of 27 and 29.** Typical features were observed in the 100-MHz NMR spectrum of 27. The peak separations ($\Delta\delta$ in hertz) for several protons are indicated in structure 27. The peak separations for the specified protons denote the difference in $^1$H NMR absorption for these protons in the diastereoisomers of 27 as well as of 29. The largest separation was observed for the proton absorption of the $OCH_3$ group, which is relatively far from the asymmetric centers. A specific conformation, probably a folded one as indicated in structure 30, could account for the large diastereomeric influence at the $OCH_3$ group. Many reports exist dealing with folded conformations in solution, and when aromatic rings are involved in these molecules, charge-transfer interactions are possible.[11]

Further support for the idea that interactions between the aromatic moieties in a folded conformation determine to some extent the difference between the diastereoisomers was found in the $^1$H NMR spectrum of 29. The shift differences of the diastereoisomers 29 indicate that a folded conformation (31) could be present. Stronger interactions of the *p*-nitro-substituted aromatic ring with the aromatic moiety of the tetrahydronaphthalene system, which contains five electron-donating substituents, can be expected. Examples of diastereomeric charge-transfer interactions have been published.[12] The fact that larger diastereomeric

(9) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974).

(10) J. Jacobus and M. Raban, *J. Org. Chem.*, **33**, 1142 (1968).

(11) For a literature survey, see: R. M. Tel, Ph.D. Thesis, Groningen University, 1977, Chapter I; R. van Est-Stammer and J. B. F. N. Engberts, *Tetrahedron Lett.*, 3215 (1971).

(12) H. Wynberg and K. Lammertsma, *J. Am. Chem. Soc.*, **95**, 7912 (1973).

(13) Extended studies have been published concerning absolute configuration correlations and interpretation of ORD and CD Cotton effects of aromatic chromophores.[14] The quadrant rule for the $^1$Lb transition (Kuriyama and co-workers[15]), the quadrant rule for the $^1$La transition (De Angelis and Wildeman[16]), and the general helicity and sector rules (Snatzke and co-workers[17]) describe the correlations for "benzylic centers of asymmetry".

(14) F. Ciardelli and P. Salvadori, Eds., "Fundamental Aspects and Recent Developments in ORD and CD", Heyden and Son Ltd., London, 1973.

(15) K. Kuriyama, T. Iwata, K. Moriyama, K. Kotera, Y. Hamada, R. Mitsui, and K. Takeda, *J. Chem. Soc. B*, 46 (1967).

(16) H. H. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969).

Scheme III. Synthesis of (*S*)-(+)-Trimethyl-5,6,7,8-tetrahydro-2-naphthol

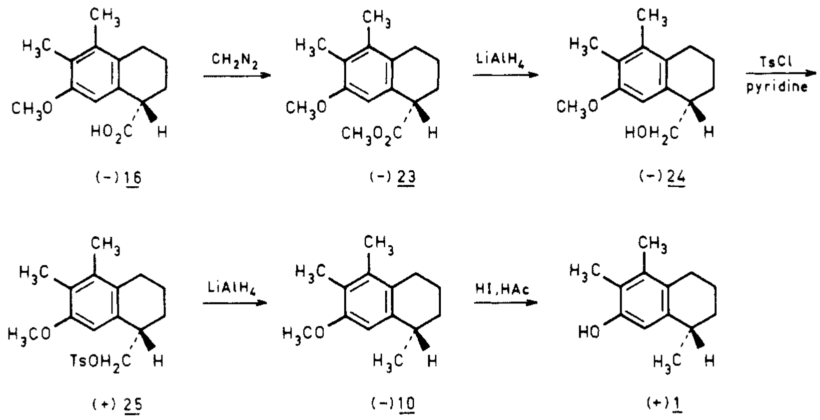


Table II. Melting Points, UV Data, and Chiroptical Properties of 1, 10, 16, and 23-25

| compd | mp, °C: *R,S* isomer | mp, °C: *S* isomer | $[\alpha]^{22}_{578}$, deg | UV (95% EtOH): $\lambda_{max}$ | UV (95% EtOH): log $\epsilon$ | ORD λ ($10^{-3}[\Phi]$) | CD λ ($10^{-3}[\Theta]$) |
|---|---|---|---|---|---|---|---|
| 16 | 161.5-162.5 | 125-127 | −16.8 (*c* 0.99, $CHCl_3$) | 287<br>279<br>224 | 3.37<br>3.36<br>4.04 | 310 (−0.9), 287 (−1.8), 277 (0), 264 (−1.7), 240 (−10.7), 232 (0), 225 (+10.5), 220 (+3.65), 207 (+14.0) | 290 (−0.9), 232 (−15.2), 225 (−12.4), 206 (−22.4), 205 (−17.8) |
| 23 | 40-44 | 63.5-64.5 | −17.5 (*c* 0.32, $CHCl_3$) | 288<br>279<br>225 | 3.40<br>3.37<br>4.04 | 308 (−0.6), 278 (−1.1), 268 (−0.2), 239 (−8.6), 233 (0), 225 (+16.1), 219 (+11.3), 210 (+22.7) | 284 (−1.2), 233 (−18.7), 220 (−7.5), 210 (−14.2), 206 (−7.6) |
| 24 | 100.5-101.5 | 124.5-125.5 | −13.8 (*c* 0.52, $CHCl_3$) | 286<br>279<br>222 | 3.36<br>3.35<br>4.07 | 330 (+0.9), 296 (0), 287 (−1.0), 274 (+1.35), 248 (0), 232 (−4.3), 228 (0), 210 (+25.0) | 278 (−3.0), 268 (−2.3), 250 (−0.6), 229 (−10.1), 218 (−4.0), 213 (−9.4), 207 (+8.2), 209 (0) |
| 25 | 94-96 | 88-89 | +22.1 (*c* 0.28, $CHCl_3$) | 286<br>279<br>223 | 3.36<br>3.35<br>4.34 | 320 (−0.4), 288 (−1.1), 278 (0), 260 (+2.0), 251 (+1.75), 239 (0), 231 (−1.0), 227 (0), 225 (+8.2) | 278 (−1.6), 250 (0), 232 (−7.8), 222 (+2.2), 214 (−7.8), 210 (0), 208 (+9.1) |
| 10 | 125-135[a] (0.8-0.9 mm) | - | −14.5[b] (*c* 0.36, $CHCl_3$) | 286<br>279<br>222 | 3.34<br>3.33<br>4.04 | 318 (−0.8), 287 (−2.1), 278 (−1.2), 269 (0), 261 (+0.5), 249 (0), 236 (−4.3), 225 (0), 215 (+14.0) | 277 (−2.5), 248 (0.3), 230 (−15.3), 218 (−15.5), 208 (0), 207 (+3.8) |
| 1 | 88.5-89.5 | - | +14.8 (*c* 0.30, $C_2H_5OH$) | 286<br>283<br>224 | 3.30<br>3.29<br>3.88 | 280 (+2.3 sh), 260 (+4.8), 238 (+3.9, sh), 224 (+0.3), 210 (+1.2) | 279 (−3.3), 242 (0), 228 (+3.6), 216 (0), 212 (−1.6) |

[a] Boiling point. [b] $[\alpha]^{22}_{436}$.

differences are observed at a larger distance from the asymmetric centers could be of interest in elucidating the mechanism of asymmetric synthesis.

**Synthesis of (*S*)-(+)-1.** The conversion of (−)-16 into (+)-1 is summarized in Scheme III. The esterification with diazomethane was followed by reduction to alcohol **24**. Reaction of **24** with *p*-toluenesulfonic acid chloride furnished **25**. This compound was reduced to **10**. Bond fission of the ether with hydroiodic acid yielded (+)-1. The overall yield was 3.2% starting from **3**. The spectral data for these compounds were in agreement with the structures (partly summarized in Table II). Furthermore, the optically active compounds were identical in all respects (except for melting points and rotations) to the racemic compounds prepared independently.

**Chiroptical Properties of 1, 10, 16, and 23-25.** The specific rotations and ORD/CD data are summarized in Table II. (+)-3,4,8-Trimethyl-5,6,7,8-tetrahydro-2-naphthol ((+)-1) was prepared from enantiomerically pure (−)-16. Although every contact with strong bases was avoided and the reaction conditions were as mild as possible, the possibility of some racemization during one of the five steps necessary for the conversion of (−)-16 into (+)-1 could not be excluded. An attempt to determine the enantiomeric excess of **10** by using chiral Eu(*d*-tfacCam)$_3$ failed. Attempts to separate chromatographically the two diastereomeric *l*-menthoxyacetic acid esters of *dl*-1, in order to obtain a method for the determination of the enantiomeric excess of **1**, were not successful. In the dimerization of *d*-1 (see next sections), no products resulting from a coupling of *d*-1 with *l*-1 were observed. On the basis of these results, it could be concluded that *d*-1 was enantiomerically pure and that no racemization during the conversion of *l*-16 into *d*-1 had occurred.

The UV spectra of 1, 10, 16, and 23-25 all showed the characteristic absorptions of the aromatic rings. The weak $^1$Lb band at 260-280 nm, a shoulder at 200-230 nm ($^1$La), and a strong absorption at 180-190 nm ($^1$Ba) were observed. These characteristics were also found in the ORD/CD spectra (Table II). The absolute configurations of the compounds were determined by using the correlations of the sign of the Cotton effects in the ORD and CD spectra with those of known compounds; chemical correlation was also used.

Scheme IV. Oxidative Coupling of (*S*)-(+)- and (*R*,*S*)-(1)

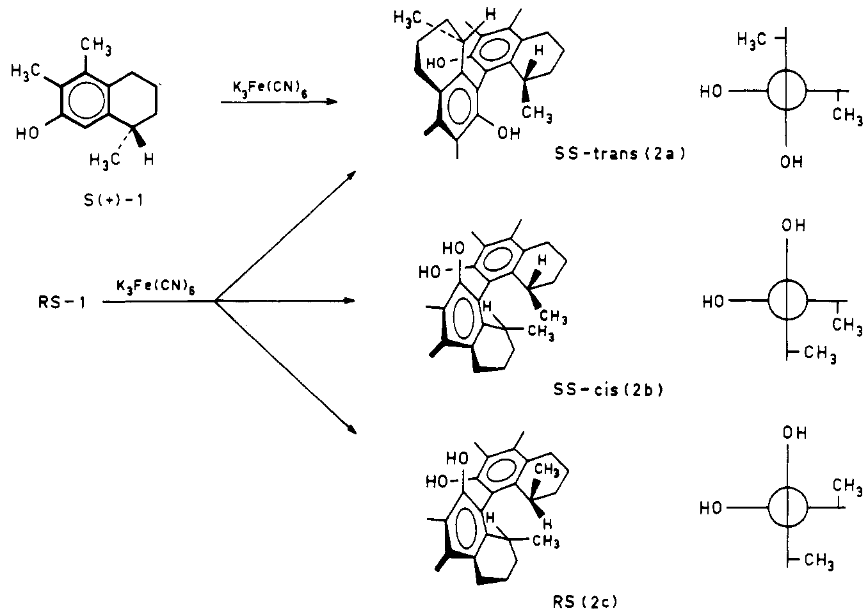
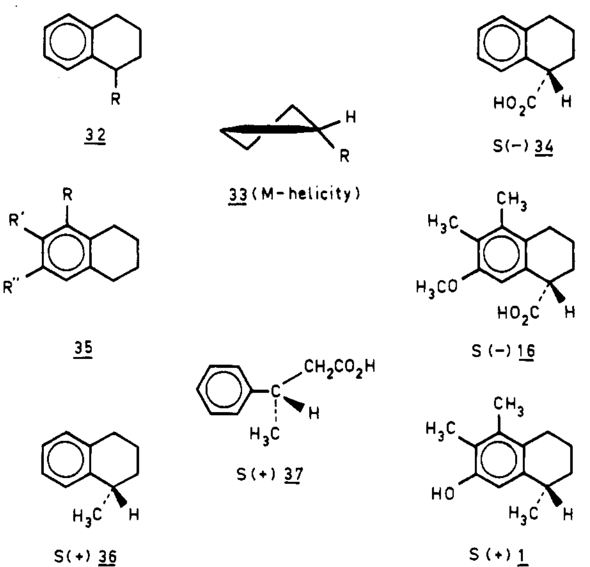



Chart I




Molecules of type **32** (Chart I) adopt a half-chair conformation in which the substituent R for the case of $CH_3$ or $CO_2H$ is in a pseudoaxial position.[18] *M* helicity as pictured in structure **33** was established for (*S*)-(−)-carboxylic acid **34** on the basis of the sector rule for the chiral 2$^e$ sphere and the observed negative $^1$Lb Cotton effect. Chemical correlation of (*S*)-(−)-**34** with D-glyceraldehyde unequivocally established the absolute configuration. (−)-**16** showed a negative $^1$Lb band in the CD spectrum and was therefore related to (*S*)-(−)-**34**. A substitution pattern for the chiral 2$^e$ sphere as indicated in **35** gave rise to *M* helicity for negative $^1$Lb Cotton effects on the basis of the sector rules,[17] although no exact substituent influences could be determined.

On the basis of these helicity and sector rules[17] in analogy to the determination of the configuration of (*S*)-(−)-**16**, an *S* configuration and *M* helicity as shown in Scheme III and **33** could be established for (+)-**1**. A correlation with (*S*)-(+)-**36** was made. For both compounds, (*S*)-(+)-**36** and (*S*)-(+)-**1**, a negative $^1$Lb Cotton effect was observed. (*S*)-(+)-**36** was chemically correlated with (*S*)-(+)-**37** of known absolute configuration. The chemical correlation as shown in Scheme III established an *S* configuration for (+)-**1** obtained by starting with (*S*)-(−)-**16** and therefore independently correlates the configuration. Thus, the configurations of **23**–**25** and **10** are therefore established.

**Oxidation of (*S*)-(+)-1 and (*R*,*S*)-1.** The oxidations of (*S*)-(+)-3,4,8-trimethyl-5,6,7,8-tetrahydro-2-naphthol ((*S*)-(+)-**1**) and (*R*,*S*)-**1** (Scheme IV)[19] were performed by using $K_3Fe(CN)_6$ as an oxidant. From the crude reaction mixture were obtained monomer **1** (7.5%) and dimer **2** (62%). The workup procedure was completely quantitative and nonfractionating. This procedure was necessary to avoid any change in diastereomeric ratio prior to analysis. The constitution of the isomeric mixture **2** was carefully examined by using 100-MHz $^1$H NMR and HPLC techniques, and the products were analyzed by spectroscopic techniques. A correct elemental analysis for **2** was obtained. Besides C–C-coupled product **2**, small amounts of other oxidized products were found. Although spectral data indicate quinones and C–O-coupled products, no exact structures for these products were determined. Compound **2** showed hydroxyl absorptions at 3510 and 3300 cm$^{-1}$ (free and H-bridged OH) in the IR spectrum. In the $^1$H NMR spectra, no aromatic proton absorptions were present. The other proton absorptions were almost identical with those of **1**, except for the $C_8$- and $C_8'$-methyl protons, which showed multiplets in the case of racemic **2**.

In the coupling of (*S*)-(+)-**1** only dimer **2a** was formed. No trace of the other dimers (**2b**,**c**) could be detected by using HPLC and 100-MHz $^1$H NMR. The coupling product of (*R*,*S*)-**1** consisted of a mixture of three isomers as was clearly shown by the 100-MHz $^1$H NMR spectrum. In addition to these identifications, all three isomers were also isolated by using HPLC and characterized separately

(17) (a) G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Heyden, London, 1967, p 208; (b) G. Snatzke, M. Kajtár, and F. Snatzke in ref 14, Chapter 3.4; (c) G. Snatzke and F. Snatzke in ref 14, Chapter 3.5.

(18) Assignments of pseudoaxial conformations are based on NMR studies. Minimalization of steric repulsion and $\sigma$–$\pi$ interactions are possible in this conformation.

(19) Each isomer in Scheme IV has an enantiomeric form which is not shown. The projections indicate the stereochemical relationship between the $C_8$,$C_8'$-methyl groups.

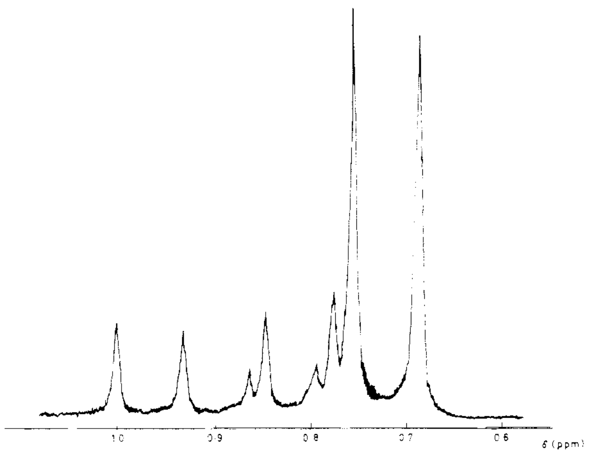



**Figure 1.** 100-MHz $^1$H NMR spectrum of (*R*,*S*)-**2a–c** ($CDCl_3$) ($C_8$- and $C_8'$-$CH_3$ absorptions).

via spectroscopic techniques. The observation that no trace of (*R*,*S*)-**2** is formed during the oxidation of (*S*)-(+)-**1** indicates that (*S*)-(+)-**1** was enantiomerically pure and that no racemization during its formation from (*S*-(–)-**16** had occurred.

**Stereochemistry of the Oxidative Coupling of (*S*)-(+)-1 and (*R*,*S*)-1.** In Scheme IV are shown the different stereoisomers which can be formed during the oxidation of racemic **1**.

Coupling of an *S* monomer with an *S* monomer can proceed in two ways. The $C_8$- and $C_8'$-methyl groups are cis- or trans-oriented with respect to each other and therefore (*S*,*S*)-*cis*-**2b** and (*S*,*S*)-*trans*-**2a** are formed. These two isomers differ only in the configuration around the biaryl bond and are therefore diastereomers and also atropisomers. A rotation of 180° around the biaryl linkage could, in principle, convert the (*S*,*S*)-*cis*-**2b** to the (*S*,*S*)-*trans*-**2a**. This process is prevented, however, by steric hindrance. In a manner identical with the coupling of (*S*)-(+)-**1**, the coupling of (*R*)-(–)-**1** with (*R*)-(–)-**1** can lead to (*R*,*R*)-*cis*-**2b** and (*R*,*R*)-*trans*-**2a**, which are enantiomers of (*S*,*S*)-*cis*-**2b** and (*S*,*S*)-*trans*-**2a**. The coupling of an *S* monomer with an *R* monomer can give *R*,*S* and *S*,*R* dimers **2c**, which differ only in the biaryl configuration. Normally a coupling of (*S*)-**1** and (*R*)-**1** would give a meso compound, but due to restricted rotation around the biaryl bond, this coupling mode yields an enantiomeric pair.

In summary, in the dimerization of (*R*,*S*)-**1** there is the possibility of obtaining three enantiomeric pairs: the (*RR*,*SS*)-cis pair (**2b**), the (*RR*,*SS*)-trans pair (**2a**) and the *RS*,*SR* pair (**2c**). The coupling of enantiomerically pure (*S*)-(+)-**1** can only lead to isomers (*S*,*S*)-*cis*-**2b** and (*S*,*S*)-*trans*-**2a**.

The expanded part of the 100-MHz $^1$H NMR spectrum of the $C_8$- and $C_8'$-methyl proton absorptions of racemic **2** is shown in Figure 1. Molecular models of the *RS*,*SR* pair (**2c**) clearly indicate that the $C_8$- and $C_8'$-methyls are situated in different environments in the molecule and are therefore not equivalent. The two doublets of equal intensity at δ 0.96 and 0.813 are attributed to the *RS*,*SR* pair (**2c**). Due to $C_2$ symmetry in the cis (**2b**) and the trans isomers (**2a**), the $C_8$- and $C_8'$-methyl groups are equivalent, and therefore a doublet can be expected for each isomer. The two doublets of unequal intensity at δ 0.830 and 0.72 are attributed to the *cis*-**2b** and *trans*-**2a** isomers. The assignment of the doublet at δ 0.72 to the trans isomer **2a** is based on the following considerations. Models of the two isomers (**2a** and **2b**) show subtle but definite differences in the extent to which the protons of the pseudoaxially oriented $C_8$- and $C_8'$-methyl substituents are influenced by the shielding zones of the aromatic rings. The protons of the $C_8$- and $C_8'$-methyl groups in the trans isomer **2a** are more situated in the shielding zones compared to the same protons in the cis isomer. Furthermore, for steric reasons better intramolecular hydrogen bonding of the OH's is indicated in the trans isomer **2a**. Separate hydroxyl proton signals were observed at δ 4.93 and 4.46 for the trans and cis isomers.

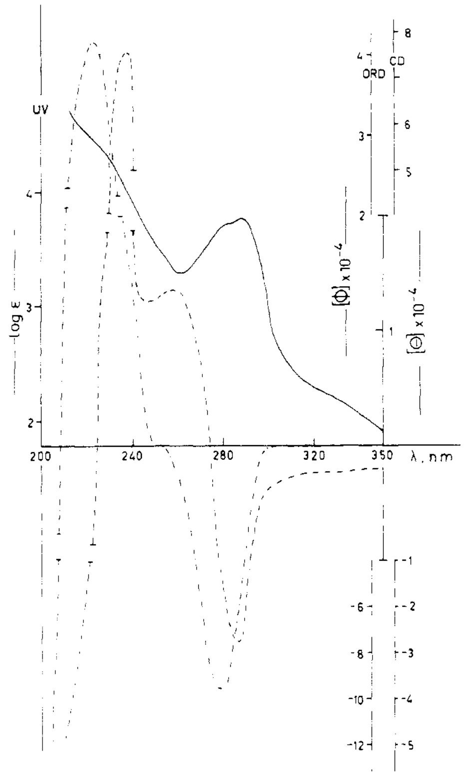



**Figure 2.** UV (—), ORD (- - -), and CD (···) spectra of (*S*,*S*)-*trans*-**2a** (95% ethanol).

Differences in the extent of downfield shift of the $C_8$- and $C_8'$-methyl proton absorptions were observed in the 100-MHz $^1$H NMR spectra of the three isomers by using $Eu(DPM)_3$ as a shift reagent. The doublet due to the trans isomer showed the largest shift. On the basis of molecular structures (Scheme IV) and with the realization that complexation occurs at the OH groups, a larger shift is expected for the $C_8$- and $C_8'$-methyl proton signals of the *trans*-**2a** compared to that for *cis*-**2b**. Exact assignments could not be made, due to the fact that no other accurate signal shifts could be established which could be used for comparison purposes.

Further evidence for these assignments was based on chiroptical data. The ORD and CD spectra of (*S*,*S*)-*trans*-**2a** (Figure 2) showed a negative Cotton effect at 278 nm corresponding to the $^1$Lb band, a positive Cotton effect for the $^1$La band (225 nm), and probably a short-wavelength negative Cotton effect centered at the $^1$Ba band (180–190 nm).

Mislow and co-workers[20] investigated a series of biaryl compounds and correlated the biaryl configurations with the sign of the Cotton effects.[21] Theoretical treatments by Mason and co-workers[22] and Hug and Wagnière[23] were

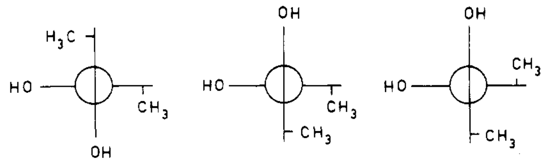
(20) K. Mislow, *Top. Stereochem.*, **4**, 1–42 (1968); K. Mislow in ref 16a, pp 153–172; K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962).

(21) Independently, chemical correlations and configurational correlations via asymmetric synthesis and X-ray analysis were made.

(22) S. F. Mason, R. H. Seal, and D. R. Roberts, *Tetrahedron*, **30**, 1671 (1974).

(23) W. Hug and G. Wagnière, *Tetrahedron*, **28**, 1241 (1972).

Chart II. Product Distribution of the Oxidative Coupling of (*S*)-(+)- and (*R*,*S*)-1




| | SS-trans | SS-cis | RS |
|---|---|---|---|
| S -monomer | >97.5% | – | – |
| RS-monomer | 66.0% | 7.9% | 26.1% |

consistent with these results.

No clearly separated conjugation band was found in nonbridged biphenyls, and large torsional angles were present. A positive Cotton effect at the long-wavelength absorption band indicated an (*R*)-biaryl configuration. According to the rules as established by the authors cited above[20,22,23] and the results of the configurational assignments by means of ORD and CD in the lythraceae alkaloid series,[24] which show the *S* configuration and negative $^1$Lb Cotton effect and positive $^1$La Cotton effect relationships, an (*S*)-biaryl configuration can be assigned to (+)-**2a**. Since the monomer (+)-**1** had the *S* configuration at $C_8$, the dimer (+)-**2** must be the (*S*,*S*)-trans enantiomer **2a** (correct configuration pictured in Scheme IV). Although the substituent influences on the aromatic chromophores are uncertain, a negative $^1$Lb Cotton effect probably indicates a cis conformation (OH's cis to each other) of the biaryl moiety.[20,24b]

The results of the oxidative coupling of (*S*)-(+)-**1** show that the reaction yielded the (*S*,*S*)-trans dimer **2a** in a stereospecific manner (Scheme IV and Chart II). The least sterically hindered isomer **2a** is formed. This indicates that nonbonded (steric) interactions are the main reasons for the stereochemical control during the coupling of two monomer molecules **1**.

The dimerization of racemic **1** ((*R*,*S*)-**1**) yielded a mixture of three enantiomeric pairs (Scheme IV and Chart II). The coupling process is partly stereoselective in the fact that there is a preference for coupling of monomers having identical configuration: 74% *R*–*R*- and *S*–*S*-coupled product, 26% *R*–*S*-coupled product. This enantiomeric recognition effect has been previously observed in dimerization reactions and has been extensively discussed.[25] The extent of stereoselectivity of the biaryl formation during the coupling of (*R*,*S*)-**1** can be interpreted from the product distribution. Since (*S*,*S*)-*trans*-**2a** (66.0% of the dimer fraction) and (*S*,*S*)-*cis*-**2b** (7.9%) differ only in the biaryl configuration, the diastereoselectivity of this oxidation is 80%.

As is shown in Scheme IV and Chart II, a mixture of diastereoisomers is formed when (*R*,*S*)-**1** is dimerized (with 7.9% (*S*,*S*)-*cis*-**2b**) with a stereoselectivity in the biaryl formation of 80%, whereas the dimerization of enantiomerically pure (*S*)-(+)-**1** proceeds in a fully stereospecific manner. The formation of (*S*,*S*)-*cis*-**2b**, expected on the basis of the results of the coupling of (*R*,*S*)-**1**, was not observed in the case of (*S*)-(+)-**1**. This means that in the case of (*R*,*S*)-**1** one enantiomer has an influence on the stereochemistry of the coupling of the other enantiomer. This antipodal or enantiomeric interaction effect has been discussed elsewhere.[25]

Bobbitt and co-workers[5] observed a stereoselective and stereospecific electrochemical dimerization of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline.

The results were explained on the basis of a surface reaction between two radicals on the graphite electrode. Furthermore, they oxidized enantiomerically pure 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline with $K_3Fe(CN)_6$ and obtained two isomeric dimers analogous to the cis and trans forms of **2**. High stereoselectivity in this chemical oxidation was, however, not observed. As different factors must be essential when the reacting species are absorbed on a surface compared to reacting species in solution, a difference in stereochemistry between electrochemical and $K_3Fe(CN)_6$ oxidations is not unexpected.

The stereospecific dimerization described in this paper reflects the importance of asymmetric centers present in the substrates for phenol oxidations. An example of the selective conversion of one of the enantiomers of a racemic phenol by tyrosinase was described.[26] Examples are known in which an optically active phenol coupling product, isolated from natural sources, contains no other chiral elements than its own biaryl dissymmetry.[20,27] Since the biosynthetic pathways to these diphenols have not been entirely elucidated, chiral precursors to the final products are not excluded.

On the basis of our results we conclude that stereochemical control in intermolecular phenol oxidations can be exerted by an asymmetric center present in the substrate.

## Experimental Section

All reagents and solvents were purified where necessary by standard methods. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus equipped with a Mettler FP-21 microscope. Infrared spectra were recorded on a Unicam SP-200 infrared spectrophotometer. Ultraviolet spectra were measured on a Zeiss PMQ 11. $^1$H NMR spectra were recorded on a Varian A-60, a JEOL C-60 HL, or a Hitachi Perkin-Elmer R24B spectrometer using tetramethylsilane as an internal standard. A Varian XL-100 was used for the $^{13}$C NMR and 100-MHz $^1$H NMR spectra. Mass spectra were obtained on an AEI MS-902. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The ORD and CD spectra were recorded on a Cary 60 recording spectropolarimeter equipped with a Cary 6002 CD accessory. High-pressure liquid chromatography was performed on a Waters HPLC apparatus, ALC/GPC 201, equipped with a differential refractometer and a Schoeffel Spectroflow SF 770 monitor.

**2-Methoxy-3,4,8-trimethyl-5,6-dihydronaphthalene (9).** To a solution of methylmagnesium iodide, prepared from 2.0 of Mg and 6.25 g (0.065 mol) of $CH_3I$ in 25 mL of dry diethyl ether, was added over a period of 30 min under stirring 2.90 g (0.014 mol) of **7** dissolved in 25 mL of dry diethyl ether. The resulting mixture was stirred and refluxed for an additional 2 h, and after being cooled, it was poured into 100 g of crushed ice. Diluted aqueous hydrochloric acid (50 mL) and diethyl ether (50 mL) were added. The organic layer was separated, and the aqueous layer was

(24) (a) J. P. Ferris, C. B. Boye, R. C. Briner, U. Weiss, I. H. Qureshi, and N. E. Sharpless, *J. Am. Chem. Soc.*, **93**, 2963 (1971). (b) The main isomer obtained in the oxidative coupling of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline was assigned the cis form by Bobbitt and co-workers and Lyle.[5] On the basis of the spectroscopic and optical data of the dimer (*S*,*S*)-(+)-**2a**, we have to conclude that this compound has the trans form, although there is quite a similarity between our data and the data obtained by the authors cited. The clarification of this point awaits an X-ray structure determination.

(25) H. Wynberg and B. Feringa, *Tetrahedron*, **32**, 2831 (1976); P. Hobza, R. Zahradnik, B. Feringa, and H. Wynberg, submitted for publication.

(26) M. Morrison and G. Bayse in "Oxidases and Related Redox Systems. Proceedings of the Second International Symposium", T. E. King, H. S. Mason, and M. Morrison, Eds., University Park Press, Baltimore, MD, 1973, p 375.

(27) S. Shibata and Y. Ogihara, *Tetrahedron Lett.*, 1777 (1963); S. Shibata, *Chem. Br.*, **3**, 110 (1967).

extracted with diethyl ether (2 × 25 mL). The combined ether layers were washed with water until neutral, dried over $MgSO_4$, and filtered, and the solvent was removed by distillation. Carbinol 8 (3.0 g, 0.0135 mol, 96%) was obtained as a slightly yellow oil: IR (neat) 3500 $cm^{-1}$ (m, OH); $^1H$ NMR ($CCl_4$) δ 1.2 (s, 3 H, $C(OH)CH_3$), 1.5–3.0 (m, 12 H, 2 $CH_3$, 3 $CH_2$), 3.92 (s, 3 H, $OCH_3$), 4.9 (br s, 1 H, OH), 6.65 (s, 1 H, aromatic).

The carbinol 8 (3.0 g, 0.0135 mol) and 0.010 g of $I_2$ were heated at 130–140 °C for 1 h. After the mixture cooled, the red oil was dissolved in 50 mL of diethyl ether. The ether solution was washed with saturated sodium thiosulfate solution (3 × 40 mL) and water (2 × 30 mL) and dried over $MgSO_4$, and the diethyl ether was removed by distillation. The 2.78 g of crude yellow compound was purified by column chromatography (silica gel, 60–120 mesh, benzene) and furnished **9** (2.35 g, 0.011 mol, 82%) as a colorless crystalline compound: mp 49–50.0 °C; IR (Nujol) 1540 $cm^{-1}$ (m, olefinic); $^1H$ NMR ($CCl_4$) δ 1.6–2.9 [m, 2 $CH_3$ + 3 $CH_2$ (exocyclic double bond) or 2 $CH_3$ + 2 $CH_2$ + $CH_3$ (endocyclic double bond)], 3.8 (s, 3 H, $OCH_3$), 5.78 (m, 1 H, olefinic, endocyclic double bond), 6.2 (m, 2 H, olefinic, exocyclic double bond) (endo/exo ratio of 9:2), 6.6 (s, 1 H, aromatic). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.96. Found: C, 83.14; H, 9.04.

The Grignard reaction starting with 0.2 mol of **7** afforded after dehydration a mixture of **9** (90%) and **12** (10%) not separable by chromatography. The $^1H$ NMR ($CCl_4$) indicated multiplets at δ 7.0–7.3 and 7.7–7.9 due to the aromatic H's of **12**.

**2-Methoxy-3,4,8-trimethyl-5,6,7,8-tetrahydronaphthalene (10).** A suspension of 2.1 g (10.4 mmol) of **9**, 1.0 g of palladium on carbon (5% Pd), and 200 mL of absolute ethanol was shaken for 19 h at 20 °C in a Parr apparatus under a hydrogen atmosphere (3 atm of $H_2$, repeated degassing and saturation with $H_2$). The solution was filtered and the solvent removed by distillation to afford 1.8 g of an oil. Column chromatography [silica gel, 60–120 mesh, benzene–petroleum ether (bp 40–60 °C) 1:5 ratio] furnished 1.49 g (7.3 mmol, 70%) of **10** as a colorless oil: bp 125–135 °C (0.8–0.9 mm); IR (neat) 1600 $cm^{-1}$ (aromatic C=C stretch); mass spectrum, *m/e* 204 ($M^+$); $^1H$ NMR ($CCl_4$) δ 1.22 (d, 3 H, *J* = 7.0 Hz, $C_8$-$CH_3$), 1.5–2.8 (m, 13 H, 2 $CH_3$, 3 $CH_2$, CH), 3.74 (s, 3 H, $OCH_3$), 6.45 (s, 1 H, aromatic). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: C, 81.80; H, 9.66.

**2-Hydroxy-3,4,8-trimethyl-5,6,7,8-tetrahydronaphthalene (1).** A mixture of 1.49 g (7.3 mmol) of **10**, 7.1 mL of acetic acid, and 2.35 g of hydroiodic acid (70% solution in water) was refluxed for 2 h. To the solution were added, after cooling, 50 mL of water and 40 mL of diethyl ether. The organic layer was separated and subsequently washed with 60 mL of water (4 × 15 mL portions), saturated $NaHCO_3$ solution (2 × 15 mL), sodium thiosulfate solution (2 × 15 mL), and water (20 mL). After the mixture was dried over $Na_2SO_4$ and the diethyl ether removed by distillation, 1.48 g of an orange oil was obtained. Column chromatography (silica gel, 60–120 mesh, benzene) afforded 1.11 g (5.8 mmol, 78%) of **1**. Three crystallizations from petroleum ether (bp 40–60 °C) furnished pure **1** as a colorless solid: mp 88.5–89.5 °C; IR (Nujol) 3300 $cm^{-1}$ (m, OH); $^1H$ NMR ($CDCl_3$) δ 1.12 (d, 3 H, *J* = 6.7 Hz, $C_8$-$CH_3$), 1.5–2.8 (m, 13 H, 2 $CH_3$, 3 $CH_2$, CH), 5.25 (s, 1 H, OH), 6.3 (s, 1 H, aromatic). Anal. Calcd for $C_{13}H_{18}O$: C, 82.05; H, 9.53. Found: C, 82.34; H, 8.96.

In this case **1** was contaminated by aromatic byproduct, and pure **1** was obtained by the following procedure. To a solution of crude 1 (1.0 g, 5.18 mmol) in 20 mL of ethanol was added 15 mL of a 25% picric acid solution in ethanol. The solution turned dark red, and crystalline picrate separated. The mixture was stirred for 5 min, and the solid material was separated by filtering with suction. After the crystals were washed with 5 mL of cold ethanol and dried in the air, 0.256 g (0.59 mmol, 11%) of picrate of **12** was obtained (mp 168–169 °C).

The yellow filtrate was filtered through a silica gel column, and ethanol was removed from the resultant colorless solution by distillation to afford 0.88 g (4.6 mmol, 88%) of **1**.

**1-Menthoxyacetic Acid Ester 13.** 1-Menthoxyacetic acid chloride was prepared according to the literature.[28] To a refluxing solution of 3.0 g (15.8 mmol) of **1** and 6.0 g (26.5 mmol) of 1-menthoxyacetic acid chloride in dry benzene (70 mL) was added, over a period of 20 min, 3.5 mL of dry pyridine. The mixture was heated under reflux for an additional 2 h, and after the mixture cooled 30 mL of water and 40 mL of diethyl ether were added. The organic layer was separated and washed with 60 mL of water (2 × 30 mL), $NaHCO_3$ solution (4 × 30 mL), diluted hydrochloric acid (3 × 30 mL), and water (2 × 20 mL). The ether solution was dried over $MgSO_4$ and the diethyl ether removed by distillation to afford 6.2 g (15.5 mmol) of a colorless oil. Column chromatography [silica gel, petroleum ether (bp 40–60 °C)/benzene 1:3] furnished pure **13** (5.1 g, 12.7 mmol, 81%) as a colorless oil: mass spectrum, *m/e* 386 ($M^+$); IR (neat) 1775 $cm^{-1}$ (s, C=O); $^1H$ NMR ($CDCl_3$) δ 1.7–3.5 (m, 20 H, 6 $CH_2$, $CH_3$, 5 CH), 0.90 (d, 6 H, *J* = 5.5 Hz, $CH(\mathbf{CH_3})_2$), 1.25 (d, 3 H, *J* = 6.5 Hz, $CH_3$), 2.03 (s, 3 H, $CH_3$), 2.11 (s, 3 H, $CH_3$), 4.30 (s, 3 H, $OCH_3$), 4.36 (m, 2 H, $OCH_2$), 6.72 (s, 1 H, aromatic).

***d*-Camphor-10-sulfonic Acid Ester 14.** *d*-Camphor-10-sulfonic acid chloride was prepared from the acid and $SOCl_2$. A mixture of 0.50 g (2.6 mmol) of **1**, 0.70 g (2.8 mmol) of *d*-camphor-10-sulfonic acid chloride, and 2 mL of dry pyridine was stirred over a 30-min period at 20 °C. Under stirring, 30 g of ice and 20 mL of diluted hydrochloric acid were added. The resulting mixture was extracted with 90 mL of diethyl ether (3 × 30 mL), and the ether solution was washed with water (2 × 30 mL), $NaHCO_3$ solution (25 mL), and water (20 mL). After the ether solution was dried over $Na_2SO_4$ and the ether removed by distillation, 0.93 g (2.5 mmol) of crude **14** was obtained. Column chromatography (silica gel, benzene) afforded 0.80 g (2.1 mmol, 80%) of pure **14** as a colorless oil: IR (neat) 1740 $cm^{-1}$ (s, C=O), 1370 (s, $SO_2$); $^1H$ NMR ($CDCl_3$) δ 0.90 (s, 3 H, $CH_3$), 1.16 (s, 3 H, $CH_3$), 1.23 (d, 3 H, $CH_3$), 1.4–2.8 (m, 20 H, camphor H's, 2 $CH_3$, 3 $CH_3$, CH), 3.45 (AB system, 2 H, *J* = 15 Hz, $SO_2CH_2$), 6.88 (s, 1 H, aromatic). Crystallization from $CH_3OH$ afforded white amorphous material melting at 3–5 °C.

***d*-3-Bromo-π-camphorsulfonic Acid Ester 15.** *d*-3-Bromo-π-camphorsulfonic acid chloride was prepared according to literature procedures.[29] Ester **15** was prepared by following the procedure described for **14**. From 0.20 g (1.04 mmol) of **1** and 0.35 g (1.7 mmol) of acid chloride was obtained, after 15 h at 20 °C and an additional 30 min at 50 °C, 0.15 g (0.43 mmol, 40%) of pure crystalline **15** [isolated via column chromatography ($Al_2O_3$, benzene)]: mp 120.0–126.1 °C; IR (Nujol) 1735 $cm^{-1}$ (s, C=O), 1380 (s, $SO_2$); $^1H$ NMR ($CDCl_3$) δ 1.03 (s, 3 H, $CH_3$), 1.25 (d, 3 H, $CH_3$), 1.32 (s, 3 H, $CH_3$), 1.4–2.9 (m, 18 H, camphor H's, 2 $CH_3$, 3 $CH_2$, CH), 3.38 (AB system, *J* = 14 Hz, 2 H, $SO_2CH_2$), 4.52 (d, 1 H, CHBr), 6.84 (s, 1 H, aromatic); $[\alpha]^{20}_{578}$ +64.7° (*c* 0.26, ethanol). After one crystallization from absolute ethanol: mp 130–137 °C; $[\alpha]^{20}_{578}$ +63.5° (*c* 0.26, ethanol). After two crystallizations from absolute ethanol: mp 132–138 °C; $[\alpha]^{20}_{578}$ +62.9° (*c* 0.21, ethanol). Hydrolysis of **15** after two crystallizations according to standard procedures afforded **1**, isolated via column chromatography (silica gel, benzene); $[\alpha]^{20}_{578}$ −0.4° (*c* 3.1, ethanol).

**Ethyl 4-(4-Methoxy-2,3-dimethylphenyl)butanoate (17).** A mixture of 50.0 g (0.22 mmol) of acid **6**, 5 mL of concentrated $H_2SO_4$, and 500 mL of dry ethanol was heated under reflux for 66 h. The main part of the ethanol was removed by distillation, and 100 mL of diethyl ether and 50 mL of water were added to the residue. The organic layer was separated, washed with saturated $NaHCO_3$ solution (2 × 50 mL) and 30 mL of water, and dried over $MgSO_4$. After removal of the solvent under diminished pressure, 55 g of a yellow oil was obtained. Distillation afforded pure **17** as a colorless oil: 50.0 g (0.2 mol, 90%); bp 194–196 °C (12 mm); IR (neat) 1720 $cm^{-1}$ (s, C=O); $^1H$ NMR ($CCl_4$) δ 1.18 (c, 3 H, *J* = 7 Hz, $OCH_2\mathbf{CH_3}$), 1.6–2.7 (m, 6 H, 3 $CH_2$), 2.04 (s, 3 H, $CH_3$), 2.1 (s, 3 H, $CH_3$), 3.60 (s, 3 H, $OCH_3$), 3.94 (q, 2 H, *J* = 7 Hz, $O\mathbf{CH_2}CH_3$), 6.35, 6.7 (AB system, 2 H, *J* = 8.0 Hz, aromatic). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.94; H, 8.87.

**7-Methoxy-5,6-dimethyl-3,4-dihydro-1-naphthoic Acid (20).** In the general procedure for the preparation of **20**, the compounds **18** and **19** were not isolated in an analytically pure form. After the decarboxylation step the presence of anhydride **21** and cyclized product **20** in the crude reaction product **19** was the main reason for direct conversion of this product into a mixture of final

(28) *Org. React.*, **2**, 398 (1944).

(29) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **63**, 548 (1893).

products 20 and 21, which were then separated.

Extremely dry conditions were essential during the condensation reaction. Diethyl ether was dried and purified by distillation from $P_2O_5$, followed by distillation from $LiAlH_4$. Absolute ethanol was prepared by distillation from magnesium ethoxide. "Sodium sand" was prepared according to literature procedures.[7,30] Diethyl oxalate was dried over 3-Å molecular sieves.

Into a 500-mL, three-necked flask, secured from moisture by drying tubes and equipped with dropping funnel and cooler, was placed 3.05 g (0.135 mol) of freshly prepared "Na sand" covered with 75 mL of diethyl ether. Absolute ethanol (6.3 g, 0.135 mol) dissolved in 25 mL of diethyl ether was added over a period of 30 min at 20 °C. The mixture was stirred for an additional 2 h. Over a period of 1 h, 28.5 g (0.195 mol) of diethyl oxalate dissolved in 25 mL of diethyl ether was added to the sodium ethoxide suspension. The resulting mixture was stirred at 20 °C for an additional 45 min, and 30.0 g (0.12 mol) of 17 dissolved in 25 mL of diethyl ether was then added over 45 min. The yellow solution was stirred and heated under reflux for 41 h. The resulting yellow suspension was cooled in an ice bath, and an ice-cold solution of 7.5 mL of concentrated $H_2SO_4$ in 110 mL of $H_2O$ was added. An additional 25 mL of $H_2O$ was added, and after a few minutes of stirring all the solid material dissolved. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined ether layers were washed with water (2 × 20 mL) and dried over $MgSO_4$, and the solvent was removed by distillation. A red oil (55 g) was obtained, consisting mainly of a mixture of 18 and the excess diethyl oxalate. TLC and $^1H$ NMR revealed that only traces of ester 17 were present. For 18: IR (neat) 1690, 1720 $cm^{-1}$ (C=O); $^1H$ NMR ($CCl_4$) $\delta$ 1.21 (t, $J$ = 7 Hz, 3 H, $CH_3$), 1.30 (t, $J$ = 7 Hz, 3 H, $CH_3$), 1.8–2.9 (m, 5 H, $2CH_2$, CH), 2.13 (s, 3 H, $CH_3$), 2.22 (s, 3 H, $CH_3$), 3.70 (s, 3 H, $OCH_3$), 4.21 (q, $J$ = 7 Hz, 2 H, $OCH_2$), 4.24 (q, $J$ = 7 Hz, 2 H, $OCH_2$), 6.71 (AB system, $J$ = 8 Hz, 2 H, aromatic).

To 45 g of the crude product (18) was added 450 mL of a 5% $H_2SO_4$ solution. The mixture was heated at 100 °C under intensive stirring over a period of 64 h. After cooling, 200 mL of diethyl ether was added and the organic layer separated. The aqueous layer was extracted with diethyl ether (200 mL and then 2 × 100 mL), and the combined ether layers were washed with $H_2O$ (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. The yellow solid obtained (24.5 g) consisted of a mixture of cyclic acid 20 and anhydride 21. These compounds were separated by column chromatography (silica gel, 50 × 10 cm column, 500 g of $SiO_2$). Elution with $CH_2Cl_2$ (3.5 L) afforded the anhydride 21: 7.70 g (0.030 mol, 25%); mp 169–171 °C; IR (Nujol) 1755, 1830 $cm^{-1}$ (s, C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 2.20 (s, 6 H, 2 $CH_3$), 2.5–3.05 (m, 4 H, 2 $CH_2$), 3.75 (s, 3 H, $OCH_3$), 7.29 (s, 1 H, aromatic).

Elution with diethyl ether afforded acid 20 as a pale yellow solid (14.8 g, 0.064 mol, 53%). Crystallization from hexane/benzene furnished analytically pure 20 as colorless needles: mp 189–190 °C; IR (Nujol) 2500–3000 (br, OH), 1690 (C=O), 1620, 1595 $cm^{-1}$ (C=C); $^1H$ NMR ($CDCl_3$) $\delta$ 2.22 (s, 6 H, 2 $CH_3$), 2.2–2.9 (m, 4 H, 2 $CH_2$), 3.83 (s, 3 H, $OCH_3$), 7.4 (m, 2 H, olefinic and aromatic H's), 11.73 (br s, 1 H, $CO_2H$); mass spectrum, $m/e$ 232 ($M^+$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.17; H, 6.96.

In an alternative procedure the crude condensation product (15 g) was stirred and refluxed for 17 h with 100 mL of a 5% $H_2SO_4$ solution, after which period via the workup procedure described above 10.5 g of a yellow solid was obtained. This product mixture was dissolved in 80 mL of a 65% $H_2SO_4$ solution and stirred and heated for 1 h. Ice–water (100 g) was added and the aqueous solution extracted with diethyl ether (3 × 100 mL). The ether solutions were washed with water (4 × 50 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo. There was obtained 8.5 g of a yellow semisolid which was separated into 4.8 g (57%) of 21 and 1.7 g (22%) of 20.

When a 20% $H_2SO_4$ solution was used in the conversion of 18 for a 26-h period, following the above-described procedure, the anhydride 21 was formed in 82% yield, and only small amounts of 20 were present.

(30) A. I. Vogel, "Practical Organic Chemistry", 3rd ed., Longman, London, 1956, p 86.

Isolation of 20 by using $NaHCO_3$ extraction of the ether solution of the mixture of 20 and 21 furnished after several extractions only small amounts of pure 20. The main part of 20 remained in the organic solution.

The $\alpha$-keto acid 19 was isolated from the product mixture obtained via hydrolysis and decarboxylation of 18, after 17 h: mp 109.5–110.5 °C; IR (Nujol) 2800 $cm^{-1}$ (br, OH), 1690, 1700 (2 C=O).

**dl-7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoic Acid (16).** Acid 20 (10.0 g, 0.043 mol) was dissolved in 200 mL of hot ethanol, and 1 g of palladium on carbon (5% Pd) was added. The mixture was degassed several times, saturated with hydrogen under 4 atm of hydrogen pressure, and shaken for 27 h at room temperature. The suspension was filtered and the solvent removed by distillation under diminished pressure. Crystallization of the resulting solid from benzene/petroleum ether (bp 40–60 °C) mixtures afforded 16 (9.1 g, 0.039 mol, 90%) as white needles: mp 161.5–162.5 °C; mass spectrum, $m/e$ 234 ($M^+$); IR (Nujol) 2700 $cm^{-1}$ (br, OH), 1700 (C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 1.70–2.80 (m, 7 H, 3 $CH_2$, CH), 2.12 (s, 6 H, 2 $CH_3$), 3.73 (s, 3 H, $OCH_3$), 6.58 (s, 1 H, aromatic), 11.5 (s, 2 H, OH). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.90; H, 7.72.

**Resolution of dl-7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoic Acid (dl-16).** The white suspension formed from 10.0 g (0.045 mol) of *dl*-16 and 6.4 g (0.0224 mol) of *d*-dehydroabietylamine ((+)-DHAA) in 250 mL of 96% ethanol was stirred and heated under reflux for 20 min. The resulting solution was filtered hot and then very slowly cooled. After 2.5 h the temperature of the solution was 40 °C, and white needles were crystallizing from the solution. The white solid was collected by filteration with suction, washed with cold 96% ethanol, and dried in vacuo (60 °C, 30 mm, 16 h) to give 4.45 g of the (+)-DHAA salt of 16: mp 184.4–185.8 °C; $[\alpha]^{20}_{578}$ +36.3° ($c$ 0.068, 95% ethanol). This salt was crystallized three times from 96% ethanol and, in addition, from benzene to afford 1.55 g of (+)-DHAA salt as white needles: mp 186.7–187.7 °C $[\alpha]^{20}_{578}$ +23.05° ($c$ 0.151, $CHCl_3$).

**l-7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoic Acid (l-16).** The (+)-DHAA salt of 16 after five crystallizations (1.39 g, 2.6 mmol) was dissolved in 200 mL of 50% aqueous acetic acid, and the resulting solution was heated under reflux for 45 min. After the mixture cooled, 50 mL of $H_2O$ and 50 mL of diethyl ether were added. The ether layer was separated and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined ether layers were washed with water (4 × 30 mL) and extracted with 1 N NaOH solution (5 × 30 mL). The basic solution was acidified with hydrochloric acid. The white solid material that precipitated was dissolved in 40 mL of diethyl ether. The aqueous layer was extracted with ether (3 × 30 mL), and the combined ether layers were washed with water (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed by distillation to afford 0.55 g (2.3 mmol, 88%) of colorless crystalline *l*-16: mp 125–127 °C; $[\alpha]^{22}_{578}$ −16.8° ($c$ 0.99, $CHCl_3$). All spectral data were identical with those of *dl*-16.

**Amides 27 and 29.** The acid chloride of *dl*-16 was prepared from 0.20 g (0.86 mmol) 16 and 0.19 g (0.95 mmol) of $PCl_5$ in benzene, according to standard procedures. A mixture of the acid chloride dissolved in benzene (4 mL), 0.41 g (3.44 mmol) of *d*-$\alpha$-phenylethylamine, and 0.1 g of pyridine was stirred at 20 °C for 1 h. To the mixture were added 20 mL of 2 N hydrochloric acid and 20 mL of diethyl ether. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 20 mL). The combined ether solutions were washed with water (3 × 10 mL), $NaHCO_3$ solution (2 × 10 mL), and water (10 mL) and dried over $MgSO_4$. After removal of the solvent by distillation, 0.32 g (0.82 mmol, 96%) of the amides *d,d*-27 and *d,l*-27 were obtained as white crystalline compounds: mp 135–144 °C; exact mass for $M^+$ peak calcd $m/e$ 337.204, found 337.201; IR (Nujol) 1655 (s, C=O), 3370 $cm^{-1}$ (m, NH); $^1H$ NMR ($CDCl_3$) $\delta$ 1.31, 1.33 (2 d, 3 H, $J$ = 7 Hz, $NCH(CH_3)$), 1.5–2.7 (m, 7 H, 3 $CH_2$, CH), 2.1 (br s, 6 H, 2 $CH_3$), 3.56, 3.60 (2 s, 3 H, $OCH_3$), 5.17 (q, 1 H, $J$ = 7 Hz, $NCH(CH_3)$), 5.92 (br t, 1 H, - NH), 6.33, 6.36 (2 br s, 1 H, aromatic), 7.15 (m, 5 H, aromatic).

The *d,l*-amide 27 was prepared from *l*-16 in an identical way: mp 183–185 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.34 (d, 3 H, $J$ = 7 Hz, $NCH(CH_3)$), 1.5–2.7 (m, 7 H, 3 $CH_2$, CH), 2.12 (br s, 6 H, 2 $CH_3$), 6.68 (s, 3 H, $OCH_3$), 5.17 (q, 1 H, $J$ = 7 Hz, $NCH(CH_3)$), 5.65 (m, 1 H, NH), 6.39 (s, 1 H, aromatic), 7.18 (br s, 5 H, aromatic).

The *d,d*- and *d,l*-amides **29** were prepared in an identical way from *dl*-**16** and *d*-α-(*p*-nitrophenyl)ethylamine (**28**): mp 159–165 °C; mass spectrum, *m/e* 384 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 1.37 (d, 3 H, $J$ = 7 Hz, $NCH(CH_3)$), 2.18 (br s, 6 H, 2 $CH_3$), 1.6–2.8 (m, 7 H, 3 $CH_2$, CH), 3.67, 3.72 (2 s, 3 H, $OCH_3$), 5.22 (q, 1 H, $J$ = 7 Hz, $NCH(CH_3)$), 5.81 (m, 1 H, NH), 6.35, 6.41 (2 br s, 1 H, aromatic), 7.32 (m, 3 H, aromatic), 8.10 (m, 2 H, aromatic).

**Methyl *d,l*-7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoate (*dl*-23).** To a solution of 0.20 g (0.86 mmol) of *dl*-**16** in 10 mL of diethyl ether was added under stirring an excess (±4.5 mmol) of diazomethane dissolved in diethyl ether. The mixture was stirred for an additional 5 min and the excess diazomethane was decomposed with acetic acid. The solvent was removed under diminished pressure, and 0.20 g (0.82 mmol, 95%) of *dl*-**23** was obtained as a colorless solid: mp 40–44 °C; mass spectrum, *m/e* 258 ($M^+$); IR (Nujol) 1740 $cm^{-1}$ (C═O); $^1H$ NMR ($CDCl_3$) δ 1.7–2.8 (m, 7 H, 3 $CH_2$, CH), 2.11 (s, 6 H, 2 $CH_3$), 3.68 (s, 3 H, $OCH_3$), 3.72 (s, 3 H, $OCH_3$), 6.50 (s, 1 H, aromatic). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12. Found: C, 72.34; H, 8.13.

**Methyl *l*-7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydro-1-naphthoate (*l*-23).** This compound was prepared by following the procedure described for *dl*-**23**: mp 63.5–64.5 °C; $[\alpha]^{22}_{578}$ −17.5° (*c* 0.32, $CHCl_3$).

***dl*-1-(Hydroxymethyl)-7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene (*dl*-24).** A mixture of 0.54 g (2.17 mmol) of *dl*-**23** and 1.0 g of $LiAlH_4$ in 30 mL of diethyl ether was stirred and heated under reflux for 1 h. The solution was cooled to 0 °C, and 30 mL of water was slowly added. The aqueous solution was extracted with diethyl ether (3 × 30 mL), and the ether extracts were washed with water (20 mL) and dried over $MgSO_4$. The solvent was removed by distillation to yield 0.475 g (2.14 mmol, 99%) of colorless crystalline *dl*-**24**: mp 100.5–101.5 °C; mass spectrum, *m/e* 220 ($M^+$); IR (Nujol) 3400 $cm^{-1}$ (s, OH); $^1H$ NMR ($CDCl_3$) δ 1.65–2.75 (m, 7 H, 3 $CH_2$, CH), 2.13 (s, 6 H, 2 $CH_3$), 2.88 (br s, 1 H, OH), 3.75 (br d, 2 H, $CH_2O$), 3.76 (s, 3 H, $OCH_3$), 6.60 (s, 1 H, aromatic). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.95; H, 9.17.

***l*-1-(Hydroxymethyl)-7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene (*l*-24).** The compound was prepared by following the procedure described for *dl*-**24**: mp 124.5–125.5 °C; $[\alpha]^{22}_{578}$ −13.8° (*c* 0.52, $CHCl_3$).

***dl*-1-[(*p*-Toluenesulfonyl)methyl]-7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene (*dl*-25).** The alcohol *dl*-**24** (0.47 g, 2.13 mmol) was dissolved in 10 mL of dry pyridine, and the solution was cooled to 0 °C. Under stirring there was added over a period of 30 min 0.8 g of *p*-toluenesulfonic acid chloride. The mixture was stirred at 20 °C for an additional period of 28 h. The resulting mixture was poured into 30 g of crushed ice and 50 mL of water. A slight excess of 2 N hydrochloric acid and 50 mL of diethyl ether were added. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined ether solutions were dried over $MgSO_4$, and the solvent was removed by distillation. The tosylate *dl*-**25** was obtained in 97% yield (0.77 g, 2.07 mmol) as a colorless crystalline compound: mp 94–96 °C; exact mass for $M^+$ peak calcd *m/e* 374.155, found 374.156; $^1H$ NMR ($CDCl_3$) δ 1.60–2.70 (m, 7 H, 3 $CH_2$, CH), 2.04 (s, 3 H, $CH_3$), 2.08 (s, 3 H, $CH_3$), 2.38 (s, 3 H, $CH_3$), 3.67 (s, 3 H, $OCH_3$), 3.9–4.4 (m, 2 H, $OCH_2$), 6.40 (s, 1 H, aromatic), 7.26, 7.73 (AB system, $J$ = 8 Hz, 4 H, aromatic).

***d*-1-[(*p*-Toluenesulfonyl)methyl]-7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene (*d*-25).** This compound was synthesized analogously to the preparation of *dl*-**25**: mp 88–89 °C; $[\alpha]^{22}_{578}$ +22.1° (*c* 0.28, $CHCl_3$).

***dl*-10 via $LiAlH_4$ Reduction of *dl*-25.** The tosylate *dl*-**25** (0.75 g, 2.0 mmol) dissolved in 10 mL of diethyl ether was added to a stirred suspension of 1.0 g of $LiAlH_4$ in 30 mL of diethyl ether at 0 °C over a period of 30 min. The mixture was stirred and heated under reflux for an additional 60 min. After the mixture was cooled to 0 °C, 50 mL of ice-cold water, 10 mL of 2 N hydrochloric acid, and 30 mL of diethyl ether were added. The organic layer was separated and the aqueous layer extracted with diethyl ether (4 × 20 mL). The combined ether solutions were washed with water (3 × 15 mL) and dried over $MgSO_4$, and the solvent was removed by distillation. Racemic **10** was obtained as a colorless oil (0.37 g, 1.8 mmol, 90%). The product was in all respects identical with *dl*-**10** prepared via hydrogenation of **9**.

***l*-10 via $LiAlH_4$ Reduction of *d*-25.** *l*-**10** (a colorless oil) was prepared in the same way as the racemic compound *dl*-**10**; $[\alpha]^{22}_{436}$ −14.5° (*c* 0.36, $CHCl_3$). All spectral data of *l*-**10** were identical with those of the racemic compound (except for chiroptical data).

***d*-1 from *l*-10.** Optically active naphthol *d*-**1** was prepared from *l*-**10** by ether bond fission with hydroiodic acid in acetic acid in the same way as for the preparation of racemic **1**: oil; $[\alpha]^{22}_{578}$ +14.8° (*c* 0.3, ethanol). All spectral data were identical with those of *dl*-**1** (except for chiroptical data).

**Oxidative Coupling of (*S*)-(+)-1 and (*R,S*)-1.** To a solution of 0.235 g (1.23 mmol) of *dl*-**1** in 43 mL of diethyl ether was added 0.448 g of $K_3Fe(CN)_6$ dissolved in 18.5 mL of 0.2 N NaOH solution. Water (5 mL) was added, and the mixture was stirred at 22 °C for 2 h. The ether layer slowly turned light red. Diethyl ether (20 mL) and water (10 mL) were added and the layers separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined ether solutions were washed with water (3 × 10 mL) and dried over $MgSO_4$. After removal of the solvent under diminished pressure, 0.210 g of a pale yellow semisolid was obtained.

The crude reaction mixture was separated into the different compounds by means of chromatography [TLC, silica gel 60PF, petroleum ether (bp 40–60 °C)/ether, 20:1]. Three main fractions were obtained: (1) phenol **1**, 0.017 g (0.90 mmol, 7.5%), identical with the starting material; (2) a mixture of quinones and ethers (0.034 g, 15%), IR (Nujol) 1680 $cm^{-1}$ (C═O); (3) dimeric product *dl*-**2**, 0.145 g (0.76 mmol, 62%), mp 127–137 °C, mixture of diastereoisomers, according to the 100-MHz $^1H$ NMR spectrum [100-MHz $^1H$ NMR ($CDCl_3$) δ 0.72 (d, $J$ = 7 Hz, $C_8$ and $C_{8'}$-$CH_3$, **2a**), 0.813 (d, $J$ = 7 Hz, $C_8$- and $C_{8'}$-$CH_3$,**2c**), 0.83 (d, $J$ = 7 Hz, $C_8$-$C_{8'}$-$CH_3$, **2b**), 0.96 (d, $J$ = 7 Hz, $C_8$- or $C_{8'}$-$CH_3$, **2c**), (together 6 H), 1.37–2.85 (m, 14 H, 6 $CH_2$, 2 CH), 2.13 (s, 6 H, 2 $CH_3$), 2.15 (s, 6 H, 2 $CH_3$), 4.49 (br s, OH), 4.54 (br s, OH), 4.63 (br s, OH) (together 2 H); mass spectrum, *m/e* 378 ($M^+$); IR (Nujol) 3150 $cm^{-1}$ (s, OH), 3300 (m, br, OH). Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.62; H, 9.03]. Racemic **2** can be crystallized from petroleum ether (bp 40–60 °C)/benzene (10:1).

The diastereomeric mixture containing **2a–c** was separated into the individual components by means of HPLC (Waters liquid chromatograph, 50 cm × $^3/_8$ in. column, SI 60-5, propyl chloride/hexane, 1:1). The diastereomeric ratio was determined by peak integration. A ratio of **2a**/**2b**/**2c** of 66:8:26 (±2) was established, in agreement with the $^1H$ NMR determination. Complete separation was achieved by using the recycling technique.

From 0.095 g of *dl*-**2** (mixture of diastereoisomers) was obtained the following. *dl*-*cis*-**2b**: 0.0075 g (7%); mp 160–161 °C; exact mass for $M^+$ peak calcd *m/e* 378.2558, found 378.2577. *dl*-*trans*-**2a**: 0.061 g (64%); mp 120–121 °C; exact mass for $M^+$ peak calcd *m/e* 378.2558, found 378.2570. *dl*-**2c**: 0.023 g (25%); mp 196–197 °C; exact mass for $M^+$ peak calcd *m/e* 378.2558, found 378.2577.

The oxidation of (*S*)-(+)-**1** was performed by following exactly the same procedure as described for (*R,S*)-**1**. From 0.235 g (1.23 mmol) of (*S*)-(+)-**1** was obtained 0.147 g (0.76 mmol, 62%) of (*S,S*)-(+)-*trans*-**2a**: mp 173–174 °C; $[\alpha]^{22}_{578}$ +10.5°, $[\alpha]^{22}_{365}$ 0° (both *c* 0.5, 95% ethanol); IR (Nujol) 3510 (s, OH), 3300 $cm^{-1}$ (br, m, OH); 100-MHz $^1H$ NMR ($CDCl_3$) δ 0.72 (d, $J$ = 7 Hz, 6 H, $C_8$- and $C_{8'}$-$CH_3$), 1.37–2.85 (m, 14 H, 6 $CH_2$, 2 CH), 2.13 (s, 6 H, 2 $CH_3$), 2.15 (s, 6 H, 2 $CH_3$), 4.65 (br s, 2 H, OH); mass spectrum, *m/e* 378 ($M^+$). In all other respects this compound was identical with racemic *dl*-*trans*-**2a**.

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**Registry No.** *dl*-1, 60208-20-0; *d*-1, 60154-50-9; *dl*-*trans*-2a, 77059-39-3; (*S,S*)-(+)-*trans*-2a, 60208-21-1; *dl*-*cis*-2b, 77059-40-6; *dl*-2c, 77059-41-7; 6, 77028-15-0; 7, 77028-16-1; 8, 77028-17-2; 9, 77028-18-3; *dl*-10, 77028-19-4; *l*-10, 77059-42-8; 12, 77028-20-7; 12 picrate, 77028-21-8; 13 (isomer 1), 77044-37-2; 13 (isomer 2), 77044-38-3; 14 (isomer 1), 77028-22-9; 14 (isomer 2), 77059-43-9; 15 (isomer

1), 77028-23-0; **15** (isomer 2), 77028-24-1; *dl*-**16**, 77028-25-2; *l*-**16**·(+)-DHAA, 77096-10-7; *dl*-**16** acid chloride, 77028-26-3; *l*-**16**, 77059-44-0; **17**, 77028-27-4; **18**, 77028-28-5; **19**, 77028-29-6; **20**, 77028-30-9; **21**, 77028-31-0; *dl*-**23**, 77028-32-1; *l*-**23**, 77059-45-1; *dl*-**24**, 77028-33-2; *l*-**24**, 77059-46-2; *dl*-**25**, 77028-34-3; *d*-**25**, 77059-47-3; *d*-**26**, 3886-69-9; **27** (isomer 1), 77028-35-4; **27** (isomer 2), 77028-36-5; *d*-**28**, 22038-87-5; **29** (isomer 1), 77028-37-6; **29** (isomer 2), 77028-38-7; *l*-menthoxyacetic acid chloride, 15356-62-4; *d*-camphor-10-sulfonic acid chloride, 21286-54-4; *d*-3-bromo-π-camphorsulfonic acid chloride, 72002-59-6; diethyl oxalate, 95-92-1; methyl iodide, 74-88-4.

# A Procedure for Diethoxymethylation of Ketones[1]

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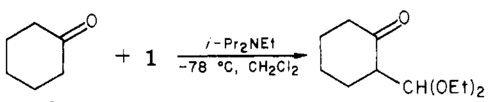
Reaction of a number of ketones with diethoxycarbenium fluoroborate in the presence of *N,N*-diisopropylethylamine at low temperature in methylene chloride results in a preparatively useful conversion to α-(diethoxymethyl) ketones. The method is compatible with arene, alkene, nitrile, chloride, and ester functional groups. With unsymmetrically substituted ketones, it is regioselective for the less substituted α-position. In favorable cases α,α′-dialkylation occurs. Conjugated ketones react normally at the saturated position adjacent to the carbonyl group. The mechanism of the reaction is considered.

Oxonium ions have unrealized potential as synthetic reagents. We describe an application of diethoxycarbenium fluoroborate (1) for the conversion of aliphatic

$$\text{EtO–CH}^{+}\text{–OEt} \underset{1}{\leftrightarrow} \text{EtO}^{+}\text{=CHOEt}$$

and aromatic ketones to protected derivatives of the formyl ketone type. Our finding is that a variety of acyclic and cyclic ketones (e.g., **2**) are transformed into β-keto acetals by **1** in methylene chloride at −78 °C in the presence of *N,N*-diisopropylethylamine (eq 1). The reactant **1** is, of




2 3 (1)

course, an analogue of the Vilsmeir reagent, a well-known formylating species,[2] and the transformation shown also has some resemblance to the Mannich reaction, with regard to functionalization of an unactivated ketone.

The characteristics of the new reaction are the subject of this investigation, which was undertaken because the product (**3**) appeared promising synthetically and because the procedure is simpler, milder, and more direct than other acid-induced formylation techniques.[2,3] We report here the results of a modest examination of the scope and mechanism of this reaction.

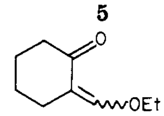
## Results

**Description of Technique.** The optimum method for carrying out the reaction of eq 1 was determined by systematic variation of experimental parameters. The preferred conditions in the case of cyclohexanone require the addition of 1 equiv of ketone to 2 equiv of in situ generated diethoxycarbenium fluoroborate (from triethyl orthoformate), slurried in methylene chloride at −78 °C with efficient stirring, followed by dropwise addition of 3 equiv of *N,N*-diisopropylethylamine over the course of approximately 0.5 h. The product is subsequently obtained by an aqueous sodium bicarbonate quench followed by phase separation, acid washing, and simple distillation. Yields are generally acceptable (Table I), although the procedure was optimized only for cyclohexanone. Minor byproducts which have been identified are **4**–**7**. The first three are

$HC(OEt)_2C(OEt)_2CO_2Et$ **4**

$HC(OEt)_2C(OEt)_3$ **5**

$HC(OEt)_2CO_2Et$ **6**




**7**

thought to arise from reactions involving diethoxycarbene, which previous work has suggested may be generated under the reaction conditions.[4] (They are also produced when no ketone is present in the reaction mixture.) Formation of **7** (an elimination product of **3**) may be avoided by exercising care in the acid extraction during workup of the reaction mixture. Under the procedure described, none of these substances amounts to more than a few percent of the distilled product. The hindered, nonnucleophilic base *N,N*-diisopropylethylamine, a fairly expensive but indispensable reagent for this transformation,[5] is routinely recovered from the aqueous extracts of the reaction mixture.

**Scope.** The method has been applied to an illustrative selection of ketones. The results are summarized in Table I. Comments on the individual examples follow. **(1) Cyclohexanone.** The minor product results from further alkylation. A 2.5-fold increase in the amount of diethoxycarbenium salt and amine diminishes the yield of the major product to 73%, while giving only 9% of dialkylation. **(2) Cyclopentanone.** Additional condensations are suggested by color development in the reaction mixture. **(3) Acetone.** Clean dialkylation occurs under the con-

(1) (a) Taken from the Ph.D. Thesis of H.-R. Tsou, University of Illinois at Chicago Circle, 1978; *Diss. Abstr. B*, **39**, 242 (1978). (b) Reported in preliminary form: W. L. Mock and H.-R. Tsou, Abstracts of the 175th National Meeting of the American Chemical Society, Anaheim, CA, Mar 1978, No. ORGN-78.

(2) G. A. Olah and S. J. Kuhn, "Friedel–Crafts and Related Reactions", Vol. 3, Wiley, New York, 1964, Part 2, Chapter 38, p 1211; F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **19**, 151 (1980).

(3) (a) T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); (b) E. C. Taylor and J. L. LaMattina, *Tetrahedron Lett.*, 2077 (1977); (c) R. R. Sauers and P. A. Odorisio, *J. Org. Chem.*, **44**, 2980 (1979).

(4) R. A. Olofson, S. W. Walinsky, J. P. Marino, and J. L. Jernow, *J. Am. Chem. Soc.*, **90**, 6554 (1968).

(5) Other successful uses of this proton scavenger with oxonium salts have been recorded: (a) ref 4; (b) D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971); (c) M. J. Diem, D. H. Burow, and J. L. Fry, *J. Org. Chem.*, **42**, 1801 (1977).

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