Proton Magnetic Resonance Spectra of Menthyl Phosphinates[1,2]

Robert A. Lewis,[3] Olaf Korpiun, and Kurt Mislow

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey 08540. *Received March 4, 1968*

Abstract: The pmr spectra of menthyl *n*-alkylphenylphosphinates are diagnostic of configuration at phosphorus: in esters derived from (−)-menthol, the $(S)_P$ configuration is indicated for the diastereomer in which the signal due to the protons of one of the methyl groups in the isopropyl group has suffered an upfield shift. Evidence is adduced which shows that shielding by the phenyl ring is responsible for the shift, and that the shifted protons (H_a) reside on the *pro-S* methyl group. A conformational analysis is presented which serves to accommodate these results, and an extension to menthyl diarylphosphinates is briefly explored.

Menthyl phosphinates are useful precursors in the synthesis of optically active phosphine oxides.[4] In the present paper we report our finding that the pmr spectra of these esters are a rich lode of structural information.

The upfield portion of the spectra features the three C–CH_3 (H_a, H_b, and H_c) doublets of the menthyl moiety, and, when present, the P–CH_3 (H_d) doublet (Table I[5]). Chemical shifts of these signals in the two diastereomers (differing in chirality at phosphorus) are sufficiently well separated so that they are conveniently employed as criteria for diastereomeric purity. For example, the upfield position of the H_a doublet in **2b** (Figure 1),[6] in a region unencumbered by other signals, readily allows detection and quantitative estimation of any significant contamination of **2a** by **2b**; separation of the diastereomers may alternatively be monitored by reference to the H_d signals near τ 8.4 which are slightly, but detectably (*ca.* 3 Hz at 60 MHz), separated. The upfield resonance of H_a, which is evident in **2b**, is also observed in **1b**, but not in **1a**. Since both menthyl *n*-alkylphenylphosphinates **1b** and **2b** have the *S* configuration at phosphorus,[4,5] the position of H_a may thus be regarded as diagnostic of phosphorus chirality, an upfield shift corresponding to the $(S)_P$ configuration.[7]

Table I. Proton Magnetic Resonance Spectra of Phosphinates

No.	Ester $R_1R_2P(O)OR_3$ R_1	R_2	Chirality at phosphorus[a]	H_a[c]	H_b[c]	H_c[d]	H_d[e]
1a[b]	C_6H_5	*n*-C_3H_7	*R*	9.11	9.05	9.25	...
1b[b]	C_6H_5	*n*-C_3H_7	*S*	9.68	9.19	9.10	...
2a[b,f]	C_6H_5	CH_3	*R*	9.11	9.05	9.24	8.38
2b[b,f]	C_6H_5	CH_3	*S*	9.66	9.19	9.11	8.34
3a[b,g,h]	C_6H_{11}	CH_3	..	9.19	9.08	9.10	8.64[i]
3b[b,g,h]	C_6H_{11}	CH_3	..	9.19	9.08	9.10	8.61[i]
4a[b,j]	C_6H_5	β-$C_{10}H_7$	*R*	9.38	9.09	9.19	...
4b[b,j]	C_6H_5	β-$C_{10}H_7$	*S*	9.47	9.13	9.16	...
5[b,j]	C_6H_5	C_6H_5	..	9.43	9.12	9.15	...
6a[k,l]	C_6H_5	CH_3	..	9.10	9.05	...	8.38
6b[k,l]	C_6H_5	CH_3	..	9.59	9.20	...	8.32
7a,7b[m]	C_6H_5	CH_3	..	...	...	*Ca.* 9.1	8.42

[a] See ref 4. [b] R_3 = (−)-menthyl. [c] J_{HCH} = 7.0 Hz. [d] J_{HCH} = 4.5–5.5 Hz. [e] J_{PCH} = 14.5 Hz, except as noted. [f] See Figure 1. [g] See Figure 2. [h] Chirality at phosphorus unknown. [i] J_{PCH} = 13.0 Hz. [j] See Figure 9. [k] See Figure 3. [l] Racemic mixture; R_3 = *trans*-2-isopropylcyclohexyl. [m] The diastereomers were not separated; racemic mixture; R_3 = *cis*-3-methylcyclohexyl.

The striking upfield shift (*ca.* 0.5 ppm) of the H_a doublet in **1b** and **2b** is attributable to the diamagnetic anisotropy of the phenyl ring,[8] rather than to that of the phosphoryl group, for this phenomenon is not observed when the phenyl group is converted to a cyclohexyl group, as shown by Figure 2, which depicts the pmr spectrum of a mixture of diastereomeric menthyl cyclohexylmethylphosphinates **3a** and **3b**. Incidentally, the doubling of the H_d doublets near τ 8.6 is illustrative of the ease with which such mixtures may be distinguished from the pure components in this series of compounds.

That the proton responsible for the upfield signal is not located in the methyl group attached to the cyclohexane ring, *i.e.*, that it is not H_c, was shown by a comparison of the pmr spectra of **2a** and **2b** with those of esters containing portions of the menthyl moiety. Thus, the two diastereomers, **6a** and **6b** (Table I), obtained by reaction of methylphenylphosphinyl chloride with racemic *trans*-2-isopropylcyclohexanol, feature two C–CH_3 doublets each, with J = 7.0 Hz (Figure 3), the chemical shifts of the doublets in the isomers designated **6a** and **6b** corresponding closely to the shifts of C–CH_3 doublets H_a and H_b (J = 7.0 Hz) in **2a** and **2b**, respectively (Table I). Since *trans*-2-isopropylcyclohexanol may be regarded as a truncated menthol, lacking the ring methyl group, and since the absolute configuration of menthol is 1*R*,3*R*,4*S*,[9] the coincidence of signals identifies the configuration of the diastereomers of **6** (Figure 3), and it follows that **6a** is an equimolar mixture of enantiomers, one of which has the menthol-like 1*R*,2*S* configuration in the cyclohexyl moiety and the *R* configuration at phosphorus, *i.e.*, the $(R)_P(1R,2S)_C$ configuration, while the other has the $(S)_P(1S,2R)_C$ configuration; similarly, **6b** is an equimolar mixture of $(S)_P(1R,2S)_C$ and $(R)_P(1S,2R)_C$ en-

(1) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67.

(2) For a preliminary account of this work, see R. A. Lewis, O. Korpiun, and K. Mislow, *J. Amer. Chem. Soc.*, 89, 4786 (1967).

(3) Public Health Service Predoctoral Fellow, 1966–1968.

(4) O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, 90, 4842 (1968).

(5) Esters numbered 1–4 in Table I correspond to the equally numbered compounds in Table I of ref 4, including letter suffix.

(6) The figures indicate the positions of the C–CH_3 signals arising from the protons identified as H_a, H_b, and H_c in the accompanying formulas. The rationale for these assignments is developed in the text.

(7) For phosphinates derived from unnatural (+)-menthol, the upfield shift would be observed for the diastereomer with the $(R)_P$ configuration.

(8) L. Pauling, *J. Chem. Phys.*, 4, 673 (1936); J. A. Pople, *ibid.*, 24, 1111 (1956).

(9) V. Prelog, *Helv. Chim. Acta*, 36, 308 (1953); numbering of carbons as in *p*-menthan-3-ol.

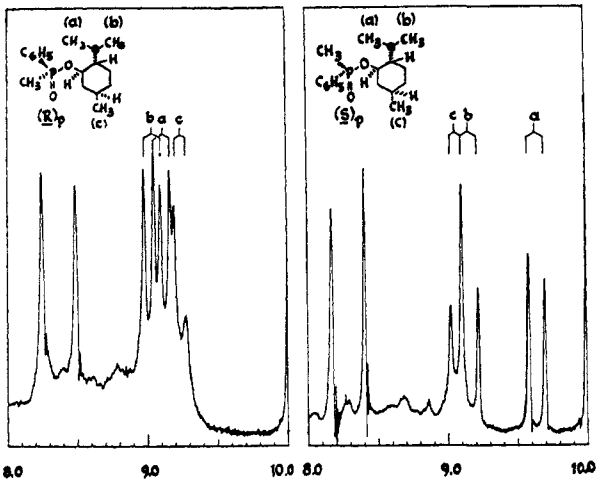


Figure 1. Pmr spectra of diastereomeric menthyl methylphenylphosphinates **2a** (left) and **2b** (right), τ scale.

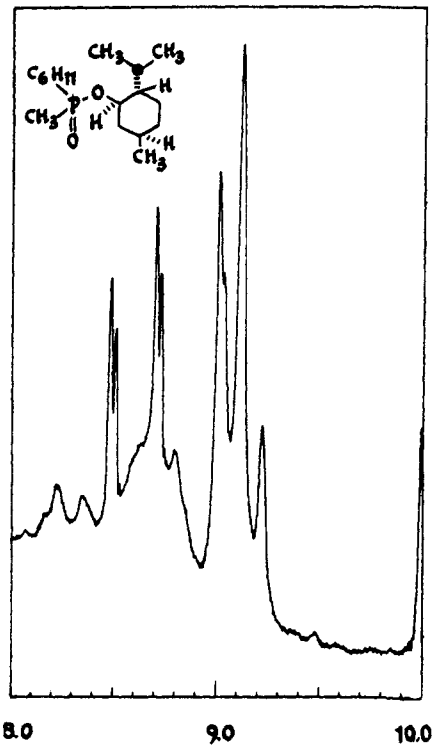


Figure 2. Pmr spectrum of a mixture of diastereomeric menthyl cyclohexylmethylphosphinates **3a** and **3b**, τ scale.

antiomers. In addition, a mixture of the two diastereomers, **7a** and **7b** (Table I), obtained by reaction of methylphenylphosphinyl chloride with racemic *cis*-3-methylcyclohexanol,[10] exhibits only a single C–CH_3 doublet, J = 5.0 Hz, which corresponds in position and coupling constant[11,12] to the third C–CH_3 proton (*i.e.*, H_c) in **2a** and **2b**. The site of the proton responsible for the upfield doublet (H_a) in the $(S)_P$ isomers of **1** and **2** having thus been narrowed down to one of the two isopropyl

(10) This compound may be regarded as a truncated menthol, lacking the isopropyl group.

(11) The coupling constants reported are obtained by first-order analysis; they indicate the separation of signals in the doublet (60-MHz spectrum) and should not be construed as true coupling constants. The H_c resonance is broadened because of virtual coupling to the ring protons at C-2 and C-6, thus creating an apparent decrease in coupling constant.[12]

(12) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

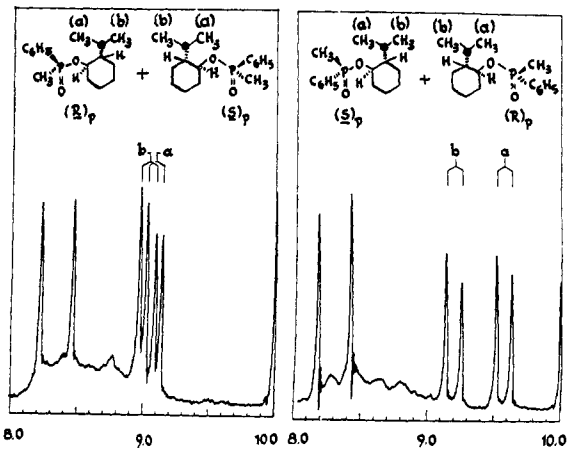


Figure 3. Pmr spectra of diastereomeric *trans*-2-isopropylcyclohexyl methylphenylphosphinates **6a** (left) and **6b** (right), τ scale.

methyl groups, it remained to establish the identity of the diastereotopic[13] methyl group which contains H_a.

Although numerous instances are reported in which diastereotopic isopropyl methyl groups exhibit chemical shift nonequivalence,[14,15] only one example has heretofore been recorded in which the identity of such methyl groups has been rigorously established.[16,17] As in the previous work,[16,17] the diastereotopic groups in the present study were identified by examination of the pmr spectra of derivatives in which the prochiral center (*i.e.*, the carbon atom to which the methyl groups are attached) had been converted into a chiral center by stereospecific replacement of the protium atoms in one of the methyl groups by deuterium atoms.

The synthetic pathway, as outlined in Chart I, started from the common precursor, (−)-isopulegol (**8**), and led to two appropriately deuterated (−)-menthols: (−)-(8*S*)-menthol-9-d_1 (**11**), in which the *pro-S* methyl group has been replaced by a deuteriomethyl group, and (−)-(8*R*)-menthol-9-d_3 (**19**), in which the *pro-R* methyl group has been replaced by a trideuteriomethyl group. The key step in the synthesis was the generation of a new chiral center at C-8 by oxidative hydroboration of **8**,[18] an asymmetric synthesis which proceeds in a highly stereospecific manner[18] to give (−)-(1*R*,3*R*,-4*S*,8*R*)-*p*-menthane-3,9-diol (**9**);[19] by the same token

(13) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, Chapter 1.

(14) *Cf.*, *e.g.*, N. S. Bowman, D. E. Rice, and B. R. Switzer, *J. Amer. Chem. Soc.*, 87, 4477 (1965). Although such chemical shift differences do not usually exceed 0.2 ppm, much greater shift differences, as in **1b** and **2b**, are not unprecedented[15] in compounds with a nearby source of diamagnetic anisotropy.

(15) E. W. Garbisch, *J. Org. Chem.*, 27, 4243 (1962); T. S. Sorensen, *Can. J. Chem.*, 45, 1585 (1967).

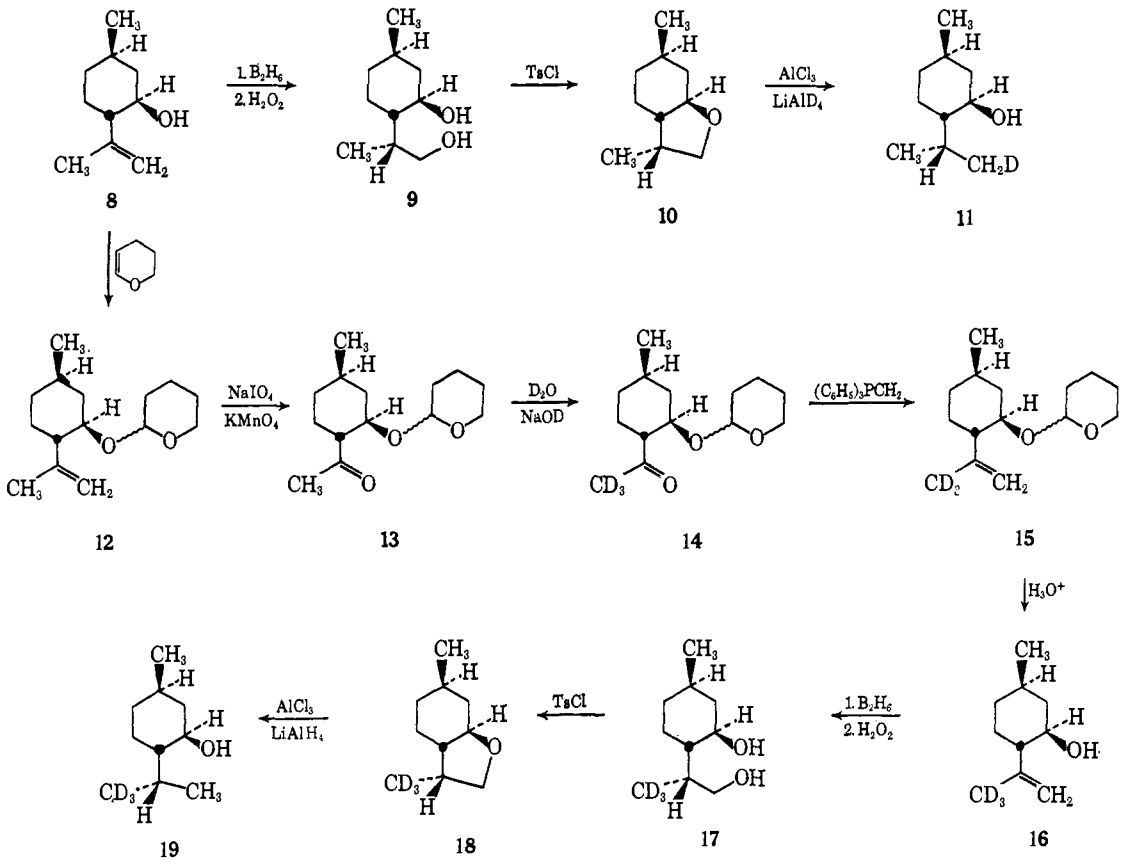
(16) M. Raban and K. Mislow, *Tetrahedron Lett.*, 3961 (1966). It was shown that in isopropyl (*R*)-O-methylmandelate, the *pro-R* methyl group[17] in the isopropyl moiety gives rise to the upfield doublet, while the *pro-S* methyl group[17] gives rise to the downfield doublet.

(17) This specification of prochirality has been proposed by K. R. Hanson, *J. Amer. Chem. Soc.*, 88, 2731 (1966). Since the terms "*pro-R*" and "*pro-S*" do not refer to the prochiral center itself but to the paired ligands of that center, the methyl groups themselves may not properly be said to have "*pro-R* chirality" or "*pro-S* chirality." We thank Professor Hans Hirschmann for directing our attention to this point.

(18) K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **50**, 153 (1967).

(19) The assignment[18] of configuration at C-8, which is crucial to our argument, was confirmed by X-ray analysis of **9**. This work was done by Dr. Michael G. B. Drew, whom we thank for permission to cite his results prior to publication.

Chart I[a]



[a] A dot signifies a hydrogen atom projecting toward the observer.

the oxidative hydroboration of **16** gave (−)-(1*R*,3*R*,-4*S*,8*R*)-*p*-methane-3,9-diol-10-d_3 (**17**). Subsequent ring closure of **9** to **10**, followed by reductive cleavage[20] of the CH_2–O bond with $LiAlD_4$–$AlCl_3$, gave **11**; similarly, ring closure of **17** to **18**, followed by reductive cleavage[20] with $LiAlH_4$–$AlCl_3$, gave **19**.

Comparison of the pmr spectra of menthol and its deuterated derivatives, **11** and **19**, permitted assignment of the three C–CH_3 doublets in menthol (Figure 4). As expected (see above) the doublet at τ 9.10, which is unaltered in all three spectra and is therefore assigned to the ring methyl (H_c), has the smaller observed coupling constant (5.5 *vs.* 7.0 Hz). Of the remaining two doublets, the one at τ 9.18 is due to the *pro-S* methyl group (H_a) and the one at τ 9.07 to the *pro-R* methyl group (H_b), since in **11** the upfield doublet is decreased in intensity and broadened by H–D coupling[21] whereas in **19** it is the downfield doublet which has been sharply reduced in intensity, the remaining signal testifying to the presence of some undeuterated contaminant. On the basis of this analysis, it is now possible to conclude that in the pmr spectrum of racemic *trans*-2-isopropylcyclohexanol (Figure 5), the protons in the *pro-S* methyl group of the 1*R*,2*S* (menthol-like) enantiomer and the protons in the *pro-R* methyl group of the 1*S*,2*R* enantiomer are responsible for the upfield doublet (H_a) at τ 9.18 (J = 7.0 Hz), while the diastereotopic protons are responsible for the downfield doublet (H_b) at τ 9.07 (J = 7.0 Hz).

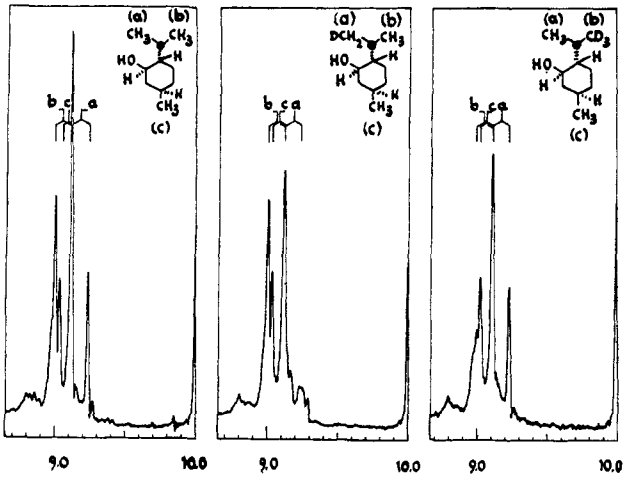


Figure 4. Pmr spectra of menthol (left), and of deuteriomenthols **11** (center) and **19** (right), τ scale.

As anticipated, the pmr spectra of the deuterated diastereomers of **2**, prepared by reaction of methylphenylphosphinyl chloride with **11** or **19**, led to an unequivocal identification of the diastereotopic methyl groups in the isopropyl portion of the menthyl moiety.

(20) It was found that the direction of cleavage by this reagent mixture is quite specific; thus, 2-methyltetrahydrofuran on cleavage with $LiAlH_4$–$AlCl_3$ gave more than 80% of 2-pentanol and less than 20% of 1-pentanol, and cleavage of 10 by this reagent mixture afforded a product whose infrared spectrum even prior to purification was nearly superimposable on that of menthol.

(21) It might be noted that an additional complication arises through the circumstance that in 11 and its derivatives the methylene protons on the carbon bearing the deuterium atom are diastereotopic and thus in principle anisochronous. However, the chemical shift difference, though nonvanishing, is nevertheless expected to be negligibly small.

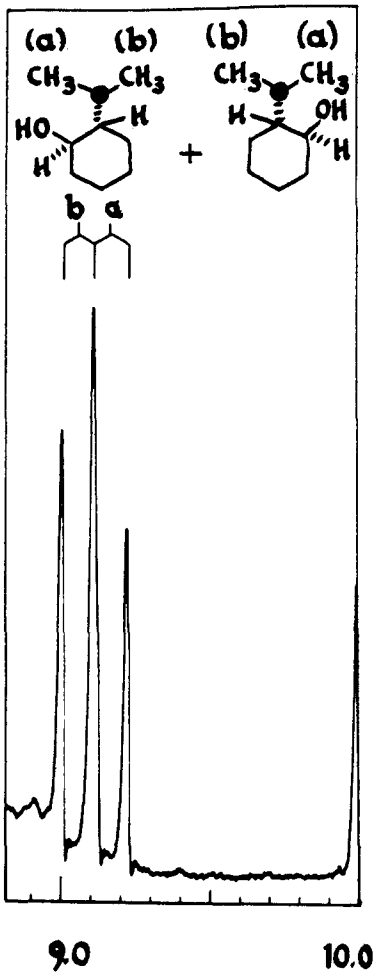


Figure 5. Pmr spectrum of *trans*-2-isopropylcyclohexanol, τ scale.

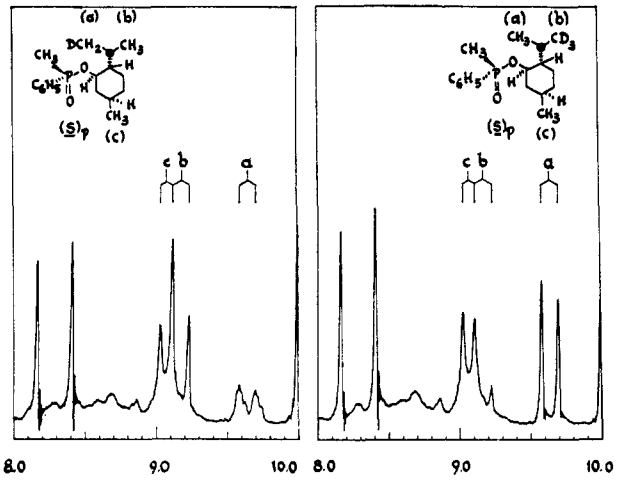


Figure 6. Pmr spectra of $(S)_P$ diastereomers of deuteriomenthyl methylphenylphosphinates prepared from **11** (left) and **19** (right), τ scale.

As shown in Figure 6, in the pmr spectrum of the deuterated analog[22] of **2b** which was derived from **11**, the upfield C–CH_3 doublet (H_a) is broadened by H–D coupling[21] and decreased in integrated intensity from three to two protons, whereas the downfield doublet (H_b) is unaffected (compared with Figure 1). On the other hand, in the pmr spectrum of the deuterated analog[22] of **2b** which was derived from **19**, the upfield C–CH_3 doublet (H_a) is unaffected (compare with Figure 1), and it is the downfield doublet (H_b) which is now sharply reduced in intensity, the remaining signal testifying to the presence of some undeuterated contaminant. Thus, H_a in **2b** is identified as residing in the *pro-S* methyl group, and H_b in **2b** as residing in the *pro-R* methyl group. Similarly, the assignments to H_a and H_b in **2a** (Figure 1) were made on the basis of the pmr spectrum (Figure 7) of the deuterated analog[22] derived from **11**; comparison with the spectrum of undeuterated **2a** immediately reveals the virtual disappearance (through decreased intensity and signal broadening) of the doublet at τ 9.11, which is accordingly due to the H_a proton in the *pro-S* methyl group; by difference, the signal at τ 9.05 is due to the H_b proton in the *pro-R* methyl group. The diastereotopic methyl groups in **1a** and **1b** were assigned by analogy, as shown in Table I, H_a corresponding to the *pro-S* and H_b to the *pro-R* methyl group. The diastereotopic methyl groups in **3a** and **3b** were assigned as shown in Table I by comparison of the pmr spectra of deuterated (from **11**) and undeuterated esters; the doublet at τ 9.19, evident in the former, has apparently disappeared in the latter, and is consequently assigned to H_a (*pro-S*).[23] The di-

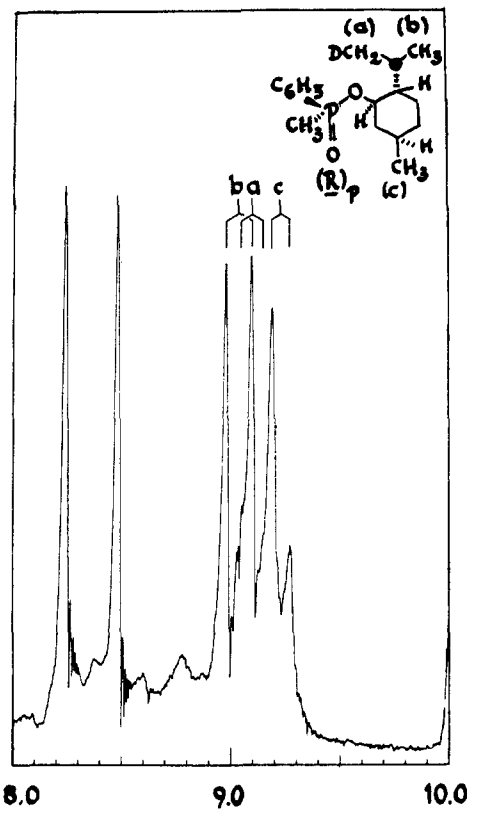
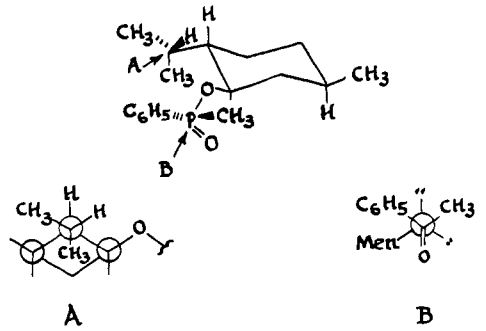


Figure 7. Pmr spectrum of the $(R)_P$ diastereomer of deuterio menthyl methylphenylphosphinate prepared from **11**, τ scale.

(22) The deuterated esters were separated and assigned their diastereomeric identities by comparison of melting point, solubility, specific rotation, and P–CH_3 chemical shift with the corresponding properties of the undeuterated esters.

(23) In contradistinction to **1** and **2**, where signals in the $(S)_P$ diastereomers (**b**) due to H_a and H_b are shifted upfield relative to the $(R)_P$ diastereomers (**a**), by 0.56 and 0.14 ppm, respectively, neither H_a nor H_b is significantly shifted in the two diastereomers of **3**. In contrast to the menthyl alkylarylphosphinates, chirality at phosphorus thus cannot be assigned by pmr.



A B

Figure 8. Center: a conformation of menthyl methylphenylphosphinate, **2b**, which is consistent with the pmr spectra: A, view along the isopropyl–ring bond; B, view along P–O–menthyl bond; Men = (−)-menthyl.

astereotopic methyl groups in **6** were assigned as shown in Table I and Figure 3, by analogy with the corresponding signals in **2a** and **2b**. Finally, the upfield doublet in (−)-menthyl *p*-iodobenzenesulfinate (**20b**), a signal which has proven its usefulness as a gauge of the content of **20b** in mixtures of **20b** and its diastereomer (**20a**)[24] (just as the corresponding doublet in **2b** serves as a gauge of the content of **2b** in mixtures of **2b** and **2a**), was assigned to the *pro-S* methyl group in the menthyl moiety by comparison of the pmr spectrum of **20b** with that of the deuterated esters prepared from *p*-iodobenzenesulfinyl chloride and **11**. Since **20b** has the *S* configuration at sulfur,[25] the parallelism between the phosphinate and sulfinate systems is complete.

Granted that the upfield shift of H_a may be attributed to the diagmagnetic anisotropy of the phenyl group and that the highly shielded proton is situated on the *pro-S* methyl group in the menthyl moiety of the $(S)_P$ esters, the question remains whether the upfield shift is primarily a consequence of conformational preference or of "intrinsic diastereotopism."[26] Although the contribution of the $\Delta\nu_{1d}$ term[26b] was not quantitatively assessed, the importance of the conformer population term ($\Delta\nu_{cp}$[26b]) is indicated by the data in Table II, which demonstrate that a lowering in temperature increases

Table II. Temperature Dependence of the Pmr Spectrum[a] of **2b**

	Solvent						
	Toluene				Acetone-d_6		
	115°	75°	37°	−60°	37°	−60°	−75°
H_a	9.46	9.50	9.56	9.76	9.61	9.82	9.89
H_b	9.19	9.19	9.19	*Ca.* 9.16	9.19	9.19	9.19
H_c	9.18	9.18	9.18	*Ca.* 9.17	9.09	9.09	9.08
H_d	8.57	8.58	8.60	8.62	8.34	8.23	8.19

[a] J_{HCH} of H_a and H_b = 7.0 Hz, and of H_c 5.0 Hz; J_{PCH} = 14.5 Hz.

the upfield shift of the signal due to H_a but leaves the positions of the other methyl proton signals relatively unaffected. The phenomenon under discussion is therefore associated with the conformer of lowest

(24) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow *J. Amer. Chem. Soc.*, 90, 4835 (1968).

(25) E. B. Fleischer, M. Axelrod, M. Green, and K. Mislow, *ibid.*, 86, 3395 (1964).

(26) (a) H. S. Gutowsky, *J. Chem. Phys.*, 37, 2196 (1962); (b) M. Raban, *Tetrahedron Lett.*, 3105 (1966). The term here introduced is suggested in place of (a) "intrinsic asymmetry" or (b) "intrinsic diastereomerism" in order to conform with present usage of related terminology.[13]

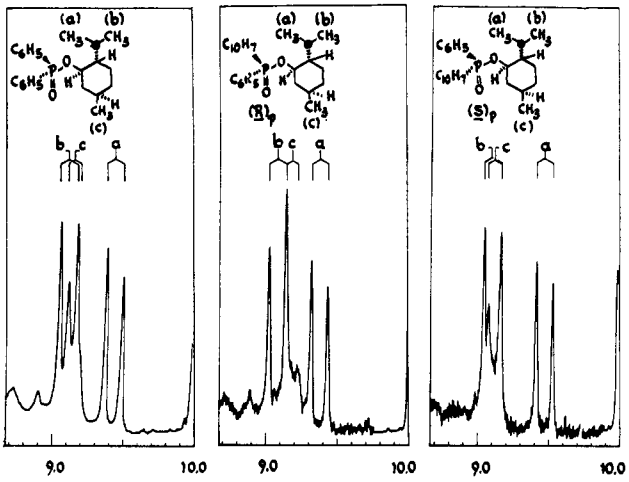


Figure 9. Pmr spectra of menthyl diarylphosphinates **5** (left) **4a** (center), and **4b** (right), τ scale.

energy, whose population might be expected to increase with decreasing temperature. This interpretation is further simplified by the observation that the chemical shifts are fairly insensitive to changes in solvent polarity (Table III).

Table III. Solvent Dependence of Chemical Shifts[a] for **2a** and **2b**

	2a				2b			
	$CDCl_3$	CCl_4	C_5H_6	C_5H_5N	$CDCl_3$	CCl_4	C_6H_6	C_5H_5N
H_a	9.11	9.12	9.04	9.05	9.66	9.68	9.54	9.54
H_b	9.05	9.05	9.00	9.05	9.19	9.21	9.19	9.21
H_c	9.24	9.22	9.38	9.37	9.11	9.07	9.17	9.20
H_d	8.38	8.49	8.60	8.31	8.34	8.42	8.58	8.27

[a] See footnote *a* in Table II.

Figure 8 depicts a geometry which is consistent with the condition that in a stable conformer of (1*R*,3*R*,4*S*)-menthyl (*S*)-methylphenylphosphinate, the *pro-S* methyl group be situated in a shielded region, approximately above the center of the phenyl ring.[27] In this arrangement, the menthyl moiety is in the all-equatorial conformation,[28] the isopropyl group is staggered with respect to the cyclohexane ring and so oriented that there are no CH_3/OH 1,3-*syn*-diaxial interactions,[29] and the phosphorus grouping is so oriented that C-1 of the menthyl moiety occupies a staggered position between the phosphoryl oxygen and the phenyl ring.[30,31] On the other hand, if the $(R)_P$ isomer is placed in a similar conformation, no shielding of the isopropyl moiety by the aromatic ring results.

The conclusions of this study may be extended to the conformational analysis of menthyl diarylphosphinates. The pmr spectrum (Figure 9) of menthyl diphenylphosphinate (**5**) features one of the C–CH_3 doublets in an upfield position comparable to that of the H_a proton

(27) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(28) H. Feltkamp and N. C. Franklin, *Tetrahedron*, 21, 1541 (1965).

(29) E. L. Eliel, S. H. Schroeter, T. J. Brett, and F. J. Biros, *J. Amer. Chem. Soc.*, 88, 3327 (1966).

(30) T. H. Siddall, III, and C. A. Prohaska, *ibid.*, 84, 3467 (1962).

(31) As shown by inspection of space-filling molecular models, these requirements severely restrict the remaining degree of freedom, *i.e.*, rotation around the C–O bond. To avoid excessive nonbonded interaction, the molecule most probably assumes the conformation depicted in Figure 8.

in **1b**, **2b**, and **6b** (Table I); the over-all similarity of the spectra of **5** and **2b** in the region between τ 9.0 and 10.0 suggests a similarity in conformations. Comparison of the pmr spectra of diastereomeric menthyl β-naphthylphenylphosphinates **4a** and **4b** (Figure 9) indicates that the H_a proton in the $(S)_P$ isomer, **4b**, has suffered a slight upfield shift relative to the H_a proton in the $(R)_P$ isomer, **4a**.[32,33] If the arguments on which the preceding conformational analysis were based may be extended to the present case, the *pro-S* methyl group is shielded by the phenyl ring in **4a**, but by the naphthyl ring in **4b**. This result therefore signifies that the naphthyl ring system exerts a greater shielding effect than does the phenyl.[34-37]

Finally, to the extent that a parallelism exists between the menthyl phosphinate and sulfinate systems, it may be justifiable to conclude, tentatively, that the conformational analysis advanced for the phosphinates applies with equal force to the sulfinates, the lone pair of electrons on sulfur in menthyl *p*-iodobenzenesulfinates **20a** and **20b** taking the position in space occupied by the methyl group on phosphorus in menthyl methylphenylphosphinates **2a** and **2b**, respectively.

Experimental Section[38]

(−)-(8*S*)-Menthol-9-d_1 (11). Hydroboration of (−)-isopulegol (77 g) by the method of Schulte-Elte and Ohloff[18] afforded 29 g of (−)-(1*R*,3*R*,4*S*,8*R*)-*p*-menthane-3,9-diol (**9**), which was recrystallized from hexane: mp 104–107°, $[\alpha]D$ −20° (*c* 1.4, chloroform) (lit.[16] mp 107°, $[\alpha]D$ −18° (chloroform)). A mixture of **9** (22.6 g), *p*-toluenesulfonyl chloride (27.5 g), and pyridine (100 ml) was stirred overnight[39] and diluted with ether. Pyridine hydrochloride was removed by filtration; the filtrate was washed with dilute (*ca.* 0.1 *N*) hydrochloric acid, dried, and concentrated under reduced pressure. The residue was distilled at 58° (2.4 mm) to yield 18 g of a colorless liquid, which was shown by glpc to be identical in composition with the furan mixture obtained by cyclization of the diol with sulfuric acid,[18] (+)-(1*R*,3*R*,4*S*,8*R*)-3,9-epoxy-*p*-menthane (**10**, 96%) and (+)-(1*R*,3*S*,4*S*,8*R*)-3,9-epoxy-*p*-menthane (4%).

Lithium aluminum deuteride (0.8 g, 0.021 mol) was added to aluminum chloride (0.95 g, 0.007 mol) slurried in benzene (10 ml) under nitrogen. The resulting slurry was stirred for 5 min, and the above furan mixture (4.0 g, 0.026 mol) was injected through a serum cap. The reaction mixture was heated under reflux for 10 hr, cooled, and poured onto a mixture of ice (50 g) and 1 *N* sulfuric acid (100 ml). The mixture was extracted three times with 50-ml portions of ether, and the organic layers were combined, dried, and concentrated under reduced pressure. The residual oil was distilled (kugelrohr) at 80° (0.05 mm) to yield 2.8 g of deuteriomenthol **11**[40,41] identified by glpc retention time and by the properties of its phosphinate derivatives (see below). The compound was found (by mass spectral analysis) to contain d_0 (7%), d_1 (84%), and d_2 (9%) species.

(−)-Isopulegol-10-d_3 (16). Concentrated hydrochloric acid (1 ml) was added to a well-stirred solution of (−)-isopulegol (154 g, 1.45 mol) and dihydropyran (123 g, 1.47 mol, distilled from potassium hydroxide). The temperature of the mixture rose to 40°, and then dropped slowly. After 5 hr, 2 g of potassium hydroxide was added, and the mixture was distilled. The fraction removed between 85 and 92° (0.3 mm) was redistilled, bp 89–90° (0.3 mm), to provide 152.5 g of isopulegyl 2′-tetrahydropyranyl ether (**12**), as a mixture of diastereomers,[42] ν_{max}^{neat} 1650 cm^{-1} (C=C stretch).

Oxidation of **12** was accomplished by a modification of the method of Lemieux and von Rudloff.[43] Potassium carbonate (134 g, 0.97 mol) in water (1 l.) was added to a solution of **12** (71.4 g, 0.315 mol) and dioxane (1 l.), contained in a 12-l. flask equipped with a magnetic stirrer. Potassium permanganate (6.6 g, 0.042 mol) and sodium metaperiodate (514 g, 2.4 mol) in water (7 l.) was added, and the purple solution was stirred for 4 days, until the color had turned to red-orange and a large amount of precipitate had formed. The mixture was filtered, and the filtrate was extracted twice with 1500-ml portions of ethyl acetate. The combined organic layers were dried and evaporated under reduced pressure, and the residual yellow oil was distilled to yield ***trans*-2-acetyl-*cis*-5-methylcyclohexyl 2′-tetrahydropyranyl ether (13)**:[42] 53 g; bp 103–118° (0.7 mm); ν_{max}^{neat} 1710 cm^{-1} (C=O stretch). A mixture of **13** (108 g) and 1 *N* sodium deuterioxide (100 ml) was stirred rapidly for 12 hr and extracted three times with 50-ml portions of ether. The combined organic layers were dried and evaporated under reduced pressure, and the residual oil was again stirred with sodium deuterioxide (100 ml, 0.5 *N*) for 12 hr. The mixture was extracted as before, and the residue was distilled (bp 117–125° (2 mm)) to provide ***trans*-2-acetyl-d_3-*cis*-5-methylcyclohexyl 2′-tetrahydropyranyl ether (14)**, 80 g, as a mixture of diastereomers,[42] ν_{max}^{neat} 2230 cm^{-1} (C–D stretch) and 1710 cm^{-1} (C=O) stretch. The pmr spectrum was similar to that of **13** except that the acetyl methyl resonances[42] were absent.[44]

Triphenylmethylphosphonium bromide (125 g, 0.35 mol) was slurried in ether, under nitrogen, and 2 *M* phenyllithium in benzene (150 ml) was added. The mixture was stirred for 15 min and ketone **14** (67.2 g, 0.275 mol) was added to the bright yellow solution. A voluminous precipitate formed and the color was dissipated. The mixture was stirred for 2 hr and filtered; the filtrate was washed with water, and the ether layer was dried and evaporated under reduced pressure. Since the residue evidently still contained some unreacted ketone (ν_{max}^{neat} 1710), the Wittig reaction[45] was repeated on the mixture, using 61 g of phosphonium salt and 73 ml of phenyllithium solution. The product was recovered as before and distilled at 110–119° (2.5 mm) to yield 38 g of **isopulegyl-10-d_3**

(32) The protons responsible for the signals shown in Figure 9 were identified by preparing the deuterated analogs of 4 (from 11) and comparing the pmr spectra of deuterated and undeuterated esters.

(33) The H_b proton in **4b** is also shifted upfield relative to that in **4a**, but to a lesser extent (Table I).

(34) Although the greater shielding effect of the naphthyl group might be ascribed[27] to differences in orientation of the two aromatic ring systems relative to the affected (*pro-S*) methyl group, it is interesting to note that calculations of ring current intensities[35] and ring current contributions to shielding[36] allot higher values to naphthalene than to benzene.

(35) N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, **36**, 2443 (1962).

(36) G. W. Parker and J. D. Memory, *ibid.*, **43**, 1388 (1965).

(37) Preliminary investigation of other menthyl arylphenylphosphinates (unpublished results) has shown that when aryl = *p*-anisyl or *p*-biphenylyl, both diastereomers have H_a, H_b, and H_c signals which are indistinguishable (within 1 Hz at 60 MHz) from those of **5**, whereas when aryl = α-naphthyl, the separation of H_a and H_b doublets in the two diastereomers is significant (for H_a, τ 9.38, 9.58; for H_b, τ 9.10, 9.28; for H_c, τ 9.17, 9.17).

(38) Elemental analyses (Table I) were by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Pmr spectra were recorded on a Varian A-60A spectrometer and refer to *ca.* 10% solution in deuteriochloroform at 37° unless otherwise specified, with tetramethylsilane as internal standard; chemical shifts are given in parts per million on the τ scale. Rotations were measured on a Schmidt and Haensch visual polarimeter, and mass spectra on an AEI MS-9 high-resolution mass spectrometer. We thank the National Science Foundation for providing the funds for the purchase of the mass spectrometer under Grant No. GP-5200.

(39) A similar cyclization has been described by R. Granger, J. Boussiuesq, J.-P. Girard, and J.-C. Rossi, *C. R. Acad. Sci., Paris, Ser. C.*, 264, 1717 (1967).

(40) Since the immediate precursor to 11 (the furan 10) contained 4% of the 3*S* diastereomer, the menthol-d_1 would be expected to contain *ca.* 4% of (+)-neomenthol-d_1, assuming that cleavage does not alter the stereochemistry at C-3. Glpc analysis revealed *ca.* 2% of an unidentified impurity.

(41) Cleavage of tetrahydrofuran by lithium aluminum hydride and aluminum chloride has been noted by W. J. Bailey and F. Marktscheffel, *J. Org. Chem.*, **25**, 1797 (1960).

(42) The pmr spectrum of the ketone (13) prepared from 12 featured two acetyl methyl resonances (τ 2.15, 2.22) of nearly equal height, indicating a distereomeric ratio of *ca.* 1:1. In contrast, A. C. Ott, M. F. Murray, and R. L. Pederson, *J. Amer. Chem. Soc.*, 74, 1239 (1952), have reported the predominant formation of one diastereomer in the synthesis of the tetrahydropyranyl ether of dehydroepiandrosterone.

(43) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(44) Under the heterogeneous reaction conditions, the exchange rate of the α-methine proton was much less than that of the α-methyl protons; this is indicated by the >C*H*(OH) resonance in **16** (see below), a complex multiplet which is identical with that in isopulegol. Had the methine proton exchanged, this resonance would have simplified to a doublet of doublets.

(45) Precedent for a Wittig reaction on a pyranyl ether is provided by H. H. Inhoffen, J. F. Kath, and K. Brückner, *Angew. Chem.*, **67**, 276 (1955).

2′-tetrahydropyranyl ether (15) as a mixture of diastereomers,[42] ν_{max}^{neat} 2230 and 1650 cm^{-1}. The pmr spectrum of **15** is similar to that of **12**, except that the allylic methyl resonance is considerably attenuated[46] and the vinyl proton resonance at *ca.* τ 4.8 is notably sharpened. The pyranyl ether **15** (41 g, 0.17 mol) was partially dissolved in a mixture of water (70 ml) and methanol (350 ml), and concentrated sulfuric acid (10 ml) in methanol (100 ml) was added with stirring. The mixture rapidly became homogeneous, and after 10 min was poured into water (700 ml) and extracted twice with 300-ml portions of ether. The combined ether layers were washed with a saturated sodium bicarbonate solution (200 ml), dried, and concentrated under reduced pressure. The residue was distilled at 51–54° (0.07 mm) to yield 19 g of **16**, ν_{max}^{neat} 2230, 1650 cm^{-1}, whose pmr spectrum displays a vinylic resonance at τ 4.88 and a methine (C*H*OH) resonance centered at τ 3.48.

The glpc retention time for all pairs of deuterated and undeuterated species (**8**/**16**, **12**/**15**, and **13**/**14**) were the same on Carbowax or silicon rubber columns.

(−)-(8*R*)-Menthol-9-d_3 (19) was prepared from **16** as described for the preparation of **11** from **8**. The starting material **(−)-(1*R*,3*R*,4*S*,8*R*)-*p*-menthane-3,9-diol-10-d_3 (17)** was recrystallized from acetone, mp 100–103°, $[\alpha]^{23}D$ −20° (*c* 2.5, chloroform). The composition was determined by mass spectral analysis as d_0 (19%), d_1 (4%), d_2 (11%), d_3 (56%), and d_4 (9%). Ring closure of **17** gave **(+)-(1*R*,3*R*,4*S*,8*R*)-3,9-epoxy-*p*-menthane-10-d_3 (18)**, identified by glpc retention time. Cleavage with $LiAlH_4$–$AlCl_3$, gave **19** in 80% yield, ν_{max}^{neat} 3350, 2200 cm^{-1}, identified by glpc retention time and by the properties of its methylphenylphosphinate derivative (see below).

***trans*-2-Isopropylcyclohexanol.** A mixture of *cis*- and *trans*-2-isopropylcyclohexanols (Dow Chemical Co.) was converted to 2-isopropylcyclohexanone by the method of Sandborn,[47] followed by reduction with sodium, to give the product, mp 60–62° (lit.[48] mp 63–64°) after recrystallization from pentane.

***cis*-3-Methylcyclohexanol** was prepared by the method of Hückel;[49] distillation at 65° (7 mm) afforded a 80:20 mixture of *cis*–*trans* isomers (as determined by pmr) which was used to prepare the methylphenylphosphinate described below.

Alkyl phosphinates were prepared from the appropriate phosphinyl chloride and alcohol in the presence of pyridine by the method previously described for the preparation of compounds **1–4**.[4] Characteristics of new compounds are given below and in Table I.

Menthyl diphenylphosphinate (5) was obtained from (−)-menthol and diphenylphosphinyl chloride[50] and purified by chromatography on silica gel and elution with benzene. The eluate was recrystallized several times from pentane to give the desired product, mp 66–69°, $[\alpha]^{23}D$ −56.5° (*c* 6.3, benzene).

Anal. Calcd for $C_{22}H_{29}PO_2$: C, 74.13; H, 8.20. Found: C, 73.86; H, 8.17.

***trans*-2-Isopropylcyclohexyl methylphenylcyclohexylphosphinates 6a and 6b** were prepared from racemic *trans*-2-isopropylcyclohexanol and methylphenylphosphinyl chloride[4] and purified by chromatography on silica gel, eluting with benzene. Several recrystallizations of the eluate from pentane afforded one of the racemic diastereomers, **6b**, mp 95–97°.

Anal. Calcd for $C_{16}H_{25}PO_2$: C, 68.55; H, 8.99; P, 11.05. Found: C, 68.43; H, 9.03; P, 10.85.

Careful recrystallization of the material recovered from the mother liquor afforded two types of crystals, needles and hexagons. The latter were manually removed and recrystallized from pentane to yield the other diastereomer, **6a**, mp 67–70°.

Anal. Calcd for $C_{16}H_{25}PO_2$: C, 68.55; H, 8.99; P, 11.05. Found: C, 68.21; H, 9.16; P, 11.16.

***cis*-3-Methylcyclohexyl methylphenylphosphinates 7a and 7b** were prepared from racemic *cis*-3-methylcyclohexanol and methylphenylphosphinyl chloride and purified by chromatography on silica gel, eluting with benzene–ether, 1:1. The eluate was fractionally distilled, bp 138–139° (0.8 mm), and rechromatographed, to yield a mixture of **7a** and **7b**, as an oil.

Anal. Calcd for $C_{14}H_{21}PO_2$: C, 66.65; H, 8.39; P, 12.28. Found: C, 65.62; H, 8.37; P, 11.97.

(−)-(8*S*)-Menthyl-9-d_1 methylphenylphosphinate diastereomers were prepared from **11** and methylphenylphosphinyl chloride. The procedure described[4] for the preparation and separation of **2a** and **2b** was strictly followed. The less soluble isomer, mp 77–80°, $[\alpha]^{23}D$ −91° (benzene), is the monodeuterio analog of **2b**; the other isomer, obtained in low yield, had mp 86–89°, $[\alpha]^{23}D$ −19° (benzene), and is the monodeuterio analog of **2a**. Identification was completed by comparison of pmr spectra.

(−)-(8*R*)-Menthyl-9-d_3 methylphenylphosphinate diastereomers were prepared from **19** and methylphenylphosphinyl chloride in an identical manner. Only the less soluble diastereomer, the trideuterio analog of **2b**, was isolated, mp 77–80°, $[\alpha]^{23}D$ −94° (benzene). The identification was completed by comparison of pmr spectra.

The monodeuterio analogs of **3** and **4** were prepared from **11** and the appropriate phosphinyl chlorides[4] and were purified by chromatography on silica gel. The diastereomers were not separated since comparison of the pmr spectra of the mixtures with those of the separated, undeuterated isomers gave sufficient information for the assignment of chemical shifts.

(46) The sharpness of the allylic methyl signal in **15** testifies to the presence of some **12** which must have formed by proton exchange in the course of the Wittig reaction. The deuterium analysis of the subsequent product, **17**, confirms this conclusion.

(47) L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 340.

(48) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, 78, 4604 (1956).

(49) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Ann. Chem.*, **616**, 78 (1958).

(50) N. Kreutzkamp and H. Schindler, *Arch. Pharm.*, **293**, 296 (1960)