Articles

Mitsunobu Reaction of Unbiased Cyclic Allylic Alcohols

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The stereochemical inversion of unbiased allylic alcohols using triphenylphosphine, diethyl azodicarboxylate, and benzoic acid, commonly known as the Mitsunobu reaction, was studied in three different solvents with specific attention toward the product composition. The results generated for the Mitsunobu reaction of (*R*)-3-deuterio-2-cyclohexen-1-ol and the cis and trans isomers of 1-deuterio-5-methyl-2-cyclohexen-1-ol, 1-deuterio-5-*tert*-butyl-2-cyclohexen-1-ol, and optically active *cis* and *trans* 5-isopropyl-2-methyl-2-cyclohexen-1-ol all gave similar product distributions with respect to inversion and retention at the carbinol center as well-as syn and anti S_N2' type addition when THF or benzene was used as the solvent (CH_2Cl_2 gave less selective product distributions). Interestingly, it was found that the quasi-equatorial and quasi-axial nature of the starting allylic alcohol does not appear to affect the product distribution for this reaction, nor does methyl substitution at the central carbon of the allylic alcohol. In all cases, significant amounts (8−28%) of non-S_N2 type products were detected for these sterically unbiased allylic alcohols; only 72−77% of the product was from S_N2 type reaction when sterically undemanding (*R*)-3-deuterio-2-cyclohexen-1-ol was subjected to Mitsunobu conditions.

Introduction

Of the various methods available[1] for the stereochemical inversion of hydroxyl groups, the Mitsunobu reaction,[2] utilizing triphenylphosphine, diethyl azodicarboxylate (DEAD), or diisopropyl azodicarboxylate (DIAD) and an acid component (usually a carboxylic acid, phenol, or phthalimide), is undoubtedly one of the most utilized and studied. The mechanism of this reaction has been the subject of much scrutiny and debate, and recently free radicals have been implicated.[3] The initial interaction between triphenylphosphine and DEAD leads to the irreversible[4] formation of a betaine (**1**),[5] which in the presence of alcohols and phenols form dioxytriphenylphosphoranes **2**,[6] intermediates detectable only when the acid is added last.[7] In the presence of a carboxylic acid, the dioxytriphenylphosphorane is in equilibrium with an alkoxyphosphonium carboxylate salt[8] and this equilibrium (as well as the resultant yield of the reaction)[9] is extremely sensitive to the acidity of the reaction mixture as well as the nature of the solvent. However, if the betaine (**1**) is treated with the acid before introduction of the alcohol, the acid phosphonium salt **4** is formed.[10] Introduction of the alcohol then allows for the slow formation of alkoxyphosphonium carboxylate salt **3**. It was reported that alkoxyphosphonium carboxylate salt **3** can also be generated by treating triphenylphosphine first with benzoyl peroxide, forming a mixture of bis(acyloxy)triphenylphosphorane **5** in equilibrium with its conjgate salt, (acyloxy)triphenylphosphonium carboxylate **6**. Subsequent addition of an alcohol then produces alkoxyphosphonium carboxylate salt **3** (Scheme 1).

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(1) Cooper, E. L.; Yankee, E. W. *J. Am. Chem. Soc.* **1975**, *96*, 5876. (b) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183. (c) Vorbruggen, H. *Justus Leibigs Ann. Chem.* **1974**, 821. (d) Floyd, D. M.; Crosby, G.; Weinshenker A. *Tetrahedron Lett.* **1972**, 3265, 3269. (e) Latrell, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 901. (f) Raduchel, B. *Synthesis* **1980**, 292. (g) Kruizinga, W. H.; Strijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1981**, *46*, 4321. (h) Huffman, J. W.; Desai, R. C. *Synth. Commun.* **1983**, *13*, 553. (i) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195. (j) Mukaiyama, T.; Hojo, K. *Chem. Lett.* **1976**, 893. (k) Sato, T.; Otera, J. *Synlett* **1995**, 336. (l) Castro, J. L.; Matassa, V. G. *J. Org. Chem.* **1994**, *59*, 2289. (m) Boivin, J.; Henriet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1994**, *116*, 9739. (n) Moriarty, R. M.; Zhuang, H.; Penmasta, R.; Liu, K.; Awasthi, A. K.; Tuladhar, S. M.; Rao, M. S. C.; Singh, V. K. *Tetrahedron Lett.* **1993**, *34*, 8029.

(2) (a) Mitsunobu, O.; Masahiko, E. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. (b) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (c) Wada, M.; Sano, T.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2833. (d) Morimoto, H.; Furukawa, T.; Miyazima, K.; Mitsunobu, O. *Chem. Lett.* **1973**, 821. Reviews: (e) Mitsunobu, O. *Synthesis* **1981**, 1. (f) Hughes, D. L. *Organic Reactions*; John Wiley & Sons: New York, 1972; Vol. 42, Chapter 2, pp 335−656. (g) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.

(3) (a) Camp, D.; Hanson, G. R.; Jenkins, I. D. *J. Org. Chem.* **1995**, *60*, 2977. (b) Crich, D.; Yao, Q.; Filzen, F. *J. Am. Chem. Soc.* **1995**, *117*, 11455.

(4) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257.

(5) (a) Morrison, D. C. *J. Org. Chem.* **1958**, *23*, 1072. (b) Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 513.

(6) (a) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767. (b) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557; (c) **1984**, *37*, 2447. (d) Von Itzstein, M.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 437; (e) **1987**, 2057. (f) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876.

(7) (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235. (b) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

(8) (a) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045, 3049.

(9) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172. (c) Saïsh, M.; Besspdes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317. (d) Koppel, I.; Koppel, J.; Koppel, I.; Leito, I.; Pihl, V.; Wallin, A.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 655. (e) Warmerdam, E. G. J. C.; Brussee, J.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1993**, *49*, 1063. (f) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (g) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967.

(10) (a) Pautard, A. M.; Evans, S. A. *J. Org. Chem.* **1988**, *53*, 2300. (b) Pautard-Cooper, A.; Evans, S. A. *J. Org. Chem.* **1989**, *54*, 2485.

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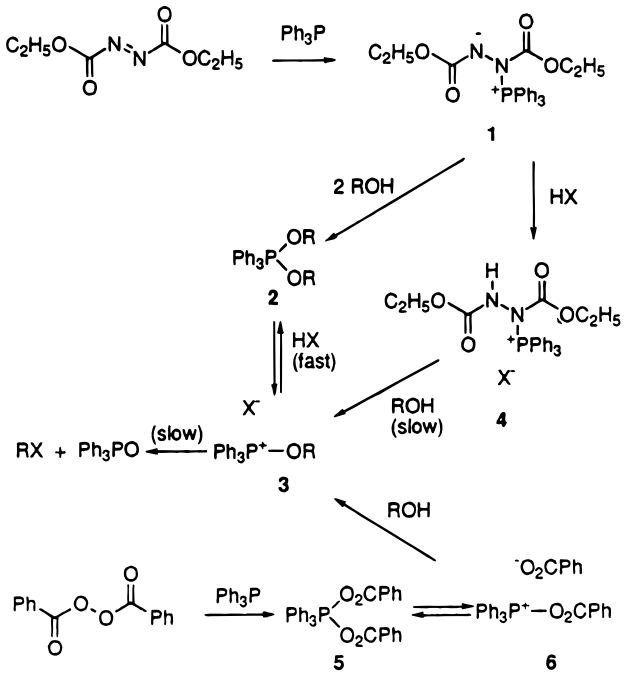
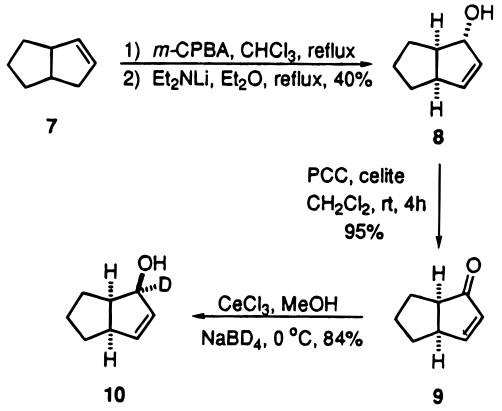
Scheme 1



Scheme 2



Although the protocol for the Mitsunobu reaction has been extensively utilized for saturated alcohols and the mechanism well studied and defined, there exists considerable ambiguity as to the factors that govern the course of this reaction when allylic or benzylic alcohols are employed.[11] When allylic or benzylic alcohols are used, a dramatic rate enhancement is observed and the yields are greatly improved. However, this comes at the expense of the amount of inversion vs retention of configuration, and allylic migration[12] or loss in optical purity[13] has been reported in many cases. There have been several reports of this reaction on unbiased acyclic[14] and cyclic[15] systems but only one, that of a tricyclic cyclopentenol, that was systematically studied and differentiated between each of the four possible products from the reaction.[16] Herein we report the results of the study on the Mitsunobu reaction of several unbiased cyclic allylic alcohols.

Results and Discussion

The first system we were interested in studying was the bicyclo[3.3.0]oct-2-en-1-ol system, in connection with the work toward the synthesis of pentalenolactone E methyl ester and a related study of the [2,3]-Wittig rearrangement on this cyclic skeleton. The required cyclic allylic alcohols were synthesized starting with commercially available bicyclooctene (**7**) (Scheme 2). Oxidation (*m*-CPBA) followed by treatment of the resulting epoxide with Et_2NLi provided allylic alcohol **8** in 40% overall yield. Oxidation to the enone followed by Luche[17] reduction for the introduction of the deuterium label provided deuterated allylic alcohol **10** in 80% yield for the two steps (32% overall from **7**). This allylic alcohol was accompanied with 3% of its diastereomer, easily separable by silica gel chromatography. Unexpectedly, the extent of deuterium incorporation was relatively low—only 85% as judged by both ^1H and ^2H NMR analysis. The origin of this low incorporation of deuterium remains puzzling since the deuteride (98% D) is not likely exchanged under the Luche conditions.

With the requisite allylic alcohol in hand, the Mitsunobu reaction was performed using three different solvents typically used for the reaction: THF, benzene, and CH_2Cl_2. The product benzoates obtained from the Mitsunobu inversion reaction were compared to those obtained directly from allylic alcohols **8** and nondeuterated **10** wtih benzoyl chloride. The diagnostic carbinol protons could not be completely resolved from the olefinic ones in the ^1H NMR spectra, and thus it was necessary to hydrolyze the product esters with LAH in order to better assess the product composition.

Examination of the product allylic alcohols revealed that all four possible products (Scheme 3) were present in the mixture. The amount of allylic alcohol that corresponds to the inversion of stereochemistry of the hydroxyl (i.e., **11**) was shown to be high (Table 1) but not complete. However, the amount of such apparent inversion product was not as high as one would expect given the majority of the reports of inversion in cyclopentenol systems.[18] The choice of solvent, at least among

(11) For examples of very similar systems with significantly different results, see: (a) Dyong, I.; Weigand, J.; Thiem, J. *Justus Liebigs Ann. Chem.* **1986**, 577. (b) Dyong, I.; Merten, H.; Thiem, J. *Justus Liebigs Ann. Chem.* **1986**, 600. (c) Schulte, G.; Meyer, W.; Starkloff, A.; Dyong, I. *Chem. Ber.* **1981**, *114*, 1809. (d) Gauchet, F.; Julia, M.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1987**, 1036. (e) Fiaud, J. C.; Aribi-Zouioueche, L. *Tetrahedron Lett.* **1982**, *23*, 5279. (f) Whitesell, J. K.; Fisher, M.; Jardine, P. D. S. *J. Org. Chem.* **1983**, *48*, 1556 and the results of ref 15 and this study. (g) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006. (h) Pingli, L.; Vandewalle, M. *Tetrahedron* **1994**, *50*, 7061. (i) Mereyala, H. B.; Gaddam, B. R. *J. Chem Soc., Perkin Trans. 1* **1994**, 2187.

(12) For some representative examples, see: (a) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, A. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891. (b) Rao, A. V. R.; Yadav, J. S.; Reddy, K. B.; Mehendale, A. R. *J. Chem. Soc., Chem. Commun.* **1984**, 453.

(13) (a) Rao, A. V. R.; Yadav, J. S.; Reddy, K. B.; Mehendale, A. R. *J. Chem. Soc., Chem. Commun.* **1984**, 453; (b) *Tetrahedron* **1984**, *40*, 4643. (c) Guindon, Y.; Delorme, D. *Can. J. Chem.* **1987**, *65*, 1438. (d) Guindon, Y.; Delorme, D.; Lau, C. K.; Zamboni, R. *J. Org. Chem.* **1988**, *53*, 267.

(14) Grynkiewicz, G.; Burzynska, H. *Tetrahedron* **1976**, *32*, 2109.

(15) (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520. (b) Castedo, L.; Mascarenas, J. L.; Mourino, A. *Tetrahedron Lett.* **1987**, *28*, 2099. (c) Johnson, B. M.; Vollhardt, K. P. C. *Synlett* **1990**, 209. (d) Fleming, I.; Higgins, D.; Lawrence, N. J.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3331. (e) Carda, M.; Marco, J. A. *Tetrahedron* **1992**, *48*, 9789. (f) Suemune, H.; Matsuno, K.; Uchida, M.; Sakai, K. *Tetrahedron: Asymmetry* **1992**, *3*, 297. (g) Balan, A.; Ziffer, H. *J. Chem. Soc., Chem. Commun.* **1990**, 175 and ref 30.

(16) Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6645.

(17) Luche, J.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(18) The only exceptions found: (a) Danda, H.; Nagatomi, T.; Maehara, A.; Umemura, T. *Tetrahedron* **1991**, *47*, 8701. (b) Takano, S.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Assymmetry* **1993**, *4*, 1043. (c) Wachtmeister, J.; Classon, B.; Samuelsson, B. *Tetrahedron* **1995**, *51*, 2029 and ref 15.

Scheme 3

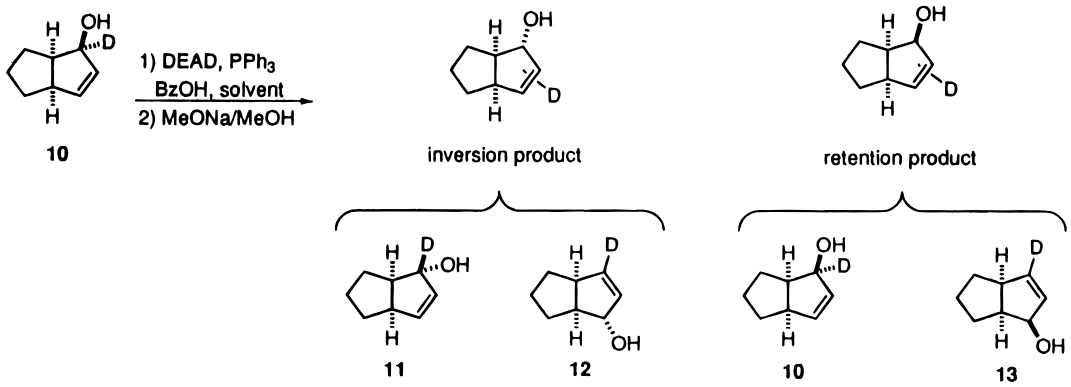


Table 1. Mitsunobu Inversion of (±)-2α-Deuterio-2β-hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (10)

solvent	% yield[a]	% inversion	% retention	product distribution, % 11	12	10	13
THF	80	93	7	79	15	1	5
benzene	90	93	7	83	10	1	6
CH_2Cl_2	80	91	9	65	26	4	5

[a] Yield of the benzoates.

Table 2. Mitsunobu Inversion of (±)-2β-Deuterio-2α-hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (11)

solvent	% yield[a]	% inversion	% retention	product distribution, %[b] 10	13	11	12
THF	80	65	35	44	27	6	23
benzene	90	55	45	46	14	21	19
CH_2Cl_2	87	50	50	32	23	17	28

[a] Yield of the benzenes. [b] Percentages corrected for the starting 9:1 mixture of **10**/**11**.

the three solvents examined, does not seem to alter the product distribution for this reaction, although CH_2Cl_2 does give a somewhat less selective product distribution. The yields for the formation of the benzoates were also in the range of what was expected. A 9:1 mixture of exo alcohol **11** and **12** was subjected to Mitsunobu conditions, and as before, the resultant benzoates had to be hydrolyzed in order to best determine the product ratios. The allylic alcohols isolated from the above sequence showed the deuterium label to be extensively scrambled, with the product with the inverted stereochemistry of the hydroxyl group accounting for less than 50% of the product (Table 2). The results obtained for this system are in accord with those reported by Farina.[15]

The next system studied, 3-deuterio-2-cyclohexen-1-ol, was made optically active in order to differentiate between retention vs inversion or allylic migration with syn vs anti addition. Deuterated 2-cyclohexen-1-one was prepared by LAD reduction[19] of 3-ethoxycyclohex-2-en-1-one, followed by acidic workup. Optically active 3-deuterio-2-cyclohexen-1-ol (**14**) was prepared by using the method of Terashima;[20] i.e. LAH reduction in the presence of *N*-methylephedrine and 2-ethylaminopyridine. The amount of chiral induction was determined by analyzing both the ^1H and ^2H NMR spectra of the (−)-MTPA ester of the product 2-cyclohexen-1-ol. Although the extent of chiral induction was not as significant as

(19) (a) Kantner, S. S.; Humski, K.; Georing, H. L. *J. Am. Chem. Soc.* **1982**, *104*, 1693. (b) Georing, H. L.; Paisley, S. D.; *J. Org. Chem.* **1987**, *52*, 943.

(20) Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* **1985**, *33*, 52.

Scheme 4

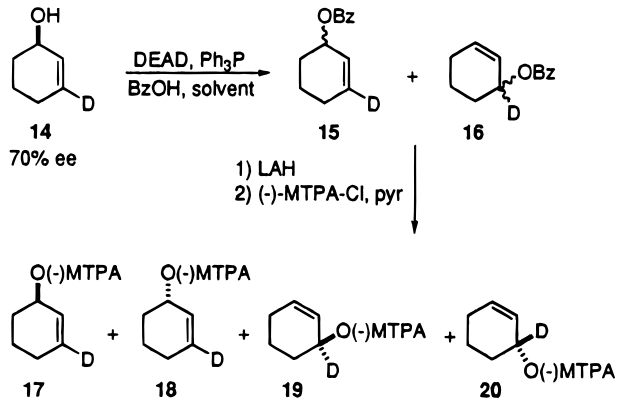


Table 3. Mitsunobu Reaction of (*R*)-3-Deuterio-2-cyclohexen-1-ol (14)

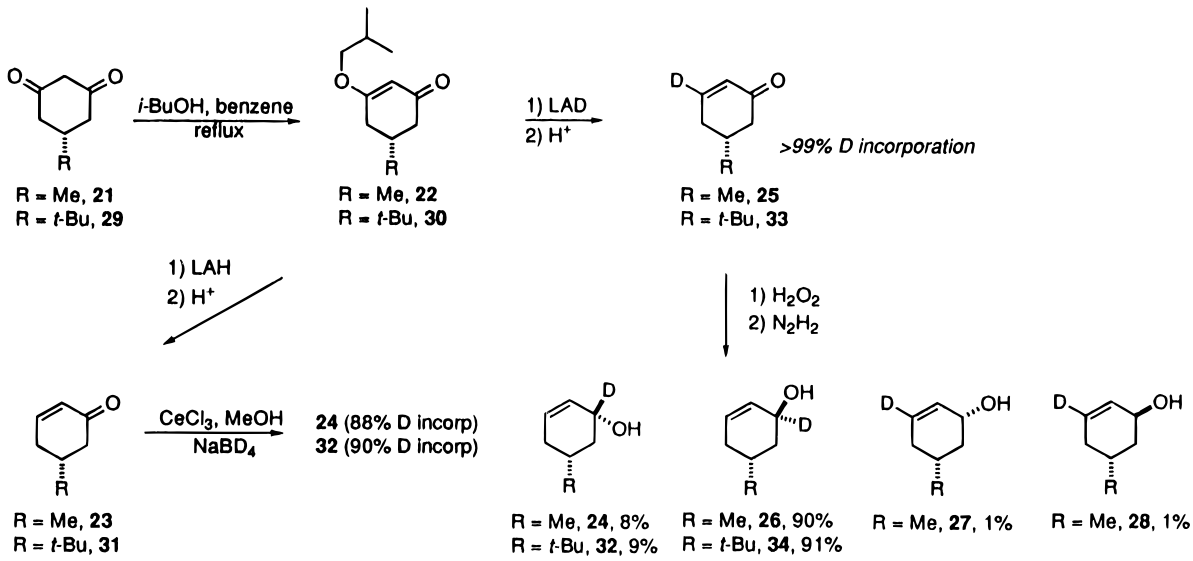
solvent	% yield[a]	15:16	% product distribution[b] 17	18	19	20
THF	82	77:23	1	72	18	9
benzene	81	78:22	0	77	14	9
CH_2Cl_2	77	75:25	0	74	19	7

[a] Yield of the isolated, chromatographically pure benzoates **15** and **16**. [b] Percentages corrected for the optical purity of (*R*)-3-deuterio-cyclohex-2-en- ol used (70% ee).

that reported by Terashima, the 70% ee obtained in the present study was sufficient for our purposes.

The Mitsunobu reaction of the deuterated, optically active 2-cyclohexen-1-ol was again performed in three different solvents, THF, benzene, and CH_2Cl_2. The product benzoates from this reaction were isolated and compared to the benzoates prepared directly from 2-cyclohexen-1-ol and benzoyl chloride, and the amount of allylic migration was determined by ^1H NMR spectroscopy. However, to fully assess the ratio of the products it was necessary to hydrolyze the inseparable mixture of benzoates **15** and **16** and convert the resulting alcohols into their (−)-MTPA esters (Scheme 4). This mixture was then analyzed by 360 and 500 MHz ^1H as well as 55.3 MHz ^2H NMR spectroscopy (Table 3) and compared to that prepared with (−)-MTPA-Cl and 2-cyclohexen-1-ol **14**. As can be seen by the yields as well as the product distribution (adjusted to take into account the 70% ee of the starting 3-deuterio-2-cyclohexen-1-ol), there is essentially no solvent effect for this reaction for the solvents tried. On the basis of the ^1H NMR analysis of the initial benzoates obtained, one-fourth of the product was produced through allylic migration and subsequent analysis of its MTPA ester derivatives indicated the virtual absence of the retention product **17**. Interestingly, of the

Scheme 5



two products resulting from allylic migration, the one from syn addition was predominant over the anti addition product by a ratio of approximately 2:1. To ensure that the loss in stereo- and regiochemistry was due to the nature of the reaction and not from the acid present in the reaction medium, both the product benzoates and starting allylic alcohol were exposed to benzoic acid in THF and the mixture was stirred for the same period of time. No change in the starting alcohol nor in the benzoates was observed. Since cyclohex-2-en-1-ol and 1-methoxycyclohex-2-ene adopt a conformation in which the hydroxyl or methoxy group is in a pseudoaxial position,[21] it is probable that the conformation of the alkoxytriphenylphosphonium carboxylate salt of 2-cyclohexene-1-ol is that in which the $O-^{+}PPh_3$ group[22] is in a pseudoaxial position. This group may direct the addition of the benzoate group from the same face, thus providing the allylic benzoate resulting from allylic migration, syn addition. This is not entirely unprecedented for S_N2' reactions,[23] for there are several reports where allylic carbamates direct addition from the same face for cuprate additions.[24]

A focus was next directed toward an effort to discern whether a preferred quasiaxial or equatorial orientation of the $O-^{+}PPh_3$ group of the allylic alcohol−phosphonium intermediate could be manifested in the relative energies of the transition states for the formation of the S_N2 and S_N2' products. To this end, the product distribution of the Mitsunobu reaction was investigated using deuterated *cis*- and *trans*-5-alkyl-2-cyclohex-1-ols. 5-Methyl-2-cyclohexen-1-ol was chosen as the first substrate because of the ease of synthesis and because it is intermediate between 2-cyclohexen-1-ol and possibly the best substrate for this study, 5-*tert*-butyl-2-cyclohexen-1-ol.

Commercially available dione **21** was readily converted into enone **23** via the keto enol ether **22** in good overall yield. Luche[25] reduction of **23** afforded deuterium-labeled allylic alcohol **24** in 80% yield. However, this product was accompanied with 3.3% of isomer **26**, which proved to be inseparable by silica gel chromatography. Additionally, the extent of D incorporation was again only 88% as judged by ^1H and ^2H NMR spectroscopy. Interestingly, when the reduction was conducted in MeOD the D incorporation into **24** increased to 92%. To obtain diastereomer **26**, it was necessary to introduce the deuterium label by LAD reduction of keto enol ether **22**. This reduction proceeded smoothly in 75% yield and essentially 100% D incorporation. Reduction of enone **25** using the protocol of Wharton[26] provided **26** as the major product, along with three other inseparable contaminants (Scheme 5). Although its ^1H NMR spectrum indicated an 11:1 mixture of isomers **26:24**, ^2H NMR spectrum showed that during the reaction sequence a small amount of allylic migration occurred. It should be emphasized here that the product was never exposed to acid during the reaction and isolation; it was always handled under slightly basic conditions.

With the requisite labeled allylic alcohols prepared, the Mitsunobu reaction was again conducted in three solvents, THF, benzene, and CH_2Cl_2, with the results outlined in Table 4. As was the case for 3-deuterio-2-cyclohexen-1-ol, the predominant product was that of direct S_N2 inversion and essentially no product from retention at the carbinol center was detected for either the cis or trans isomer. In addition, as in the case of 3-deuterio-2-cyclohexen-1-ol, little solvent effect was discerned with the exception that CH_2Cl_2 gives a less

(21) (a) Senda, Y.; Imaizumi, S. *Tetrahedron* **1974**, *30*, 3813. (b) Lessard, J.; Tan, P. V. N.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015. (c) Ouedraogo, A.; Viet, M. T. P.; Saunders, J. K.; Lessard, J. *Can. J. Chem.* **1987**, *65*, 1761.

(22) The *A* value is not expected to be much greater than that of a methoxy group. For *A* values of similar substituents, see: Eliel, E. L.; Wilen, S. L. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 690−700 (cyclohexanes) and pp 726−730 (cyclohexenes) and references cited within.

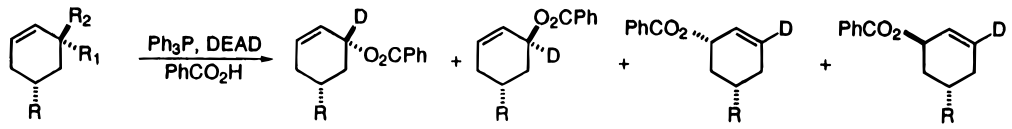
(23) The existence of a synchronous S_N2' reaction mechansim has been the subject of much debate: (a) Bordwell, F. G. *Acc. Chem. Res.* **1970**, 281. (b) Bordwell, F. G.; Mecca, T. G. *J. Am. Chem. Soc.* **1972**, *94*, 5825, 5829. (c) Yates, R. L.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1975**, *97*, 6615. For a discussion of the preference of S_N2' syn addition over anti addition, see (d) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(24) (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144. (c) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093. (d) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715. (e) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1985**, *50*, 1597. (f) Fleming, I.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1456. (g) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 3239. However, a majority of the copper-assisted S_N2' reactions are in favor of anti attack: (h) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (i) Marshal, J. A. *Chem Rev.* **1989**, *89*, 1503. (j) Corey, E. J.; Boaz, N. W. *Tetrahedron* **1984**, *25*, 3063. (k) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984.

(25) See ref 17.

(26) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

Table 4. Mitsunobu Reaction of *cis*- and *trans*-5-Alkyl-2-cyclohexen-1-ol



allylic alcohol	R	R_1	R_2	solvent	yield	product distribution, %[a]			
(±)-*cis*-5-Alkyl-2-cyclohexen-1-ol (quasi equatorial OH)									
						35	**36**	**37**	**38**
24	Me	OH	D	THF	80	2	91	0	7
24	Me	OH	D	benzene	75	0	93	2	5
24	Me	OH	D	CH_2Cl_2	69	3	77	8	12
						39	**40**	**41**	**42**
32	*t*-Bu	OH	D	THF	93	7	78	6	9
32	*t*-Bu	OH	D	benzene	88	5	78	6	10
32	*t*-Bu	OH	D	CH_2Cl_2	70	4	66	8	22
(±)-*trans*-5-Alkyl-2-cyclohexen-1-ol (quasi axial OH)									
						35	**36**	**37**	**38**
26	Me	D	OH	THF	82	79	0	13	8
26	Me	D	OH	benzene	92	79	0	12	9
26	Me	D	OH	CH_2Cl_2	93	73	6	16	5
						39	**40**	**41**	**42**
34	*t*-Bu	D	OH	THF	80	80	3	12	5
34	*t*-Bu	D	OH	benzene	72	80	3	11	6
34	*t*-Bu	D	OH	CH_2Cl_2	42	75	10	11	4

[a] Corrected for pure starting allylic alcohol.

favorable product mixture with respect to the direct inversion product. However, unlike the case of 3-deuterio-2-cyclohexen-1-ol, the anti addition adduct dominated over the syn addition adduct on average by a ratio of 2:1 in the product from allylic migration. Furthermore, there also seems to be a slight difference between the product distribution of the cis versus trans isomer, with the cis isomer giving a higher percentage of direct inversion product.

To ensure that the alkoxyphosphonium intermediate adopts the half-chair cyclohexene conformation with the 5-alkyl group in an equatorial orientation, the *tert*-butyl analogues **32** and **34** were prepared in the same manner as 5-methyl-2-cyclohexen-1-ol from 5-*tert*-butyl-1,3-cyclohexadione.[27] The cis deuterated allylic alcohol made had 90% D incorporation as well as 4.6% of the inseparable diastereomer **34**. The diastereomer **34** was prepared with complete D incorporation but was contaminated with 9% of the other isomer **32**.

The Mitsunobu reaction was performed upon the deuterium-labeled *tert*-butyl allylic alcohols under the same conditions used for their unsubstituted and methyl analogues, and the results are also summarized in Table 4. The yields for the reaction were good, except for the inversion of the trans isomer in CH_2Cl_2. The data obtained for the trans *tert*-butyl isomer (quasi axial OH) are essentially identical with those of its corresponding methyl analogue. This was not unexpected since the hydroxyl (or phosphonium salt) is more stable in the axial conformation, as previously discussed and thus both *trans*-5-methyl-2-cyclohexen-1-ol (**26**) and *trans*-5-*tert*-butyl-2-cyclohexen-1-ol (**34**) are likely to exist exclusively in a half-chair conformation with the alkyl group in an equatorial position and the hydroxyl or phosphonium salt in an axial position. In contrast, a comparison of the data from the *cis*-5-*tert*-butyl-2-cyclohexen-1-ol (**32**) (quasi equatorial OH) with its methyl analogue **24** shows a slight loss of selectivity when the *tert*-butyl group is used in an attempt to lock the conformation of the cyclohexene ring. Interestingly, inspection of the results given in Table 4 suggests that the orientation of the alcohol does not play an important role in this reaction. *trans*-5-Alkyl-2-cyclohexen-1-ol would be expected to provide more product from allylic rearrangement since the half-chair cyclohexene conformation provides the phosphonium leaving group in a quasi-axial position with maximum orbital overlap with the π-bond system, usually a requirement for S_N2'-type addition. In contrast, *cis*-5-alkyl-2-cyclohexen-1-ol would have to proceed through a twist boat-like transition state in order to accommodate S_N2' addition.[23d] At the same time, this conformation having the pseudoaxially oriented leaving group should lead to the favorable transition state for the S_N2 process as well. However, there was little difference observed in the product distribution between the *cis*- and *trans*-5-alkyl-2-cyclohexen-1-ols.

To further investigate what role substituents might play in this reaction, the Mitsunobu reaction of another unbiased 2-cyclohexenol, dihydrocarvol, was investigated. The required allylic alcohol substrates[29] were synthesized in optically active form starting from (*R*)−(−)-carvone, and thus the use of a deuterium label was not necessary. As for the case of 3-deuterio-2-cyclohexen-1-ol, the product benzoates from the Mitsunobu inversion of the two allylic alcohols, **44** and **45**, of which the 300 and 360 MHz ^{1}H NMR spectra in $CDCl_3$ could distinguish the facial selectivity (cis versus trans), had to be converted into their MTPA esters in order to ascertain the extent of allylic migration (Scheme 6). The results from these

(27) (a) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344. (b) Sardina, F. J.; Johnston, A. D.; Mourino, A.; Okamura, W. *J. Org. Chem.* **1982**, *47*, 1576.

(28) Reference deleted.

(29) (a) Grandi, R.; Pagnori, U. M.; Trave, R.; Granti, L. *Tetrahedron* **1974**, *30*, 4037. For the intermediates, see: (b) Birch, A. J.; Walker, K. A. M. *J. Chem. Soc. C* **1966**, 1894. (c) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, 1091. (d) Tadwalker, V. R.; Narayanaswamy, M.; Rao, A. S. *Indian J. Chem.* **1971**, 1223. (e) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme 6

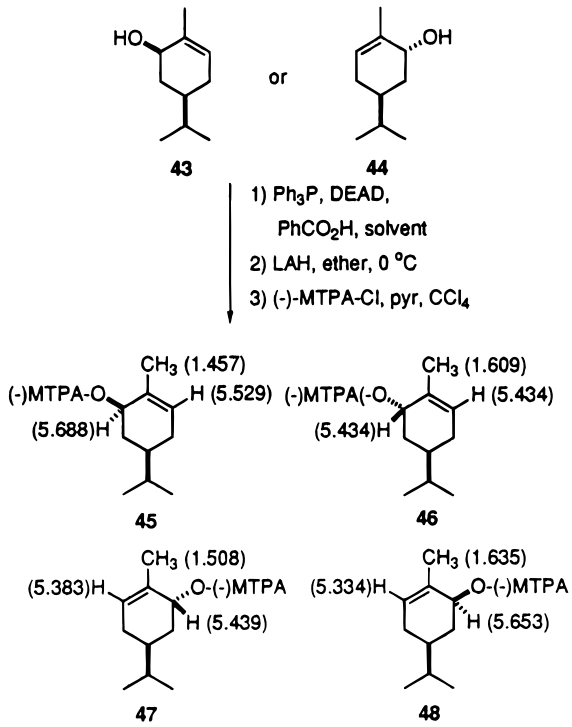


Table 5. Mitsunobu Reaction of (+)-*cis*- (43) and (−)-*trans*-5-Isopropyl-2-methyl-2-cyclohexen-1-ol (44)

allylic alcohol	solvent	cis/trans[a]	yield[a]	product distribution, % 45	46	47	48
		(+)-*cis*-5-Isopropyl-2-methyl-2-cyclohexen-1-ol (quasi-equatorial OH)					
43	THF	9/91	96	6	82	9	3
43	benzene	5/95	95	2	85	10	3
43	CH_2Cl_2	15/85	25	14	66	19	1
		(−)-*trans*-5-Isopropyl-2-methyl-2-cyclohexen-1-ol (quasi-axial OH)					
44	THF	93/7	83	3	4	3	90
44	benzene	94/6	95	11	4	2	83
44	CH_2Cl_2	91/9	14	16	4	5	75

[a] Ratio and yield of the isolated, chromatographically pure benzoates.

analyses of the Mitsunobu reactions of allylic alcohols **43** and **44** are presented in Table 5.

Inspection of these results reveals a dramatic solvent effect with respect to yield, and to a lesser extent selectivity; clearly, CH_2Cl_2 is not a suitable solvent for this reaction. The overall selectivities for this reaction are consistent with the loss of optical purity reported for this reaction on (+)-carvol[30] and are also quite similar to those for *cis*- and *trans*-1-deuterio-5-*tert*-butyl-2-cyclohexen-1-ol, and thus show little difference in the results between the quasi-axial and quasi-equatorial alcohols. Additionally, preference for anti over syn addition in the product from allylic migration increased to greater than 3:1.

The data obtained from these studies seem to suggest several features about the reaction. In all of these relatively unbiased cyclic allylic alcohols, the direct inversion is always accompanied with a certain amount of allylic migration product, which tends to be between 10 and 25% of the product. As in Farina's case,[15] even when the face for direct S_N2 displacement is greatly favored over the face for retention/allylic migration−syn addition, modes other than simple S_N2 displacement still occur. In the cases of 5-methyl- and 5-*tert*-butyl-2-cyclohexen-1-ol, and 5-isopropyl-2-methyl-2-cyclohexen-1-ol, the cis/trans relationship of the hydroxyl (thus predisposing the hydroxyl to quasi-axial or quasi-equatorial orientations) borders on irrelevant for the makeup of the product distribution, which is constant throughout this study.

With regard to the corresponding S_N2' type product distribution, in the cases of 5-methyl- and 5-*tert*-butyl-2-cyclohexen-1-ols and 5-isopropyl-2-methyl-2-cyclohexen-1-ol, the preference of allylic migration with anti addition over syn addition has theoretical precedent,[31] in which ab initio and semiempirical molecular orbital calculations led to a postulate that neutral nucleophiles would attack in a syn fashion but the approach of anionic nucleophiles (such as benzoate) would be anti. However, the observed preference for allylic migration with syn addition over that with anti addition in the case of deuterated 2-cyclohexen-1-ol is surprising, and a rationale as to why this case does not follow the pattern of the other cases remains to be sought.

Summary and Conclusions

The Mitsunobu reaction of unbiased cyclic allylic alcohols usually provides the inverted allylic alcohol in 75−90% purity, unless the face for S_N2 attack is sterically crowded, as in 2β-deuterio-2α-hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (**11**), in which case the product distribution approaches a statistical one. This range in product distribution is small for the variety of substrates chosen and dependent on the choice of solvent and on olefin substitution. When S_N2 attack is appreciably sterically less favored than attack from the same face (as for **11**), or when CH_2Cl_2 is used as a solvent, products from retention at the carbinol center are observed. Even for sterically undemanding (*R*)-3-deuterio-2-cyclohexen-1-ol, only 72−77% S_N2 type product was obtained. Most interestingly, for 2-cyclohexen-1-ols, there is virtually no difference in the product distribution when the alcohol is constrained to a quasi-axial or quasi-equatorial position, as in the case of *cis*- or *trans*-5-*tert*-butyl-2-cyclohexen-1-ol. Benzene appears to be the most useful solvent for this reaction, with product yields and purity slightly better than those in THF. Generally, CH_2Cl_2 was found to be a poor solvent for this reaction.

Experimental Section

General Methods. ^1H NMR spectra were recorded at either 300 or 360 MHz and ^{13}C NMR at 75.47 or 90.56 MHz in $CDCl_3$ unless otherwise stated. Fourier transform infrared spectra (IR) were obtained as neat films on NaCl plates (liquids) or as KBr pellets (solids). Elemental analyses were performed by Spang Microanalytical laboratory, Eagle Harbor, MI, or by the Microanalytical Laboratory, Department of Chemistry, The University of Michigan, Ann Arbor, MI. Column chromatographic separation was performed with the method of flash column chromatography with Merck 230−400 mesh silica gel.[32] Reactions were monitored by thin-layer

(30) (a) Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1992**, 443. (b) Mori, M.; Saitoh, F.; Uesaka, N.; Shibasaki, M. *Chem. Lett.* **1993**, 213. (c) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633.

(31) (a) Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. *Top. Curr. Chem.* **1977**, *70*, 1. See also ref 22c.

(32) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

chromatography (TLC) with Analtech 250 plates with fluorescent indicator. Spots were detected by ultraviolet light (254 nm) and iodine vapor or ceric ammonium sulfate−sulfuric acid.

All reagents and starting materials were purchased from Aldrich Chemical Co. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Methylene chloride and pyridine were distilled from calcium hydride. Benzene was distilled from sodium metal and stored under nitrogen. Nondeuterated benzoates and MTPA esters were prepared from nondeuterated cyclic allylic alcohols (obtained in the same manner as the deuterated ones described below with the appropriate substitution of nondeuterated reagents) in order to establish their spectral properties. All product ratios were determined by integration of the carbinol and olefinic peaks in the ^{1}H and ^{2}H NMR spectra.

(±)-2*β*,3*β*-Epoxy-1α,2*β*,3*β*,5α-bicyclo[3.3.0]oct-2-eneoxirane. In a three-necked, round-bottomed flask fitted with a reflux condenser, dropping funnel, and a vent for nitrogen was added 5.00 g (46.2 mmol) of bicyclo[3.3.0]oct-2-ene (**7**) in 100 mL of chloroform. A solution of 10.0 g (57.9 mmol) of 3-chloroperbenzoic acid in 100 mL of chloroform was added dropwise. After the addition was complete, the reaction mixture was refluxed for 2 h. The solution was cooled with an ice bath and the resultant precipitate removed by filtration. The filtrate was washed once with 100 mL of 1 N aqueous sodium bisulfate and then twice with 100-mL portions of saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesuim sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography with hexanes/ethyl acetate (97.5:2.5) to give 3.02 g (53%) of the exo epoxide as a colorless liquid: ^{1}H NMR (300 MHz) δ 1.25−1.73 (m, 7H), 2.24 (dd, 1H, J = 8.9, 14.4 Hz), 2.30−2.40 (m, 1 H), 2.61 to 2.68 (m, 1H), 3.31 (d, 1H, J = 2.4 Hz), 3.47 (d, 1H, J = 2.4 Hz); ^{13}C NMR (75.47 MHz) δ 25.54 (t), 27.58 (t), 33.46 (t), 35.22 (t), 40.20 (d), 45.93 (d), 59.26 (d), 61.71 (d); IR (neat) 3015, 2951, 2865, 1417, 1450. 1398, 1270, 1222, 1008, 837 cm^{-1}. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.46; H, 9.76.

(±)-2α-Hydroxy-1α,5α-bicyclo[3.3.0]oct-2-ene (8). In a 250 mL, three-necked, round-bottomed flask fitted with a dropping funnel, reflux condenser and a vent for nitrogen was added 2.10 mL (20.3 mmol) of diethylamine in 50 mL of ethyl ether. The solution was cooled to 0 °C and then treated with 9.40 mL of 1.45 M *n*-butyllithium in hexanes. The mixture was stirred for 20 min, and then 1.00 g (8.05 mmol) of the exo epoxide obtained above in 50 mL of diethyl ether was added dropwise. The reaction mixture was stirred at room temperature for 2 days and then refluxed for 8 h. After cooling to rt, 50 mL of saturated aqueous ammonuim chloride was added. The reaction mixture was extracted twice with 50-mL portions of ethyl acetate, and the combined organic layers were washed once with 50 mL of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with a hexanes/ethyl acetate gradient (97.5:2.5 to 90:10) to give 0.321 g (39%) of exo alcohol **8** as a colorless liquid and 0.173 g of unchanged exo epoxide: ^{1}H NMR (300 MHz) δ 1.20−1.70 (m, 7H), 2.39−2.69 (m, 1H), 3.28−3.36 (m, 1H), 4.45 (br s, 1H), 5.72 (ddd, 1H, J = 2.0, 2.1, 5.6 Hz), 5.79 (dd, 1H, J = 2.2, 5.6 Hz); ^{13}C NMR (75.47 MHz) δ 24.79 (t), 30.72 (t), 32.42 (t), 49.44 (d), 51.65 (d), 85.50 (d), 132.13 (d), 139.89 (d); IR (neat) 3325, 2945, 2903, 1034, 1012 cm^{-1}. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.13; H, 9.70.

(±)-1α,5α-Bicyclo[3.3.0]oct-3-en-2-one (9). In a 250-mL, three-necked, round-bottomed flask fitted with a dropping funnel, mechanical stirrer, and a vent for nitrogen were placed 3.50 g (16.2 mmol) of pyridinium chlorochromate, 3.50 g of Celite, and 100 mL of methylene chloride. The slurry was stirred while a solution of 2.00 g (16.1 mmol) of allylic alcohol **8** in 50 mL of methylene chloride was added dropwise. After the solution was stirred for 4 h, 75 mL of diethyl ether was added. The reaction mixture was stirred overnight and the resultant precipitate removed by filtration. The precipitate was washed with ether and the filtrate concentrated under reduced pressure. The residue was passed through Florisil with ether as the eluent. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography with hexanes/ethyl acetate (10:1) to give 1.89 g (95%) of (±)-1α,5α-bicyclo[3.3.0]oct-3-en-2-one (**9**) as a colorless liquid: ^{1}H NMR (300 MHz) δ 1.56−1.79 (m, 5 H), 1.88−1.94 (m, 1H), 2.69 (dd, 1H, J=5.4, 9.8 Hz), 3.32−3.39 (m, 1H), 6.145 (dd, 1H, J = 1.4, 5.6 Hz), 7.53 (dd, 1H, J = 2.8, 5.6 Hz); ^{13}C NMR (75.47 MHz) δ 23.25 (t), 29.06 (t), 29.70 (t), 46.23 (t), 49.21 (d), 133.95 (d), 166.82 (d), 212.56 (s); IR (neat) 2952, 2948, 2940, 1705, 1584, 1347, 1189 cm^{-1}. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.53; H, 8.34.

(±)-2*β*-Hydroxy-1α,5α-bicyclo[3.3.0]oct-2-ene (10). In a 50-mL round-bottomed flask were placed 0.100 g (0.818 mmol) of enone **9**, 0.302 g (0.818 mmol) of cerium trichloride heptahydrate, and 20 mL of methanol. The solution was cooled to 0 °C, and 31 mg (0.818 mmol) of sodium borohydride was added in several portions. The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography with hexanes/ethyl acetate (10:1) as the eluent to give 94 mg (92%) of allylic alcohol **10** as a colorless liquid: ^{1}H NMR (300 MHz) δ 1.35−1.89 (m, 6H), 2.71−2.81 (m, 1H), 3.06−3.11 (m, 1H), 4.84 (d, 1H, J = 8.1 Hz), 5.65 (dd, 1H, J = 1.9, 5.6 Hz), 5.72 (dd, 1H, J = 2.1, 5.6 Hz); ^{13}C NMR (75.47 MHz) δ 26.35 (t), 26.65 (t), 32.39 (t), 45.10 (d), 50.62 (d), 78.19 (d), 133.14 (d), 137.36 (d); IR (neat) 3342, 3336, 2946, 2863, 1007 cm^{-1}. Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.15; H, 9.75.

General Procedure for the Mitsunobu Reaction of (±)-2-Deuterio-2-hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene. *endo*- or *exo*-2-Deuterio-2-hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (0.120 g, 0.96 mmol) (**10** or **11**, respectively) was dissolved in 2 mL of solvent (THF, benzene, or CH_2Cl_2) with triphenylphosphine (0.300 g, 1.14 mmol, 1.2 equiv) and added to a solution of DEAD (0.200 g, 1.15 mmol, 1.2 equiv) and benzoic acid (0.140 g, 1.14 mmol, 1.2 equiv) in 2 mL of solvent at 0 °C. The resultant solution was stirred for 1 h at this temperature, and then the solvent was removed under reduced pressure, 10 mL of 2:1 hexanes/ethyl acetate was added, the solution was filtered, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (petroleum ether). The purified benzoate mixture was then hydrolyzed by addition of 5 mL of 5% NaOH/methanol and the resulting mixture stirred for 3 h. The solvent was removed under reduced pressure, and the crude mixture was dissolved in 10 mL of ether, washed once with 5 mL of water and 5 mL of brine, dried over Na_2SO_4, filtered, and concentrated to provide the crude product alcohols **10**−**13** which could be analyzed by ^{1}H NMR spectroscopy.

(±)-2*β*-Hydroxy-1α,5α-bicyclo[3.3.0]oct-3-enyl Benzoate. (±)-2*β*-Hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (**10**) (0.100 g, 0.80 mmol) was added to a solution of 0.126 g (0.88 mmol, 1.1 equiv) of benzoyl chloride and 0.254 g (3.22 mmol, 4 equiv) of pyridine in 3 mL of THF, and the resulting solution was stirred overnight. The reaction mixture was then poured into 50 mL of water and the resulting mixture extracted with 25 mL of ether. The organic layer was washed with 25 mL of saturated aqueous $CuSO_4$ and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was then purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.145 g, 79%): ^{1}H NMR (300 MHz) δ 1.42−1.64 (m, 4 H), 1.66−1.75 (m, 2 H), 3.06 (m, 1 H), 3.20 (br dd, 1 H, J = 7.1, 8.2 Hz), 5.74 (ddd, 1 H, J = 1.9, 1.9, 5.6 Hz), 5.90 (ddd, 1 H, J = 1.7, 2.0, 5.6 Hz), 5.94 (dd, 1 H, J = 1.4, 8.3 Hz), 7.44 (br dd, 2 H, J = 7.4, 7.6 Hz), 7.55 (br dd, 1 H, J = 7.4, 7.4 Hz), 8.05 (br d, 2 H, J = 7.6 Hz); ^{13}C NMR (75.47 MHz) δ 26.19 (t), 27.56 (t), 31.96 (t), 43.93 (d), 50.34 (d), 81.02 (d), 128.33 (d, 2 C), 128.99 (d), 129.57 (d, 2 C), 130.71 (s), 132.77 (d), 139.31 (d), 166.31 (s); IR (neat) 1713, 1176, 1113 cm^{-1}; high-resolution MS (EI) calcd for $C_{15}H_{16}O_2$ $(M)^+$ m/z 228.1150, found m/z 228.1141.

(±)-2α-Hydroxy-1α,5α-bicyclo[3.3.0]oct-3-enyl Benzoate. (±)-2α-Hydroxy-1α,5α-bicyclo[3.3.0]oct-3-ene (**8**) (0.100 g, 0.80 mmol) was added to a solution of 0.126 g (0.88 mmol, 1.1 equiv) of benzoyl chloride and 0.254 g (3.22 mmol, 4 equiv) of pyridine in 3 mL of THF and the resulting mixture stirred overnight. The solution was then poured into 50 mL of water and the

resulting mixture extracted with 25 mL of ether. The organic layer was washed with saturated aqueous (25 mL) $CuSO_4$ and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was then purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.140 g, 76%): ^{1}H NMR (300 MHz) δ 1.35−1.68 (m, 4 H), 1.70−1.83 (m, 2 H), 2.68 (ddd, 1 H, J = 1.5, 7.3, 10.9 Hz), 3.39 (ddd, 1 H, J = 2.5, 6.1, 7.3 Hz), 5.58 (d, 1 H, J = 1.8 Hz), 5.81 (ddd, 1 H, J = 2.1, 2.1, 5.5 Hz), 5.96 (dd, 1 H, J = 2.1, 5.5 Hz), 7.42 (br dd, 2 H, J = 7.4, 7.6 Hz), 7.54 (br dd, 1 H, J = 7.4, 7.4 Hz), 8.04 (br d, 2 H, J = 7.6 Hz); ^{13}C NMR (75.47 MHz) δ 24.77 (t), 30.77 (t), 32.25 (t), 48.30 (d), 49.59 (d), 88.44 (d), 128.14 (d, 2 C), 128.35 (d), 129.47 (d, 2 C), 130.71 (s), 123.58 (d), 142.15 (d), 166.48 (s); IR (neat) 1713, 1176, 1113 cm^{-1}; high-resolution MS (EI) calcd for $C_{15}H_{16}O_2$ $(M)^+$ m/z 228.1150, found m/z 228.1145.

(*R*)-3-Deuterio-2-cyclohexen-1-ol (14) was prepared by the asymmetric reduction of 3-deuterio-2-cyclohexen-1-one[33] by the method reported by Terashima et al.[33] ($LiAlH_4$, 2-ethylaminopyridine, and *N*-methylephedrine in ether). Optical purity was determined as 70.0% on the basis of ^{1}H and ^{2}H NMR analysis after conversion to its corresponding MTPA ester as described below.

General Procedure for the Preparation of MTPA Esters. The following is a slight modification of Mosher's method. A solution of 0.100 mmol of the cyclic allylic alcohol, 118 mg (1.5 mmol) of pyridine in 1 mL of CCl_4 was cooled to 0 °C, and 38 mg (0.150 mmol) of (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride in 0.5 mL of CCl_4 was added, and the solution was allowed to slowly warm to rt and stirred overnight. The reaction mixture was then poured into 15 mL of ether and washed successively with 5 mL of 5% HCl, 5 mL of aqueous saturated $CuSO_4$, 5 mL of aqueous saturated $NaHCO_3$, and 5 mL of brine. The organic layer was then dried over Na_2SO_4 and filtered and the solvent removed. The residue was purified by preparative TLC (20:1 hexanes/ether) to give the MTPA ester in 85−90% yield.

(*R*)-3-Deuterio-2-cyclohexen-1-yl MTPA ester (17): ^{1}H NMR (300 MHz) δ 1.57−2.16 (m, 6H), 3.56 (s, 3H), 5.50 (m, 1H), 5.72 (s, 0.850 H), 5.81 (s, 0.150 H), 7.37−7.41 (m, 3H), 7.47−7.59 (m, 2H).

***trans*-(1*R*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl MTPA ester**: ^{1}H NMR (300 MHz, benzene-d_6) δ 0.71 (d, 3H, J = 6.7 Hz), 0.72 (d, 3H, J = 6.7 Hz), 1.07−1.25 (m, 2H), 1.27−1.46 (m, 2H), 1.51 (s, 3H), 1.73 (m, 1H), 1.95 (m, 1H), 3.49 (s, 3H), 5.38 (m, 1H), 5.44 (m, 1H), 7.01−7.12 (m, 3H), 7.74−7.76 (m, 2H).

***cis*-(1*R*,5*R*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl MTPA ester**: ^{1}H NMR (300 MHz, benzene-d_6) δ 0.67 (d, 3H, J = 3.8 Hz), 0.71 (d, 3H, J = 6.4 Hz), 1.17−1.39 (m, 3H), 1.46 (s, 3H), 1.49 (m, 1H), 1.66 (m, 1H), 2.20 (m, 1H), 3.47 (s, 3H), 5.53 (m, 1H), 5.69 (m, 1H), 7.00−7.11 (m, 3H), 7.73−7.75 (m, 2H).

***trans*-(1*S*,5*R*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl MTPA ester**: ^{1}H NMR (300 MHz, benzene-d_6) δ 0.64 (d, 3H, J = 6.7 Hz), 0.65 (d, 3H, J = 6.7 Hz), 1.02−1.38 (m, 4H), 1.61 (s, 3H), 1.70 (m, 1H), 1.88 (m, 1H), 3.47 (s, 3H), 5.43 (m, 2H), 7.03−7.10 (m, 3H), 7.70−7.73 (m, 2H).

***cis*-(1*S*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl MTPA ester**: ^{1}H NMR (300 MHz, benzene-d_6) δ 0.66 (d, 3H, J = 6.4 Hz), 0.69 (d, 3H, J = 6.4 Hz), 1.13−1.49 (m, 4H), 1.64 (s, 3H), 2.21 (m, 1H), 3.43 (s, 3H), 5.33 (m, 1H), 5.65 (m, 1H), 7.01−7.11 (m, 3H), 7.72−7.74 (m, 2H).

5-Methyl-2-cyclohexenone (23). In a three-necked flask fitted with a Dean−Stark trap were heated 90 mL of isobutyl alcohol, 0.100 g of *p*-toluenesulfonic acid, 100 mL of benzene, and 5 g of 5-methyl-1,3-cyclohexanedione to reflux overnight. The reaction mixture was then cooled to rt and concentrated under reduced pressure to a volume of approximately 40 mL, to which 40 mL of ethyl acetate was added. The organic solution was washed three times with 20 mL portions of 10% aqueous sodium hydroxide and then with 20 mL of aqueous saturated sodium chloride. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was then dissolved in 100 mL of ether and the solution cooled to 0 °C, and 40 mL of 1 M $LiAlH_4$ (or $LiAlD_4$ for the preparation of **25**) in ether was added dropwise. The reaction mixture was stirred for 1 h and then carefully neutralized by the addition of 50 mL of water and then 50 mL of 10% aqueous HCl. The organic layer was separated, and the aqueous layer was extracted once with 100 mL of ether. The combined organic layers were then washed with 50 mL of saturated $NaHCO_3$ and 50 mL of brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude oil was then purified by silica gel chromatography with 10% ethyl acetate in hexanes as the eluent to afford 3.06 g (70%) of 5-methyl-2-cyclohexenone as a colorless oil whose spectral properties matched those previously reported.[34]

***cis*-1-Deuterio-5-methyl-2-cyclohexen-1-ol (24).** In a 50-mL round-bottomed flask were placed 1.00 g (9.08 mmol) of enone **23**, 3.35 g (9.08 mmol) of cerium trichloride heptahydrate, and 100 mL of methanol. The solution was cooled to 0 °C, and 0.381 g (9.078 mmol) of sodium borodeuteride (or 0.344 g sodium borohydride for the preparation of nondeuterated **24**) was added in several portions. The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure and the residue purified directly by silica gel column chromatography with hexanes/ethyl acetate (10:1) as the eluent to give 0.822 g (80%) of allylic alcohol **24** as a colorless liquid accompanied with 3.3% of diasteriomer **26** as an inseparable impurity. Spectral properties of nondeuterated **24** matched those reported previously.[35] Its ^{1}H NMR indicated 88% D incorporation and ^{2}H NMR failed to detect the other two isomers, **27** and **28**.

***trans*-1-Deuterio-5-methyl-2-cyclohexen-1-ol (26).** At 0 °C, 2.00 g (18.0 mmol) of 3-deuterio-5-methyl-2-cyclohexenone (**25**) (or 5-methyl-2-cyclohexenone (**23**) for the preparation of nondeuterated **26**) and 21 mL (10 equiv) of 30% hydrogen peroxide were combined in 25 mL of methanol, and one drop of concentrated aqueous NaOH was added. The reaction was stirred at this temperature for 1 h and then allowed to slowly warm to rt and stirred overnight. Ether (100 mL) was then added and the resulting mixture washed three times with 100 mL of water each and once with 50 mL of brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude oil was dissolved in 25 mL of methanol and the solution cooled to 0 °C. Hydrazine monohydrate (9.00 g, 10 equiv) followed by one drop of concentrated aqueous NaOH was then added and the reaction mixture was allowed to stir for 1 h at 0 °C and 1 h at rt. Ether (100 mL) was then added to the reaction mixture, and the organic layer was washed with 100 mL of water three times each and once with 50 mL of brine. The organic layer was then dried over Na_2SO_4 and filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography to afford 0.977 g (48%) of *trans*-1-deuterio-5-methyl-2-cyclohexen-1-ol (**26**) as a colorless oil accompanied by a small amount of inseparable *cis*-1-deuterio-5-methyl-2-cyclohexen-1-ol (**24**) (8%), *cis*-3-deuterio-5-methyl-2-cyclohexen-1-ol (**27**) (1%), and *trans*-3-deuterio-5-methyl-2-cyclohexen-1-ol (**28**) (1%) as judged by ^{1}H and ^{2}H NMR analysis.

General Procedure for the Mitsunobu Reaction of *cis*- and *trans*-1-Deuterio-5-methyl-2-cyclohexen-1-ol. *cis*- or *trans*-allylic alcohol (0.050 g, 0.44 mmol) **24** or **26**, respectively, was dissolved in 1 mL of solvent (THF, benzene, or CH_2Cl_2) with triphenylphosphine (0.128 g, 0.49 mmol, 1.1 equiv), and the mixture was cooled to 0 °C. A solution of DEAD (0.085 g, 0.49 mmol, 1.1 equiv) and benzoic acid (0.060 g, 0.49 mmol, 1.1 equiv) in 1 mL of solvent was added, and the reaction

(33) See ref 19.

(34) (a) Cain, D.; Procter, K.; Cassel, R. A. *J. Org. Chem.* **1984**, *49*, 2647. (b) Choudary, B. M.; Prasad, A. D.; Swapna, V.; Valli, V. L. K.; Bhuma, V. *Tetrahedron* **1992**, *48*, 953. (c) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173. (d) Bambridge, K.; Clark, B. P.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2535.

(35) (a) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374. (b) Adam, W.; Smerz, A. *Tetrahedron* **1995**, *51*, 13039.

mixture was allowed to warm to room temperature and stirred for 2 h. After this time, the solvent was removed under reduced pressure and 4 mL of 1:1 ether/petroleum ether was added, the solution was filtered, and the solvent was removed. Silica gel chromatography (petroleum ether) of the crude product provided the purified benzoates **35**−**38**.

***cis*-5-Methyl-2-cyclohexen-1-ol Benzoate.** *cis*-5-Methyl-2-cyclohexen-1-ol (0.100 g, 0.89 mmol) was added to 0.140 g (0.98 mmol, 1.1 equiv) of benzoyl chloride and 0.282 g (3.57 mmol, 4.0 equiv) of pyridine in 3 mL of THF and the resulting solution stirred overnight. The reaction mixture was then poured into 25 mL of ether, and the resulting mixture was washed successively with 25 mL of water, 25 mL of saturated aqueous $CuSO_4$, and 10 mL of brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.170 g, 88%): ^{1}H NMR (300 MHz) δ 1.03 (d, 3 H, J = 4.7 Hz), 1.42 (ddd, 1 H, J = 9.8, 12.1, 12.1 Hz), 1.74 (ddddd, 1 H, J = 2.9, 2.9, 2.9, 10.3, 19.9 Hz), 1.90 (m, 1 H), 2.16 (m, 2 H), 5.65 (m, 1 H), 5.72 (br d, 1 H, J = 10.1 Hz), 5.90 (dddd, 1 H, J = 2.0, 2.0, 4.9, 10.1 Hz), 7.43 (br dd, 2 H, J = 7.2, 7.6 Hz), 7.55 (dd, 1 H, J = 7.6, 7.6), 8.05 (br d, 2 H, J = 7.2 Hz); ^{13}C NMR (90.56 MHz) δ 21.81 (q), 27.87 (d), 33.58 (t), 36.88 (t), 71.30 (d), 126.96 (d), 128.26 (d, 2 C), 129.61 (d, 2 C), 130.65 (d), 130.84 (s), 132.73 (d), 166.33 (s); IR (neat) 1716, 1176, 1137, 1113 cm^{-1}; high-resolution MS (EI) calcd for $C_{14}H_{16}O_2$ $(M)^+$ m/z 216.1150, found m/z 216.1147.

***trans*-5-Methylcyclohex-2-en-1-ol Benzoate.** *trans*-5-Methylcyclohex-2-en-1-ol (0.125 g, 1.11 mmol) was added to 0.160 g (1.14 mmol, 1.03 equiv) of benzoyl chloride and 0.300 g (3.79 mmol, 3.4 equiv) of pyridine in 3 mL of THF, and the resulting solution was stirred for 12 h. The reaction mixture was then poured into 15 mL of ether, and the resulting mixture was washed successively with 25 mL of water, 25 mL of $CuSO_4$, 15 mL of $NaHCO_3$, and brine (10 mL), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was the then purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.164 g, 68%): ^{1}H NMR (300 MHz) δ 1.02 (d, 3 H, J = 6.5 Hz), 1.53 (ddd, 1 H, J = 4.2, 12.5, 14.3 Hz), 1.68 (dddd, 1 H, J = 2.4, 4.1, 10.2, 17.9 Hz), 1.98 (br d, 1 H, J = 14.0 Hz), 2.23 (ddd, 1 H, J = 4.9, 4.9, 17.9 Hz), 5.50 (br s, 1 H), 5.90 (br d, 1 H, J = 9.9 Hz), 6.05 (ddd, 1 H, J = 2.2, 5.1, 9.9 Hz), 7.42 (br dd, 2 H, J = 7.4, 7.7 Hz), 7.54 (br dd, 1 H, J = 7.4, 7.4 Hz), 8.05 (br d, 2 H, J = 7.7 Hz); ^{13}C NMR (90.56 MHz) δ 21.57 (q), 24.24 (d), 33.80 (t), 36.63 (t), 68.16 (d), 124.41 (d), 128.28 (d, 2 C), 129.63 (d, 2 C), 130.97 (s), 132.71 (d), 133.56 (d), 166.17 (s); IR (neat) 1714, 1176, 1166, 1112 cm^{-1}.

5-*tert*-Butyl-2-cyclohexenone (31). In a three-neck flask fitted with a Dean−Stark trap were heated 90 mL of isobutyl alcohol, 0.100 g of toluenesulfonic acid, 100 mL of benzene, and 6.67 g of 5-*tert*-butyl-1,3-cyclohexanedione[27] to reflux overnight. The reaction mixture was then cooled to rt and concentrated under reduced pressure to a volume of approximately 40 mL, to which 40 mL of ethyl acetate was added. The organic solution was washed three times with 20 mL portions of 10% aqueous sodium hydroxide sand then with 20 mL of brine. The organic layer was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure. The crude product was then dissolved in 100 mL of ether and the solution cooled to 0 °C, and 40 mL of 1 M $LiAlH_4$ (or $LiAlD_4$ for the preparation of **33**) in ether was added dropwise. The reaction was stirred for 1 h and then carefully neutralized by the addition of 50 mL of water and then 50 mL of 10% aqueous HCl. The organic layer was separated, and the aqueous layer was extracted once with 100 mL of ether. The combined organic layers were then washed with 50 mL of saturated $NaHCO_3$ and 50 mL of brine, dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude oil thus obtained was then purified by silica gel chromatography with 10% ethyl acetate in hexanes as the eluent to afford 4.726 g (78%) of 5-*tert*-butyl-2-cyclohexenone as a colorless oil whose spectral properties matched those previously reported.

***cis*-1-Deuterio-5-*tert*-butyl-2-cyclohexen-1-ol (32).** In a 50 mL round-bottomed flask were placed 2.00 g (13.1 mmol) of enone **31**, 4.85 g (13.1 mmol) of cerium trichloride heptahydrate, and 100 mL of methanol. The solution was cooled to 0 °C, and 0.551 g (13.14 mmol) of sodium borodeuteride (or 0.498 g of sodium borohydride for the preparation of nondeuterated **32**) was added in several portions. The reaction mixture was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure and the residue purified directly by silica gel column chromatography with hexanes/ethyl acetate (10:1) as the eluent to give 1.469 g (72%) of allylic alcohol **32** as a colorless liquid. Spectral properties of nondeuterated **26** matched those reported previously.[35] Its ^{1}H NMR spectrum indicated 90% D incorporation, and its ^{2}H NMR detected the presence of 4.6% diasteriomer **34** as an inseparable impurity.

***trans*-1-Deuterio-5-*tert*-butyl-2-cyclohexen-1-ol (34).** At 0 °C, 2.00 g (13.1 mmol) of 3-deuterio-5-*tert*-butyl-2-cyclohexenone (**33**) (or 5-*tert*-butyl-2-cyclohexenone (**31**) for the preparation of nondeuterated **34**) and 15 mL (10 equiv) of 30% hydrogen peroxide were combined in 25 mL of methanol and one drop of concentrated aqueous NaOH was added. The reaction was stirred at this temperature for 1 h and then allowed to slowly warm to rt and stirred overnight. Ether (100 mL) was then added to the reaction mixture, and the solution was washed three times with 100 mL of water each and once with 50 mL of brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the crude oil was dissolved in 25 mL of methanol and cooled to 0 °C. Hydrazine monohydrate (6.53 g, 10 equiv) followed by one drop of concentrated aqueous NaOH was then added, and the reaction mixture was stirred for 1 h at 0 °C and 1 h at rt. Ether (100 mL) was then added to the reaction mixture, and the organic layer was washed with 100 mL of water three times each and once with 50 mL of brine. The organic layer was then dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography to afford 0.507 g (25%) of a 91:9 mixture of *trans*-1-deuterio-5-*tert*-butyl-2-cyclohexen-1-ol (**34**) and *cis*-1-deuterio-5-*tert*-butyl-2-cyclohexen-1-ol **32** as judged by ^{1}H and ^{2}H NMR analysis.

General Procedure for the Mitsunobu Reaction of *cis*- and *trans*-1-Deuterio-5-*tert*-butyl-2-cyclohexen-1-ol. *cis*- or *trans*-allylic alcohol (0.120 g, 0.77 mmol) **32** or **34**, respectively, was dissolved in 5 mL of solvent (THF, benzene, or CH_2Cl_2) with triphenylphosphine (0.243 g, 0.93 mmol, 1.2 equiv) and added to a solution of DEAD (0.161 g, 0.93 mmol, 1.2 equiv) and benzoic acid (0.113 g, 0.93 mmol, 1.2 equiv) in 5 mL of solvent at 0 °C. The reaction mixture was stirred at this temperature for 0.5 h and for 3 h at room temperature. After this time, the reaction mixture was concentrated and the remaining slurry dissolved in a minimum amount of ether and then poured into 20 mL of hexane to precipitate out the triphenylphosphine oxide. This mixture was then filtered, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (10:1 hexanes/ethyl acetate) to give pure benzoates **39**−**42**.

***cis*-5-*tert*-Butylcyclohex-2-en-1-ol Benzoate.** *cis*-5-*tert*-Butylcyclohex-2-en-1-ol (0.200 g, 1.30 mmol) was added to a solution of 0.308 g (3.0 equiv) of pyridine and 0.200 g (1.43 mmol, 1.1 equiv) of benzoyl chloride in 3 mL of CH_2Cl_2, and the resulting solution was stirred overnight. The reaction mixture was poured into 20 mL of ether and the resulting mixture was washed with 20 mL of $NaHCO_3$, 25 mL of saturated aqueous $CuSO_4$, 25 mL of water, and 10 mL of brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.271 g, 81%): ^{1}H NMR (300 MHz) δ 0.91 (s, 9 H), 1.40 (dd, 1 H, J = 11.4, 11.4 Hz), 1.55 (ddd, 1 H, J = 4.8, 12.0, 12.0 Hz), 1.89 (m, 1 H), 2.09 (br d, 1 H, J = 17.5 Hz), 2.28 (ddd, 1 H, J = 1.4, 5.8, 11.4 Hz), 5.66 (m, 1 H), 5.72 (dd, 1 H, J = 1.2,1, 11.5 Hz), 5.91 (ddd, 1 H, J = 2.3, 4.8, 11.5 Hz), 7.44 (br dd, 2 H, J = 7.1, 8.5 Hz), 7.54 (br dd, 1 H, J = 7.1, 7.1 Hz), 8.07 (br d, 2 H, J = 8.5 Hz); ^{13}C NMR (75.47 MHz) δ 26.76 (t), 27.08 (q, 3 C), 30.32 (t), 32.33 (s), 43.00 (d), 72.77 (d), 127.33 (d), 128.33 (d, 2 C), 129.70 (d, 2 C), 130.98 (s, d, 2 C), 132.79 (d), 166.36 (s); IR (neat) 1717, 1176, 1160, 1112 cm^{-1}.

***trans*-5-*tert*-Butylcyclohex-2-en-1-ol Benzoate.** *cis*-5-*tert*-Butylcyclohex-2-en-1-ol (0.180 g, 1.17 mmol) was added to a solution of 0.278 g (3.0 equiv) of pyridine and 0.180 g (1.28 mmol, 1.1 equiv) of benzoyl chloride in 3 mL of CH_2Cl_2, and the resulting solution was stirred overnight. The reaction mixture was then poured into 20 mL of ether and washed with 20 mL of saturated aqueous $NaHCO_3$, 25 mL of saturated aqueous $CuSO_4$, 25 mL of water, and 10 mL of brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give a colorless oil (0.225 g, 75%): bp 157 °C, 0.2 mmHg; ^{1}H NMR (300 MHz) δ 0.92 (s, 9 H), 1.47 (ddd, 1 H, J = 3.9, 13.6, 13.3 Hz), 1.64−1.88 (m, 2 H), 2.10 (ddd, 1 H, J = 1.4, 1.4, 13.6 Hz), 2.19 (dddd, 1 H, J = 1.5, 4.8, 4.8, 17.4 Hz), 5.53 (br s, 1 H), 5.92 (br dd, 1 H, J = 9.7 Hz), 6.09 (ddd, 1 H, J = 2.0, 4.0, 9.7 Hz), 7.42 (br dd, 2 H, J = 7.4 Hz), 7.53 (br dd, 1 H, J = 7.4, 8.5 Hz), 8.04 (br d, 2 H, J = 8.5 Hz); ^{13}C NMR (75.47 MHz) δ 26.97 (t), 27.09 (q, 3 C), 29.86 (t), 31.74 (s), 38.86 (d), 68.42 (d), 124.01 (d), 128.12 (d, 2 C), 129.43 (d, 2 C), 130.08 (s), 132.49 (d), 134.27 (d), 165.96 (s); IR (neat) 1714, 1175, 1110 cm^{-1}.

***trans*-(1*R*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-ol (43)**[36] was prepared from commercially available (Aldrich Chemical Co.) (*R*)-carvone, purified as its DNB ester[37] by recrystallization from 3:1 ethanol/ethyl acetate, and regenerated by hydrolysis with sodium methoxide in methanol: bp 70−75 °C (3 mmHg); $[\alpha]^{23}_D$ −28.3° (*c* 1.24, methanol) [lit. $[\alpha]^{22}_D$ −28.21° (*c* 2.5, methanol)]; ^{1}H NMR (300 MHz) δ 0.88 (d, 3H, J = 6.5 Hz), 0.90 (d, 3H, J = 5.9 Hz), 1.17 (dt, 1H, J = 10.2, 12.4 Hz), 1.41 (m, 1H), 1.49 (qq, 1H, J = 6.5, 5.9 Hz), 1.72 (m, 1H), 1.75 (s, 3H), 1.97 (m, 1H), 2.12 (m, 1H), 4.17 (br s, 1H), 5.48 (m, 1H).

***trans*-(1*R*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl 3,5-dinitrobenzoate**: mp 115−116 °C; $[\alpha]^{23}_D$ +187.2° (*c* 1.13, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.90 (d, 6H, J = 6.60 Hz), 1.49−1.62 (m, 3H), 1.75 (s, 3H), 1.81 (m, 1H), 2.05 (m, 1H), 2.23 (m, 1H), 5.58 (m, 1H), 5.87 (m, 1H), 9.16−9.24 (m, 3H).

***cis*-(1*S*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-ol (44)** was prepared in the same manner as *trans*-(1*R*,5*S*)-5-isopropyl-2-methyl-2-cyclohexen-1-ol but from (*S*)-carvone. **44**: $[\alpha]^{23}_D$ +28.4° (*c* 1.24, methanol) [lit. $[\alpha]^{22}_D$ +28.38° (*c* 2.3, methanol)]. *cis*-(1*S*,5*S*)-5-Isopropyl-2-methyl-2-cyclohexen-1-yl 3,5-dinitrobenzoate: $[\alpha]^{23}_D$ +32.8° (*c* 1.07, methanol).

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(36) (a) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, 1091. (b) Tadwalker, V. R.; Narayanaswamy, M.; Rao, A. S. *Indian J. Chem.* **1971**, 1223 and references 29a,b.

(37) (a) Read, J.; Swann, G. *J. Chem. Soc.* **1937**, 239. (b) Mills, J. A. *J. Chem. Soc.* **1952**, 4976. (c) Schroeter, S. H.; Eliel, E. L. *J. Org. Chem.* **1965**, *30*, 1.