formed by reaction of the dichlorocarbene adducts of 3-methyl-2,5-dihydro-1*H*-phosphole 1-oxide with silver nitrate in water[5] and can be regarded as trapped intermediates. Acid-catalyzed dehydration of mixtures of **5Ab–d** and **5Bb–d** produces the regioisomers of **2** in the same ratios as those obtained from thermal transformation of **1b–d** (Table II). This result suggests that the same intermediate, cation **3**, is involved in both reactions (Scheme II).

Experimental Section

TG and DTA curves were determined with an MOM derivatograph, using 50-mg samples in platinum crucibles in static air at a heating rate of 5 °C min^{-1}. DSC measurements were performed on a 990 Du Pont thermoanalyzer at a heating rate of 5 °C min^{-1} in static air with 2-mg samples in aluminum crucibles.

The ^{31}P and ^{13}C NMR spectra were taken on a JEOL FX 100 spectrometer at 40.26 and 25.0 MHz, respectively. ^1H NMR spectra were recorded on a Perkin-Elmer 60-MHz instrument. Deuteriochloroform was the solvent in each case. Chemical shifts are downfield relative to 85% phosphoric acid and to tetramethylsilane, respectively, and have a positive sign. All coupling constants are given in hertz. Infrared spectra were recorded on a SPECORD 75 instrument. Mass spectra were obtained on a JEOL-01SG-2 spectrometer at 75 eV.

The dichlorocarbene adducts were prepared as described earlier.[4]

6,6-Dichloro-1,3-dimethyl-3-phosphabicyclo[3.1.0]hexane 3-Oxide (1a). Yield 32%; mp 90–92 °C; ^{31}P NMR δ +84.7; ^{13}C NMR δ 15.4 ($^1J_{PC}$ = 61.5, P-CH_3), 21.3 ($^3J_{PC}$ = 6.6, C-CH_3), 30.9 ($^1J_{PC}$ = 66.0, C_4), 37.0 ($^1J_{PC}$ = 66.7, C_2), 36.1 ($^2J_{PC}$ = 7.4, C_1), 36.9 ($^2J_{PC}$ = 5.8, C_5), 71.9 ($^3J_{PC}$ = 8.7, C_6), ^1H NMR δ 1.66 (s, 3 H, C-CH_3), 1.69 (d, 3 H, P-CH_3, $^2J_{PH}$ = 13), 1.90–2.74 (m, 5 H, CH_2, CH); MS *m/e* (relative intensity 212 (M^+, 13), 177 (100), 115 (21); IR (KBr disk) 1405, 1300, 1180, 820 cm^{-1}. Anal. Calcd for $C_7H_{11}Cl_2OP$: C, 39.46; H, 5.21. Found: C, 39.11; H, 51.30.

1,3- and 1,5-Dimethyl-4-chloro-1,2-dihydrophosphorin 1-Oxide (2Aa and 2Ba). **1a** (0.4 g, 1.9 mmol) was heated at 135 °C for 3 min. The crude product was purified by flash chromatography on silica gel using 97:3 chloroform–methanol as eluant to give a mixture (0.33 g, 98%) containing 74% of **2Aa** and 26% of **2Ba**: ^1H NMR δ 1.63 (d, 3 H, P-CH_3, $^2J_{PH}$ = 13), 2.07 (s, 2.22 H, C-CH_3(A)), 2.14 (d, 0.78 H, C-CH_3(B), $^4J_{PH} \sim 2$), 2.32–3.19 (m, 2 H), 6.15 (t, P-CH=(A), $^2J_{PH} = {}^3J_{HH}$ = 12), overlapping the signals of the olefinic protons in B, total intensity 1.26 H, 6.70 (dd, 0.74 H, P-CH=C*H*, $^3J_{PH}$ = 34, $^3J_{HH}$ = 13); MS *m/e* (relative intensity) 176 (M^+, 86), 161 (15), 141 (11), 79 (100); IR (neat) 2880, 1600, 1545, 1410, 1360, 1140, 740 cm^{-1}. Anal. Calcd for $C_7H_{10}ClOP$: C, 47.60; H, 5.72. Found: C, 47.36; H, 5.51.

2Aa: ^{31}P NMR δ +20.7; ^{13}C NMR δ 15.4 ($^1J_{PC}$ = 75.5, P-CH_3), 22.2 ($^3J_{PC}$ = 8.8, C-CH_3), 34.4 ($^1J_{PC}$ = 70.4, C_2), 119.8 ($^1J_{PC}$ = 90.8, C_6), 122.7 ($^2J_{PC}$ = 16.1, C_3), 130.1 ($^3J_{PC}$ = 9.5, C_4), 141.2 (C_5).

2Ab: ^{31}P NMR δ +20.0; ^{13}C NMR δ 15.0 ($^1J_{PC}$ = 75.5, P-CH_3), 23.2 ($^3J_{PC}$ = 12.5, C-CH_3), 28.5 ($^1J_{PC}$ = 69.6, C_2), 119.3 ($^1J_{PC}$ = 95.3, C_6), 122.1 ($^2J_{PC}$ = 7.3, C_3), 130.6 ($^3J_{PC}$ = 20.6, C_4), 146.7 (C_5).

3- and 5-Methyl-4-chloro-1-hydroxy-1,2-dihydrophosphorin 1-Oxide (2Af and 2Bf). **1e** (0.46 g, 2.04 mmol) was heated at 135 °C for 6 min. The chloroform extract of the mixture was purified by column chromatography as described above to give a mixture (0.16 g, 44%) consisting of 72% of **2Af** and 28% of **2Bf**: ^1H NMR δ 2.02 (s, 2.16 H, C-CH_3(A)), 2.12 (s, 0.84 H, C-CH_3(B)), 2.79 (d, CH_2(A), $^2J_{PH}$ = 20), overlapping the signal of CH_2(B), total intensity 2 H, 6.11 (t, P-CH=(A), $^2J_{PH} = {}^3J_{HH}$ = 11), overlapping the signal of the olefinic protons in B, total intensity 1.28 H, 6.71 (dd, 0.72 H, P-CH=C*H*, $^3J_{PH}$ = 40, $^3J_{HH}$ = 12), 12.3 (s, 1 H, OH); MS *m/e* (relative intensity) 178 (M^+, 91), 143 (9), 79 (100); M^+_{found} = 177.9975, $C_6H_8ClO_2P$ requires 177.9950.

2Af: ^{31}P NMR δ +32.7; ^{13}C NMR δ 23.3 ($^3J_{PC}$ = 10.2, C-CH_3), 34.2 ($^1J_{PC}$ = 100.4, C_2), 119.9 ($^1J_{PC}$ = 124.6, C_6), 123.4 ($^2J_{PC}$ = 22.7, C_3), 131.9 ($^3J_{PC}$ = 8.0, C_4), 144.1 (C_5).

2Bf: ^{31}P NMR δ + 32.0; ^{13}C NMR δ 24.6 ($^3J_{PC}$ = 15.4, C-CH_3), 28.6 ($^1J_{PC}$ = 99.7, C_2), 119.1 ($^1J_{PC}$ = 129.6, C_6), 123.3 ($^2J_{PC}$ = 8.8, C_3), 131.4 ($^3J_{PC}$ = 17.6, C_4), 150.0 (C_5). The part of the mixture that was insoluble in chloroform was washed with ethyl acetate to give the polymer of **2f** (0.07 g, 19%): MS *m/e* 178; IR (KBr disk) 1160 cm^{-1}. Anal. Calcd for $(C_6H_8ClO_2P)_n$: C, 40.34; H, 4.48. Found: C, 39.94; H, 4.41.

Acknowledgment. We thank Dr. Ilona Konkoly-Tege for DSC measurements. The advice of Prof. Louis D. Quin, University of Massachusetts, is appreciated.

Registry No. **1a**, 115141-72-5; **1b**, 109011-52-1; **1c**, 109011-53-2; **1d**, 109011-51-0; **1e**, 109011-54-3; **2Aa**, 115141-73-6; **2Ab**, 109891-13-6; **2Ac**, 109891-14-7; **2Ad**, 109891-12-5; **2Af**, 115141-74-7; **2Ba**, 115141-75-8; **2Bb**, 109891-16-9; **2Bc**, 109891-17-0; **2Bd**, 109891-15-8; **2Bf**, 115141-76-9; **5Ab**, 115141-77-0; **5Ac**, 115141-78-1; **5Ad**, 115141-79-2; **5Bb**, 115141-80-5; **5Bc**, 115141-81-6; **5Bd**, 115141-82-7.

[2,3] Wittig Ring Contraction: Synthesis of *p*-Menthane Derivatives

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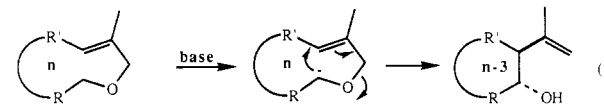
The base-induced [2,3] sigmatropic rearrangement of cyclic diallylic and allylic propargylic ethers ([2,3] Wittig ring contraction) has been shown to constitute a viable strategy for the construction of 10- and 14-membered isoprenoid systems (eq 1).[1-3] In the propargylic cases, the



R = C=C or C≡C
n = 13 or 17

(1)

use of an optically active alkylamide base led to optically active rearranged alcohols of 30–80% ee.[3] The present study was undertaken to determine the applicability of the [2,3] Wittig ring contraction to the synthesis of cyclohexenols.

A suitable substrate for these studies, the nine-membered diallylic ether **5**, was readily prepared from neryl acetate (**1**) by selective allylic oxidation, along the lines reported for geranyl acetate,[4] followed by Collington–Meyers chloride formation,[5] acetate cleavage, and cyclization of the resultant chloro alcohol **4** by treatment with EtMgBr in THF–HMPA[2] (Scheme I). The cyclization proceeded in 65% yield and gave, as a nonvolatile byproduct, the crystalline dimer **11** in 3% yield. Ether **5** underwent facile Cope rearrangement to the tetrahydrofuran **10** upon heating, so solvent removal was best carried out near room temperature. This interesting 3,4-substituted furan is assumed to possess the cis stereochemistry from transition-state considerations.[6]

Ether **5**, upon treatment with lithio-2,2,6,6-tetramethylpiperidide (LTMP), afforded the rearranged alcohol

(1) Takehashi, T.; Nemoto, H.; Kanada, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

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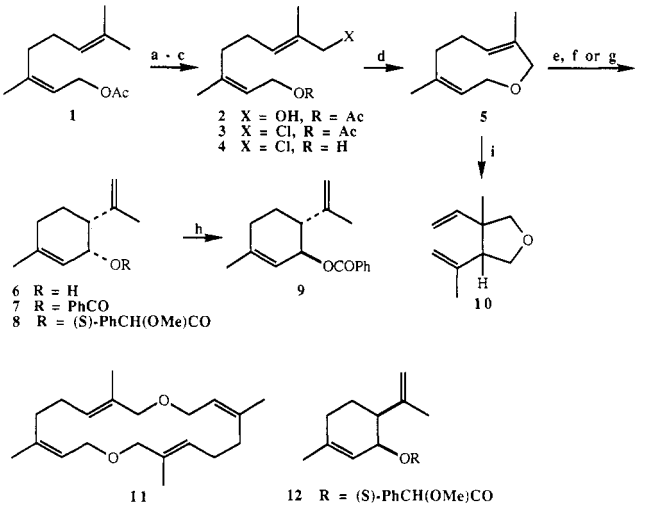
(5) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(6) The chair transition state is readily accommodated by a *cis*-bicyclo[4.3.0]-like arrangement. For calculations on bicyclo[4.4.0] Cope transition states, cf.: Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, 3303.

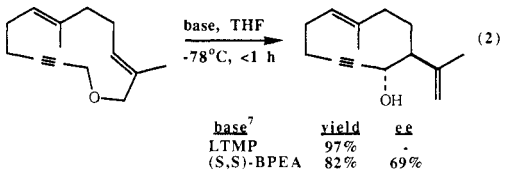
0022-3263/88/1953-4108$01.50/0

Scheme I[a,b]



[a] Footnote 7. [b] (a) SeO_2, *t*-BuOOH, CH_2Cl_2; (b) MsCl, LiCl, Et_3N; (c) K_2CO_3, MeOH; (d) EtMgBr, HMPA; (e) base (see Table); (f) $(PhCO)_2O$, DMAP; (g) (*S*)-$PhCH(OMe)CO_2H$, DMAP, DCC; (h) $PhCO_2H$, DEAD, Ph_3P; (i) toluene, Δ.

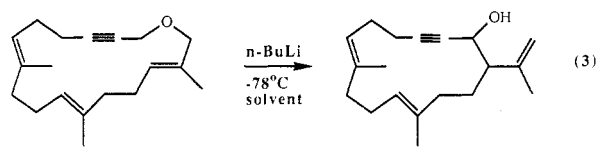
6 as a single isomer. At −78 °C, only 10% reaction had occurred after 5 h. In contrast, a 13-membered propargylic ether analogue of **5** was completely rearranged in less than 1 h under comparable conditions (eq 2).[2,3] Complete



base[7]	yield	ee
LTMP	97%	-
(S,S)-BPEA	82%	69%

rearrangement of ether **5** required 14-h exposure to LTMP[7] at 0 °C to room temperature whereupon alcohol **6** was obtained in 78% yield. The stereochemistry of alcohol **6** was ascertained through ^1H NMR analysis of the epimeric benzoates **7** and **9**. The latter was prepared by Mitsunobu inversion of alcohol **6** with benzoic acid.[8] Benzoate **9** showed the cyclohexenyl proton as a singlet and the carbinyl proton as a doublet (J = 8.6 Hz), in keeping with the pictured trans arrangement (diequatorial isopropenyl and benzoate substituents). The isomeric benzoate **7** gave a broad singlet and a doublet (J = 4 Hz) for the vinylic and carbinyl protons.[9]

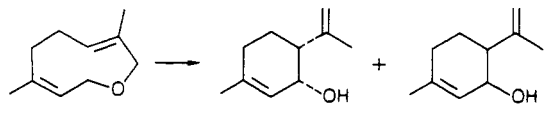
We previously found that the stereochemistry of the [2,3] Wittig ring contraction could be reversed by the presence of HMPA with *n*-BuLi as the base (eq 3).[2] In



solvent[7]	trans / cis
10% THF-hexane	71 : 29
4% HMPA-THF	25 : 75

the present case, the use of *n*-BuLi in THF–HMPA caused extensive decomposition of ether **5** and led to no recognizable product (Table I).

Table I. [2,3] Wittig Rearrangements of Ether 5



base[a]	solvent	time, h	temp,[b] °C	yield, %	ee, %
LTMP	THF	5	−78	10	
LTMP	THF	14	0	78	
n-BuLi	THF–HMPA	12	0	*c*	
(*S,S*)-BPEA	THF	24	0	40[d]	25[e]
(*S,S*)-BPEA	THF	36	25	52[f]	25[e]
(*S,S*)-BPEA	THF–HMPA[g]	24	0	45[f]	25[e]

[a] LTMP = lithio-2,2,6,6-tetramethylpiperidide, (*S,S*)-BPEA = lithiobis[(*S*)-1-phenylethyl]amide. [b] Initial temperature. The reaction mixture was allowed to reach room temperature during the indicated time. [c] Decomposition of starting material. [d] Recovered starting material (20%), $[\alpha]_D$ 0°. [e] ^1H NMR and capillary GC analysis of the (*S*)-*O*-methyl mandelate. [f] Recovered starting material (10%), $[\alpha]_D$ 0°. [g] Two equivalents.

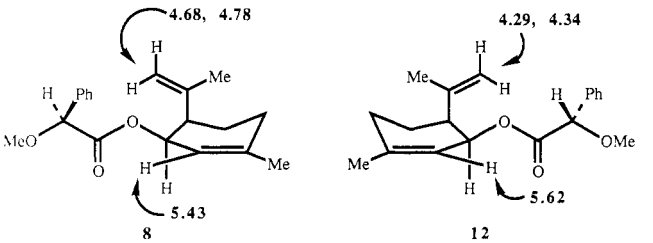


Figure 1. Chemical shifts of (*S*)-*O*-methyl mandelates **8** and **12**.

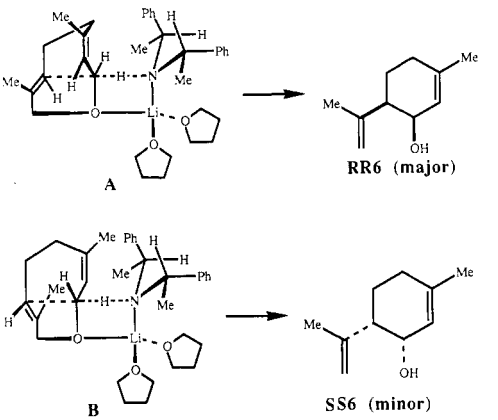


Figure 2. Transition states for [2,3] Wittig ring contractions involving lithiobis[(*S*)-1-phenylethyl]amide.

Rearrangement of ether **5** with the chiral lithiated amide base derived from bis[(*S*)-1-phenylethyl]amine[3] proceeded slowly, even at room temperature, and led to rearranged optically active alcohol **6** of 25–30% ee as measured by GC analysis of the diastereomeric (*S*)-*O*-methyl mandelates **8** and **12**.[10] These esters were also used to assign the absolute stereochemistry of C1 along the lines of Trost, Springer, et al.[11] Thus the cyclohexenyl proton of the minor (*S,S*) diastereoisomer **12** appeared at 5.62 ppm whereas the corresponding proton of the major (*R,R*) diastereoisomer **8** was found at 5.43 ppm as a consequence

(7) Abbreviations: DCC = dicyclohexylcarbodiimide; DEAD = diethyl azodicarboxylate; DMAP = 4-(*N,N*-dimethylamino)pyridine; HMPA = hexamethylphosphoric triamide; LTMP = lithio-2,2,6,6-tetramethylpiperidide; (*S,S*)-BPEA = lithiobis[(*S*)-phenylethyl]amide.

(8) Mitsunobu, O. *Synthesis* **1981**, 1.

(9) For a close analogy, see: Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964.

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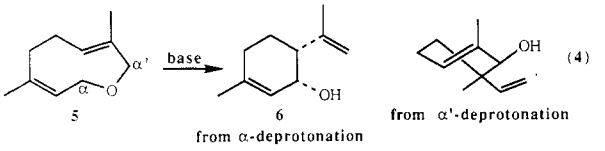
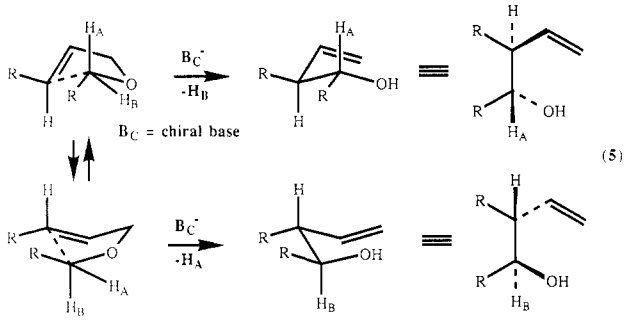
(11) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

of shielding by the phenyl grouping of the mandelate. The isopropenyl vinylic protons of mandelates **8** and **12** also showed substantial chemical shift differences (4.68 and 4.78 for **8** and 4.29 and 4.34 for **12**) in accord with the assigned stereochemistry (Figure 1).[11] The stereochemistry of the chiral base induced [2,3] rearrangement was not affected by HMPA.

The preferential formation of the *R,R* enantiomer **6** from rearrangements employing the *S,S* amide base is concordant with the chelated transition state (Figure 2) proposed for the 13- and 17-membered propargylic ring contractions.[3b] In those examples, as for most acyclic analogues, rearrangement of an (*E*)-allylic ether favors the anti product.[12] In the present case, the syn diastereoisomer alone is produced owing to steric constraints which disfavor what is essentially a highly strained *trans*-bicyclo[4.3.0] transition-state arrangement. It should be noted that even though ether **5** possesses two different sets of abstractable protons, rearrangement can only occur with the observed regiochemistry owing to the highly unlikely production of a *trans*-cyclohexene from the alternative deprotonation–rearrangement (eq 4).



For a chiral base to initiate an enantioselective [2,3] Wittig rearrangement, a distinction must be made between the enantiotopic α-hydrogens H_A and H_B (eq 5). In the



cyclic version of this rearrangement, the presence of a trans double bond introduces chirality to the ring itself[13] and the two α-hydrogens H_A and H_B are therefore diastereotopic. However, in *trans*-cycloalkenes larger than eight members and having at least one vinylic hydrogen, the interconversion of enantiomers through jump-rope rotation[14] is rapid at room temperature.[15] Thus H_A and H_B are effectively enantiotopic. In support of this assumption for the nine-membered ether **5**, we examined material recovered from rearrangements initiated by the *S,S* base in which alcohol **6** of 25–30% ee was produced. In all cases recovered **5** was racemic.

Of the three systems studied to date, the 13-membered propargylic ether shows the highest enantioselectivity in the chiral base promoted [2,3] Wittig ring contraction (eq 2).[3] This system also rearranges the most readily. Although rearrangements of allylic and propargylic systems are not strictly comparable, the nine-membered diallylic ether **5** is clearly more rigid than the 13- and 17-membered propargyl allyl ethers and the transition state appears more strained. Thus, the rearrangement is slower and less enantioselective. Conceivably, the cis double bond serves to lessen the steric (or repulsive electronic) interactions between the "axial" phenyl grouping of the phenylethyl amide base (see Figure 2) in the less favored transition state B compared to the 13-membered propargylic system. The 17-membered propargylic ether, which also shows modest enantioselectivity (ca. 20–30%)[3b] but rearranges rapidly, may possess sufficient flexibility to lessen this interaction through bond rotations. In any event, despite the relatively slow reaction times, the nine-membered diallylic ether **5** undergoes a highly diastereoselective and a moderately enantioselective [2,3] Wittig ring contraction, which, considering the ready availability of nerol,[16] constitutes an efficient and novel route to the *p*-menthane derivative "isopiperitenol" (**6**).[17]

Studies on other ring sizes and chiral bases are in progress. Results in these areas will be reported in due course.

Experimental Section

(2*Z*,6*E*)-3,7-Dimethyl-8-hydroxy-2,6-octadienyl Acetate (2). A solution of 2.2 g (19 mmol) of SeO_2 and 20 mL (0.19 mol) of 90% *tert*-butyl hydroperoxide in 90 mL of CH_2Cl_2 was stirred for 10 min at 0 °C, and then a solution of 15 g (78 mmol) of nerol acetate (**1**) in 20 mL of CH_2Cl_2 was added slowly at 0 °C. The resulting mixture was stirred for 5 h at 5 °C. Ether and water were added, the layers were separated, and the organic layer was washed twice with water. The combined aqueous layers were extracted with ether. The combined extracts were washed twice with saturated aqueous $Na_2S_2O_3$, water, and brine and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to afford a crude oil, which was chromatographed on silica gel (elution with 30% ethyl acetate–hexane) to give 7.3 g (45%) of alcohol **2** as a colorless oil: IR (film) ν 3420, 2980, 2940, 2870, 1740, 1670, 1450, 1380, 1370, 1240, 1200, 1020, 955, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, D_2O) δ 1.64 (s, CH_3), 1.74 (s, CH_3), 2.03 (s, CH_3CO), 2.12–2.14 (m, CH_2CH_2), 3.95 (s, CH_2OH), 4.53 (d, J = 7.3 Hz, CH_2OAc), 5.2–5.4 (m, vinyl H); MS 169 (M – CH_3CO), 153 (M – CH_3CO_2), 152 (M – 1 – CH_3CO_2). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.83; H, 9.46.

(2*Z*,6*E*)-8-Chloro-3,7-dimethyl-2,6-octadienyl Acetate (3). A modification of the procedure of Collington and Meyers[5] was developed. A solution of 1.2 g (28 mmol) of anhydrous LiCl in 20 mL of DMF was cooled to 0 °C, and a solution of 3.5 g (16.8 mmol) of allylic alcohol **2** in 3.6 mL (26 mmol) of triethylamine was added. After 0.5 h, 1.95 mL (25 mmol) of methanesulfonyl chloride was added, and the resulting slurry was stirred at 0 °C for 0.5 h. Water and ether were added, the layers were separated, and the organic layer was washed twice with water. The combined aqueous layers were extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$, water, and brine and dried over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by column chromatography on silica gel (5% ethyl acetate–hexanes), affording 2.75 g (75%) of chloride **3**: IR (film) ν 2980, 2950, 2930, 2880, 1740, 1670, 1450, 1385, 1370, 1240, 1030, 960, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, vinyl CH_3), 1.75 (s, vinyl CH_3), 2.03 (s, CH_3CO), 2.13–2.15 (m, CH_2CH_2), 3.98 (s, CH_2Cl), 4.53 (d, J = 7 Hz, CH_2OAc), 5.36 (t, J = 6 Hz, vinyl H), 5.40 (m, vinyl H); MS 230.5 (M), 194 (M – 1 – HCl), 135 (M – HCl – CH_3CO_2).

(2*Z*,6*E*)-8-Chloro-3,7-dimethyl-2,6-octadien-1-ol (4). A slurry of 2.75 g (13 mmol) of acetate **3** and a catalytic amount of K_2CO_3 in 50 mL of dry methanol at −20 °C was stirred overnight. The mixture was diluted with water and extracted three times with ether. The extracts were washed with brine and dried

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over anhydrous $MgSO_4$. Removal of solvent left an oil, which was purified by column chromatography on silica gel (30% ethyl acetate–hexanes), affording 2.05 g (88%) of a light oil: IR (film) ν 3350, 2940, 2870, 1670, 1445, 1390, 1380, 1265, 1165, 1070, 1000, 950, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, OH), 1.72 (s, vinyl CH_3), 1.73 (s, vinyl CH_3), 2.10–2.14 (m, CH_2CH_2), 3.99 (s, CH_2Cl), 4.08 (d, J = 7 Hz, CH_2OH), 5.4–5.61 (m, vinyl H, 2 H); MS 188.5 (M), 173.5 (M – CH_3), 152 (M – HCl).

(3*E*,7*Z*)-3,7-Dimethyl-1-oxa-3,7-cyclononadiene (5). To a stirred, cooled (0 °C) solution of 2.01 g (10.67 mmol) of chloro alcohol **4** and a catalytic amount of 1,10-phenanthroline in 7.5 mL (42 mmol) of hexamethylphosphoramide and 550 mL of dry THF was added dropwise 5.5 mL (12.1 mmol) of 2.2 M ethylmagnesium bromide in THF, whereupon a persistent violet coloration appeared. After 10 min, the cold bath was removed and the reaction solution was heated to reflux. After 5 h, the mixture was cooled to room temperature, saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed twice with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure at room temperature to afford a yellow liquid. Purification by column chromatography on silica gel (5% ethyl acetate–hexanes) and distillation gave 1.05 g (65%) of cyclic ether **5** as a volatile colorless oil: bp 48–50 °C (0.1 mmHg); IR (film) ν 2980, 2950, 2880, 1660, 1465, 1380, 1280, 1240, 1210, 1180, 1050, 1015, 960, 935, 900, 875, 830, 795, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, vinyl CH_3), 1.72 (s, vinyl CH_3), 1.9–2.1 (m, CH_2CH_2), 3.57 (dd, A of ABX, J = 13, 11.5 Hz, H2, 1 H), 3.71 (d, A of AB, J = 10 Hz, H8, 1 H), 3.84 (dd, B of ABX, J = 5, 13 Hz, H2, 1 H), 4.16 (d, B of AB, J = 10 Hz, H8, 1 H), 5.34 (dd, X of ABX, J = 5, 11.5 Hz, vinyl H, 1 H), 5.4–5.6 (m, vinyl H, 1 H); MS, m/e 152 (M), 151 (M – 1), 137 (M – CH_3), 122 (M – $2CH_3$), 107 (M – CH_2O – CH_3). Ether **5** slowly underwent Cope rearrangement affording **10** upon prolonged heating on the steam bath (see below).

Crystallization of the distillation residue gave 45 mg (3%) of the dimer **11**: mp 94–94.5 °C (pentane); IR (CCl_4) ν 2980, 2920, 2860, 1670, 1450, 1370, 1355, 1250, 1150, 1110, 1070, 985, 940, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, vinyl CH_3), 1.76 (s, vinyl CH_3), 2.1–2.2 (m, CH_2CH_2), 4.74 (d, J = 7.5 Hz, CH_2O), 3.83 (s, CH_2O), 5.31 (m, vinyl H, 1 H), 5.42 (t, J = 7.5 Hz, vinyl H, 1 H); MS 306 (M), 289 (M – CH_3). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.95; H, 10.53. Found: C, 78.87; H, 10.62.

***cis*-6-Isopropenyl-3-methyl-2-cyclohexenol (6). A. Through Use of LTMP.** The amide base was formed from 3.2 mL of 2,2,6,6-tetramethylpiperidine and 7.9 mL of 2.5 M *n*-BuLi in hexane in 20 mL of THF, initially at 0 °C, under a nitrogen atmosphere. After 30 min at room temperature, the solution of amide was slowly added via cannula to a stirred, cooled solution of 1.00 g (6.58 mmol) of cyclic ether **5** in 20 mL of THF at 0 °C. The mixture was allowed to reach room temperature, and after 14 h, water was added and the mixture was diluted with ether and extracted. The product was purified by chromatography on silica gel, affording 0.78 g (78%) of alcohol **6** eluted with 7–10% ethyl acetate–hexanes. The spectral properties of this material are detailed below in part B. Anal. Calcd for $C_{10}H_{16}O$: C, 78.98; H, 10.53. Found: C, 79.98; H, 10.62.

B. Through Use of the *S*,*S* Base. The chiral amide was formed from 2.2 mL (9.8 mmol) of (*S*,*S*)-bis(1-phenylethyl)amine in 15 mL of THF at 0 °C under a nitrogen atmosphere by dropwise addition of 2.0 mL (9.6 mmol) of 2.4 M *n*-butyllithium in hexane. After 30 min at 30 °C, the solution of amide was slowly added via cannula to a stirred, cooled (0 °C) solution of 754 mg (4.96 mmol) of cyclic ether **5** in 5 mL of THF. The resulting mixture and the bath were allowed to warm slowly to room temperature, and after 36 h, water was added and the mixture was diluted with ether. The separated aqueous layer was extracted with ether. The combined ether layers were washed with 3% aqueous HCl, water, and brine and dried over anhydrous $MgSO_4$. Filtration and concentration gave an oil, which was purified by column chromatography on silica gel (10% ethyl acetate–hexanes). The early fractions contained starting material (75 mg, $[\alpha]_D$ 0°) contaminated with some Cope product **10**. Continued elution afforded 387 mg (52%) of the alcohol **6**, a 62:38 mixture of enantiomers as determined by capillary GC analysis of the *O*-methyl mandelate derivative (see below): IR (film) ν 3410, 3100, 3020, 2960, 2880, 2840, 1670, 1650, 1450, 1380, 1250, 1215, 1070, 1030, 960, 890, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.69 and 1.80 (s, vinyl CH_3), 1.5–2.2 (m, allylic CH_2 and H6), 4.10 (s, carbinyl H), 4.78 and 4.97 (s, vinyl H), 5.64 (s, vinyl H); MS 152 (M), 135 (M – Me), 134 (M – H_2O), 121 (M – 2Me – 1), 119 (M – Me – H_2O). Anal. Calcd for $C_{10}H_{16}O$: C, 78.95; H, 10.53. Found: C, 78.98; H, 10.62.

***cis*-6-Isopropenyl-3-methyl-2-cyclohexenyl Benzoate (7).** To a stirred solution of 41.0 mg (0.27 mmol) of (±) alcohol **6** in 3 mL of THF was added 80 mg (0.35 mmol) of benzoic anhydride followed by a catalytic amount of DMAP. The resulting mixture was stirred at reflux for 12 h and then diluted with water and ether. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with saturated aqueous Na_2CO_3, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford a light yellow oil. Purification by column chromatography on silica gel (2% ethyl acetate–hexane) yielded 58 mg (84%) of a colorless oil: IR (CCl_4) ν 3100, 3080, 2980, 2950, 2920, 2880, 2860, 1715, 1650, 1610, 1455, 1385, 1350, 1320, 1270, 1255, 1180, 1115, 940, 920, 900, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 and 1.78 (s, vinyl CH_3's), 1.6–2.2 (m, allylic CH_2), 2.26 (m, H6), 4.80 and 4.82 (s, C=CH_2), 5.55 (br s, vinyl H), 5.74 (d, J = 4 Hz, carbinyl H), 7.3–8.1 (m, phenyl H); MS, m/e 256 (M), 151 (M – PhCO), 134 (M – 1 – $PhCO_2$), 119 (M – 1 – $PhCO_2$ – Me). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.69; H, 7.81. Found: C, 79.55; H, 7.92.

(1*R*,6*R*)- and (1*S*,6*S*)-6-Isopropenyl-3-methyl-2-cyclohexenyl (*S*)-*O*-Methyl Mandelate (8 and 12). To a solution of 187 mg (1.23 mmol) of alcohol **6** (from part B above), 250 mg (1.48 mmol) of (*S*)-*O*-methyl mandelic acid, and 250 mg (1.23 mmol) of DCC in 3 mL of dry THF was added a catalytic amount of DMAP. After being stirred for 2 h at room temperature under nitrogen, the mixture was concentrated under reduced pressure to afford a yellow solid. This solid was washed with ether and filtered, and the organic layer was concentrated to afford a white viscous oil, which was chromatographed on silica gel (2% ethyl acetate–hexanes), yielding 217 mg (59%) of the (*S*)-*O*-methyl mandelic esters as a colorless viscous oil. The gas chromatogram (T = 180 °C, on a superox column) showed two peaks in the ratio 62:38: IR (CCl_4) ν 3100, 3070, 3040, 2980, 2960, 2890, 2830, 1740, 1680, 1650, 1490, 1450, 1380, 1270, 1250, 1200, 1180, 1120, 1000, 910, 890, 600 cm^{-1}; MS 300 (M), 179 (M + 1 – PhCH – OMe), 151 (M – PhCH(OMe) – CO), 121 (M – PhCH(OMe)CO – 2Me). Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 75.78; H, 8.08. The oil was crystallized from pentane to give the major diastereoisomer **8** (1*R*,6*R*): mp 99–100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 and 1.71 (s, vinyl CH_3), 1.8–2.05 (m, allylic CH_2), 2.1–2.2 (m, allylic CH), 3.37 (s, MeO), 4.65 (s, CH(OMe)), 4.68 and 4.78 (s, C=CH_2), 5.39 (carbinyl H), 5.43 (vinyl H). Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.04; H, 8.06.

The minor diastereoisomer **12** (1*S*,6*S*) was purified from the mother liquid by column chromatography on silica gel (2% ethyl acetate–hexanes) to give a colorless oil (greater than 97% pure by GC analysis): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 and 1.71 (s, vinyl CH_3), 1.5–1.7 (m, CH_2), 1.9–2.2 (m, allylic CH), 3.36 (s, MeO), 4.29 and 4.34 (s, C=CH_2), 4.65 (s, CH(OMe)), 5.32 (m, carbinyl H), 5.62 (d, J = 3.6 Hz, vinyl H).

***trans*-6-Isopropenyl-3-methyl-2-cyclohexenyl Benzoate (9).** To a solution of 82 mg (0.54 mmol) of alcohol (±)-**6** and 0.30 g (1.15 mmol) of triphenylphosphine in 5 mL of dry benzene was added over 3 h at room temperature a solution of 0.20 g (1.14 mmol) of DEAD and 0.15 g (1.23 mmol) of benzoic acid in 3 mL of dry benzene. After 12 h, the mixture was concentrated under reduced pressure to afford a viscous yellow oil, which was chromatographed on silica gel (2% ethyl acetate–hexanes) to give 36 mg (28%) of benzoate as a colorless oil: IR (CCl_4) ν 3090, 3050, 2980, 2950, 2890, 2850, 1720, 1650, 1610, 1450, 1320, 1260, 1120, 915, 900, 710, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 and 1.72 (s, vinyl CH_3's), 1.6–2.2 (m, allylic CH_2), 2.48 (ddd, J = 3.9, 8.6, 11.4 Hz, H6), 4.73 and 4.77 (s, C=CH_2), 5.48 (s, vinyl H), 5.60 (d, J = 8.6 Hz, carbinyl H); MS 256 (M), 151 (M – PhCO), 134 (M – $PhCO_2$ – H).

***rel*-(3*R*,4*S*)-3-Allyl-4-isopropenyl-3-methyl-2,3,4,5-tetrahydrofuran (10).** A solution of 205 mg (1.34 mmol) of cyclic ether **5** in 1.2 mL of toluene was heated at 101 °C under argon overnight. The solution was chromatographed on silica gel (3% ethyl acetate–hexane) to yield 178 mg (87%) of the furan **10** as a colorless

oil: IR (film) ν 3090, 2980, 2940, 2880, 1720, 1670, 1450, 1370, 1060, 1030, 910, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, CH_3), 1.70 (s, vinyl CH_3), 2.54 (t, J = 7.6 Hz, H4), 3.70 (A of AB, J = 8.32 Hz, CH_2O), 3.67 (B of AB, J = 8.32 Hz, CH_2O), 3.9-4.2 (m, CH_2O), 4.7-5.1 (m, vinyl H, 4 H), 5.8-6.0 (m, vinyl H, 1 H); MS 152 (M), 137 (M - Me), 122 (M - 2Me or M - CH_2O), 107 (M - Me - CH_2O), 94 (M - Me - CH_2=$CHCH_3$).

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Registry No. 1, 141-12-8; 2, 70238-37-8; 3, 115306-94-0; 4, 115306-95-1; 5, 115306-96-2; (±)-6, 115362-62-4; (1*R*,6*R*)-6, 96555-02-1; (1*S*,6*S*)-6, 65733-29-1; (±)-7, 115306-97-3; 8, 115306-98-4; (±)-9, 115306-99-5; (±)-10, 115307-00-1; 11, 115307-01-2; 12, 115362-63-5.

Cyclization of 2-(Carbamoyloxy)- and 2-(Sulfamoyloxy)benzoates Mediated by Liver Microsomes[1]

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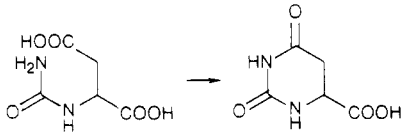
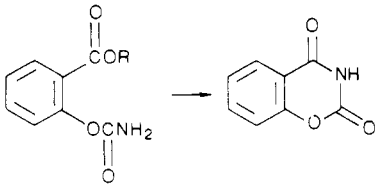
In recent years, the catalytic activity of enzymes[2] has received considerable attention in the synthesis of organic compounds. The use of enzymes for cyclization reactions has been less explored, although these may have enormous interest in view of the mild conditions employed in such reactions. In the biosynthesis[3] of pyrimidine nucleotides, the dihydroorotase-catalyzed ring closure of *N*-carbamoylaspartic acid to dihydroorotic acid is a classical example of enzyme-catalyzed cyclization for the formation of the pyrimidine ring (eq 1). Recently, we reported[4] the



(1)



(2)

1 2

cyclization of 2-(carbamoyloxy)benzoates **1** to 1,3-benzoxazine-2,4-diones **2** by rat liver microsomal fractions (eq 2). The feasibility of this concept prompted us to investigate the enzyme-catalyzed reactions of 2-(sulfamoyloxy)benzoates and 2-(carbamoyloxy)benzophenones as well as the effect on variation of incubation conditions.

Results and Discussion

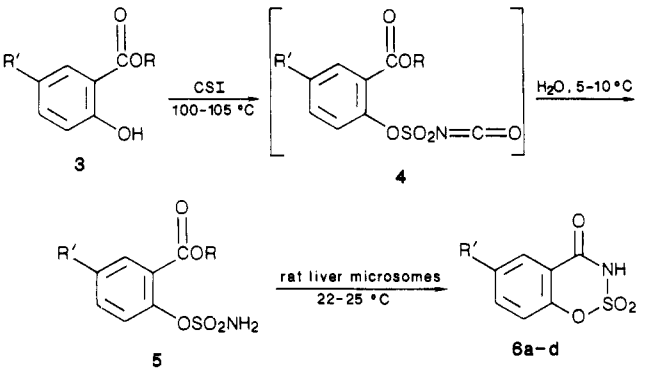
Cyclizations. Our earlier attempts to prepare 4-oxo-3,4-dihydro-1,2,3-benzoxathiazine 2,2-dioxides[5] **6** by thermal cyclization of 2-(sulfamoyloxy)benzoates **5** gave mainly 2-hydroxybenzoates **3** with the cleavage of the OSO_2 linkage. Even the use of bases such as triethylamine and pyridine for cyclization of **5** gave mainly **3** and not the desired **6**. In view of the failure of nonenzymatic cyclizations, it was worthwhile to carry out the enzymatic cyclization of **5**.

Table I. Cyclization of 2-(Sulfamoyloxy)benzoates and 2-(Carbamoyloxy)benzophenones (5 and 8) at 20-25 °C

substrate	R	R′	product	yield[a] of 6a-d and 9a-d, %	mp, °C
5a	CH_3	H	**6a**	74	218-220
5b	C_2H_5	H	**6a**	70	218-219
5c	C_6H_5	H	**6a**	76	218-220
5d	CH_3	Cl	**6b**	81	235
5e	C_2H_5	Cl	**6b**	78	234-236
5f	CH_3	Br	**6c**	71	240-241
5g	CH_3	CH_3	**6d**	75	192-193
5h	C_2H_5	CH_3	**6d**	70	193-195
8a	H	H	**9a**	71	252-255
8b	H	Cl	**9b**	68	274-276
8c	H	CH_3	**9c**	60	248-250
8d	Cl	H	**9d**	75	262
8e	CH_3	Cl	**9e**	66	243-246

[a] Isolated yield of chromatographed product.

Scheme I[a]



[a] R = CH_3, C_2H_5, C_6H_5; R′ = H, Cl, Br, CH_3.

The appropriate precursor, 2-(sulfamoyloxy)benzoate **5**, was prepared by employing chlorosulfonyl isocyanate (CSI). Various alkyl- and aryl-substituted **5** on cyclization with rat liver microsomal fractions at 22-25 °C gave **6** in good yields, Table I (Scheme I). The reactions were monitored by TLC, and it was observed that the enzymatic cyclization of 2-(sulfamoyloxy)benzoates was a slower process than the enzymatic cyclization[4] of 2-(carbamoyloxy)benzoates.

We also investigated the cyclization of 2-(carbamoyloxy)benzophenones **8**. In our earlier studies[6,7] on the reactions of CSI, the reactions of 2-hydroxybenzaldehydes and 2-hydroxyacetophenones with CSI gave 1,3-benzoxazin-2-ones. The reaction of CSI with 2-hydroxybenzophenones produced exclusively 2-(carbamoyloxy)benzophenones **8** and not the cyclized 4-phenylbenzoxazinones **9**. Our efforts to cyclize **8** nonenzymatically, such as by use of bases and thermally, mainly afforded 2-hydroxybenzophenones **7** by the cleavage of the carbamoyloxy function. In view of the above difficulties encountered during attempted cyclizations, we were led to explore the use of biocatalysts. Thus, **8** on cyclization with

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