X-ray Structural Determination of 16a. A single crystal of **16a**, obtained by slow crystallization from acetone–2-propanol, was monoclinic, space group $C2/C$, with a = 22.106 (1) Å, b = 7.207 (1) Å, c = 15.821 (1) Å, β = 117.95 (1)°, V = 2226.6 Å^3, and d_{calcd} = 1.362 g cm^{-3} for Z = 8 ($C_8H_{12}N_4O_2S$, M_n = 228.27). The intensity data were measured on an Enraf-Nonius CAD 4 diffractometer (Cu Kα radiation, λ = 1.5418 Å; graphite monochromator; ω–2θ scan mode, $1 < \theta < 70°$, $\omega = (0.8 + 0.15 \tan \theta)°$; number of reflections measured, 2101). The determination and refinement of the crystal structure is based on 1785 reflectios with $I > 3(I)$. The structure was solved by direct methods with MULTAN78[12] and was refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.038 and R_w = 0.060. All calculations were performed on a PDP 11-34 computer with an Enraf-Nonius SDP software. Bond distances, bond angles, torsional angles, final positional parameters, and anisotropic thermal parameters are presented in the supplementary material section for compound **16a**.

Reaction of 13 with Ethoxycarbonyl Isothiocyanate. A solution containing **13** (2.03 g, 10 mmol) and ethoxycarbonyl isothiocyanate (1.44 g, 11 mmol) in 50 mL of chloroform was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column by using 20% acetone–hexane mixture as the eluent. The major fraction gave 2.7 g (81%) of 4-(methoxycarbonyl)-Δ^2-1,2,4-triazoline **18** as yellow crystals (mp 126–127 °C). The spectral and analytical data are as follows: IR 3350 (NH), 1755, 1720 cm^{-1} (C=O); ^{1}H NMR δ 1.26 (t, J = 7.2, 3 H), 2.26 (s, 6 H), 2.40 (s, 3 H), 3.80 (s, 3 H), 4.16 (q, J = 7.2, 2 H); MS, m/e 334 (M$^+$, 27), 298 (25), 273 (19), 188 (100). Anal. Calcd for $C_{11}H_{18}N_4O_4S_2$: C, 39.51; H, 5.42; N, 16.75. Found: C, 39.51; H, 5.42; N, 16.55.

2,3-Dihydro-5,5-dimethyl-7-(methylthio)-3-thioxo-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazol-1-one (19). A solution containing 4-(methoxycarbonyl)-Δ^2-1,2,4-triazoline **18** (1.0 g, 3 mmol) and sodium hydroxide (0.24 g, 6 mmol) in 30 mL of 10% aqueous methanol was stirred at room temperature for 6 h. After the reaction the solution was worked up as described above for the preparation of **15**. This method gave 0.63 g (93%) of **19** as yellow crystals (mp 200–201 °C). The spectral and analytical data are as follows: IR 3590 (NH), 1770, 1730 cm^{-1} (C=O); ^{1}H NMR δ (Me_2SO-d_6) 1.84 (s, 6 H), 2.50 (s, 3 H), 7.20–7.80 (br, 1 H); MS, m/e 230 (M$^+$, 100), 157 (33), 114 (36). Anal. Calcd for $C_7H_{10}N_4OS_2$: C, 36.52; H, 4.38; N, 24.34. Found: C, 36.38; H, 4.38; N, 24.11.

N^2-Methylation of 19. To a suspension containing 0.46 g (2 mmol) of **19** in 30 mL of chloroform was slowly added diazomethane (10 mmol) in 20 mL of ethyl ether below 10 °C. The mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was chromatographed on a silica gel column by using 25% acetone–hexane as the eluent. The major fraction gave 0.41 g (84%) of **20** as white crystals (mp 110–112 °C). The structure of **20** was determined to be 2,3-dihydro-7-(methylthio)-3-thioxo-2,5,5-trimethyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazol-1-one on the basis of the following spectral and analytical data: IR 1730 cm^{-1} (C=O); ^{1}H NMR δ 1.90 (s, 6 H), 2.59 (s, 3 H), 3.26 (s, 3 H); MS, m/e 244 (M$^+$, 100), 171 (58), 114 (60), 98 (60). Anal. Calcd for $C_8H_{12}N_4O_2S$: C, 42.09; H, 5.30; N, 24.54. Found: C, 42.06; H, 5.38; N, 24.48.

Acknowledgment. We thank Professor Iwao Tabushi for many helpful comments. We also acknowledge Kazunori Yanagi for collecting X-ray data.

Registry No. 1, 27268-57-1; **3a**, 89578-89-2; **3b**, 89578-90-5; **3c**, 89578-91-6; **3d**, 89578-92-7; **6** (R^1 = H), 41208-11-1; **6a**, 89578-93-8; **6b**, 89578-94-9; **7a**, 624-83-9; **7b**, 1795-48-8; **7c**, 1609-86-5; **7d**, 103-71-9; **8a**, 89578-95-0; **8b**, 89578-96-1; **9a**, 89578-97-2; **9b**, 89578-98-3; **9c**, 89578-99-4; **9d**, 89579-00-0; **9e**, 89579-01-1; **9f**, 89579-02-2; **10**, 14673-56-4; **11**, 89579-03-3; **13**, 89579-04-4; **14a**, 89579-05-5; **14b**, 89579-06-6; **15a**, 89579-07-7; **15b**, 89579-08-8; **16a**, 89579-09-9; **16b**, 89579-10-2; **18**, 89579-11-3; **19**, 89579-12-4; **20**, 89579-13-5; ClC(O)OMe, 79-22-1; HNCO, 75-13-8; 1,1′-carbonyldiimidazole, 530-62-1; ethoxycarbonyl isothiocyanate, 16182-04-0; cyclohexyl isocyanate, 3173-53-3.

Supplementary Material Available: ^{13}C NMR values (Table II) and X-ray analytical data (Tables III–VII) (7 pages). Ordering information is given on any current masthead page.

(12) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P.; "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Universities of York, England, and Louvain, Belgium, 1978.

Chirality Transfer in the [2,3] Wittig Rearrangement

James A. Marshall* and Todd M. Jenson

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received November 7, 1983

The [2,3] Wittig rearrangement of (*S*)-1-methyl-2-methylenecyclododecyl allyl ether (**9**) was carried out and the stereochemistry of the alcohol product **10** was determined. The (*S*)-ether **9** afforded principally the (*R*)-alcohol **10**. The optically active ether **9** was prepared from 2-carbethoxycyclododecanone via the enol phosphate **3** which was coupled with lithium dimethylcuprate to give the *cis*-ester **4**. Reduction with Dibah and Sharpless epoxidation of alcohol **5** using (+)-diisopropyl tartrate as the coordinating ligand afforded the (1*S*, 2*S*)-epoxy alcohol **6**. Reduction of the mesylate derivative **7** afforded the allylic alcohol **8**, the precursor of ether **9**. The configuration of the allylic alcohol product (*R*)-**10** was determined from the CD spectrum of the *p*-bromobenzoate. The chirality transfer observed in the conversion of ether **9** to alcohol **10** is in accord with a chairlike envelope transition state for the rearrangement.

The [2,3] Wittig rearrangement of diallylic ethers has received close scrutiny recently as a carbon–carbon bond forming reaction of potential application to the stereodirected synthesis of acyclic alcohols.[1,2] The observed regioselectivity of allyl anion formation, the preference for *E* orientation in the newly formed double bond, and the *E* → threo, *Z* → erythro diastereoselectivity of the reaction suggest a highly ordered transition state (Figure 1).[1]

(1) (a) Mikami, K.; Kimura, Y.; Kishi, N.; Nakai, T. *J. Org. Chem.* **1983**, *48*, 279–281. (b) Rautenstrauch, V. *J. Chem. Soc. D* **1970**, 4–6.

(2) Nakai, T.; Mikami, K.; Taya, S. *J. Am. Chem. Soc.* **1981**, *103*, 6492–6494 and references cited therein.

0022-3263/84/1949-1707$01.50/0

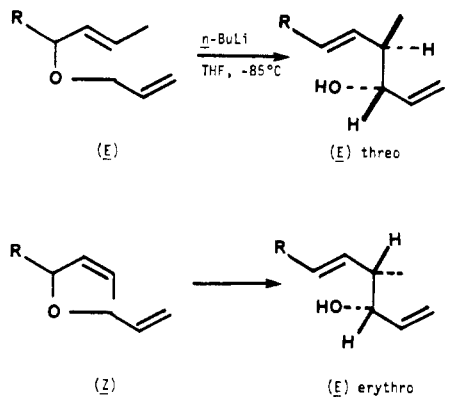


Figure 1. Regiochemical and stereochemical preferences in [2,3] Wittig rearrangements.

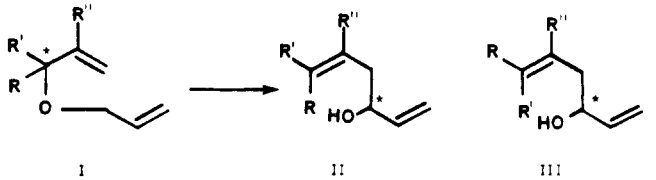
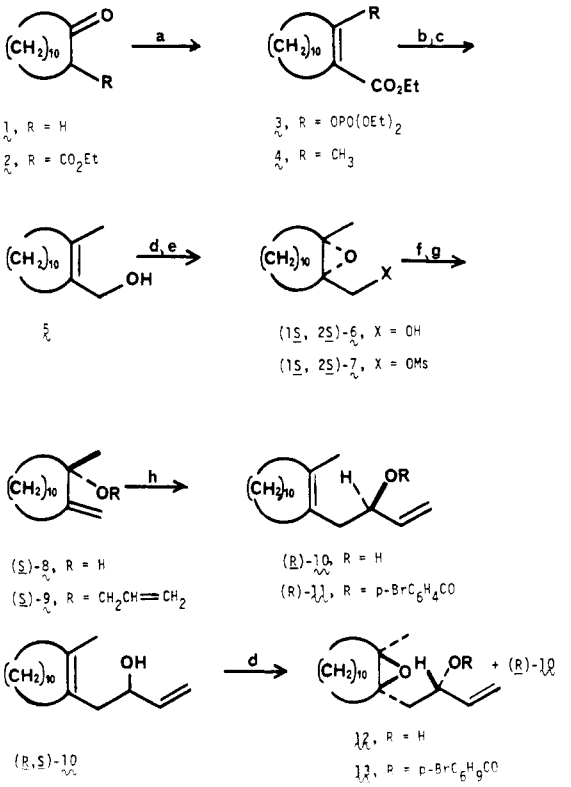


Figure 2. [2,3] Wittig rearrangement of tertiary allylic ethers.

We wished to utilize this rearrangement in synthetic projects requiring optically active 1,5-dien-3-ols. One anticipated application involved the conversion of a tertiary allylic ether such as I [R = CH_3; R′,R″ = $(CH_2)_n$] to a tetrasubstituted cycloalkenyl homoallylic alcohol II and/or III (Figure 2). When these plans were formulated, no information was available regarding the probable sense of chirality transfer in such rearrangements.[3] Neither could we be certain that the previously noted *E* preference for the newly formed double bond would be retained in a system such as II, especially with the possible constraints imposed by a carbocyclic framework. Furthermore, few examples of tertiary allylic ether [2,3] rearrangements could be found. In order to gain insight to these matters, we undertook the study described herein.

Allylic ether **9** was the target of our initial investigations. The racemic material was readily available through addition of methyllithium to 2-methylenecyclododecanone[4] followed by allylation of the resulting alcohol (±)-**8** with sodium hydride and allyl bromide–sodium iodide in 1,2-dimethoxyethane. Attempts to resolve alcohol (±)-**8** via selective Sharpless epoxidation[5] proved fruitless.[6] Consequently, the route shown in Scheme I was implemented starting with 2-carboethoxycyclododecanone (**2**). The enol phosphate derivative **3** upon treatment with lithium dimethylcuprate afforded the cis (*E*) unsaturated ester **4** as the sole product.[7] Reduction with diisobutylaluminum hydride led to the cis allylic alcohol **5** whose ^1H NMR spectrum showed a sharp singlet at 4.10 ppm for the carbinyl methylene. The characteristic AB quartet of the trans isomer[8] was totally absent. Epoxidation of allylic

Scheme I[a]



[a] a, NaH, $(EtO)_2POCl$, Et_2O; b, Me_2CuLi, Et_2O, −78 °C; c, $(i\text{-Bu})_2AlH$, hexane, −78 °C; d, $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DIT, *t*-BuOOH, CH_2Cl_2; e, $MeSO_2Cl$, C_5H_5N, 0 °C; f, Li, NH_3, THF; g, C_3H_5Br, NaI, DME; h, *n*-BuLi, hexane, HMPA, THF, −85 °C.

alcohol (±)-**5** via the Sharpless method, using (+)-diisopropyl tartrate as the chiral ligand, afforded the (−)-epoxy alcohol **6**. The configuration 1*S*, 2*S* is assigned on the basis of the Sharpless empirical rule.[5a] Analysis of the Mosher ester (2-methoxy-2-(trifluoromethyl)-2-phenylacetate) derivative of **6** via ^{19}F NMR indicated an enantiomeric excess of 94%.[9]

Reduction–elimination of the mesylate **7** with lithium in ammonia gave the tertiary allylic alcohol (*S*)-**8**.[10] Attempts to measure the optical purity of this alcohol by ^1H NMR using chiral shift reagents were not successful,[11] and we were unable to prepare the Mosher ester derivative. Thus we can only estimate the optical purity of **8** as equal to that of its precursor, alcohol **6**. The synthesis of ether **9** was completed by allylation of alcohol **8** along the lines used for the racemic material.

Initial studies on the Wittig rearrangement were carried out on racemic ether **9** in order to optimize conditions and ascertain the double bond stereochemistry. By the use of the reported conditions (1.4 equiv of *n*-butyllithium in THF at −85 °C for 6 h)[1,2] the rearranged alcohol was obtained in only 5–10% yield as a 3:4 mixture of the *E* (cis) and *Z* (trans) isomers (±)-**10** and (±)-**23** (Scheme II). At a higher temperature with a 5-fold excess of butyllithium, the yield increased to 30% of a 1:1 mixture of *E* and *Z* isomers. The addition of complexing agents TMEDA, Dabco, and 12-crown-4[12] had little effect on yield or ste-

(3) Baldwin and Patrick showed that the [2,3] Wittig rearrangement of (*E*)-(1*S*)-1-methyl-2-butenyl benzyl ether proceeds via suprafacial geometry to give (*E*)-(1?,2*R*)-1-phenyl-2-methyl-3-penten-1-ol. The stereochemistry at C-1 was not established. It is this center that the present study is concerned with. Baldwin, J. E.; Patrick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 3556–3558.

(4) Gras, J.-L. *J. Org. Chem.* **1981**, *46*, 3738–3741. Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183–5189.

(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.

(6) The alcohol was recovered unchanged.

(7) Weiler, L.; Sum, F.-W. *Can. J. Chem.* **1979**, *57*, 1431–1441. We are indebted to J. C. Peterson for experimental details.

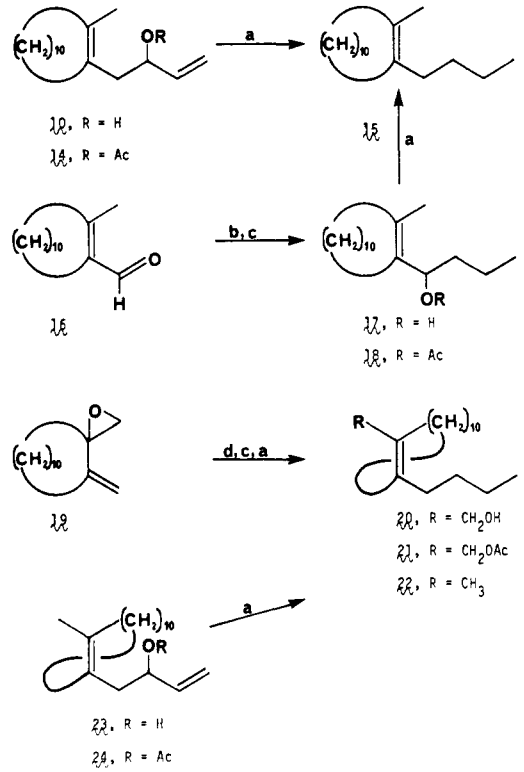
(8) Cf. Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 3360–3362.

(9) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(10) Cf. Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312–4313.

(11) Cf. Kime, K. A.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54–62.

Scheme II[a]



[a] a, Li, $EtNH_2$; b, *n*-PrMgBr, Et_2O, 0 °C; c, Ac_2O, C_5H_5N; d, *n*-PrMgBr-CuI-Me_2S, THF, −78 to 35 °C.

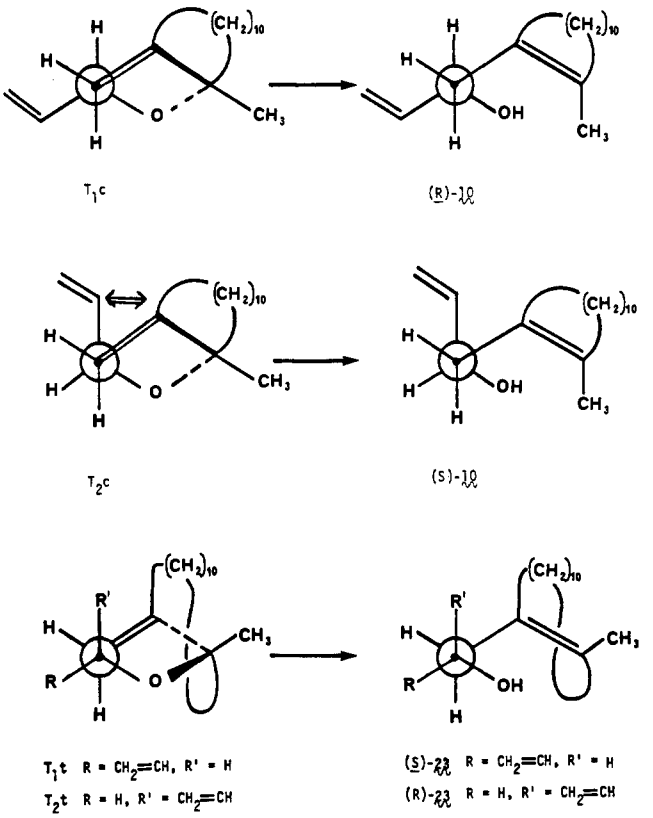


Figure 3. Transition-state conformations for [2,3] rearrangements of ether (*S*)-(+)-**9**.

reoselectivity. However, added HMPA[12] produced a dramatic increase in both. With 5.7 molar equivalents, a 50:1 mixture of *E* and *Z* olefins (±)-**10** and (±)-**23** was formed in nearly 50% yield. Further increases in HMPA and base caused a slight decrease in yield.

The double bond stereochemistry of the rearranged alcohol (±)-**10** (cis) was established through Birch reduction of the acetate **14** with lithium in ethylamine[8] to give (*Z*)-1-methyl-2-butylcyclododecene (**15**). An authentic sample of **15** was prepared via conversion of the cis allylic alcohol **5** to the aldehyde **16** followed by addition of propylmagnesium bromide, acetylation of the resulting allylic alcohol **17**, and reduction with lithium in ethylamine.

The rearranged trans alcohol (±)-**23** [admixed with (±)-**10**] was reduced via the acetate derivative **24** to (*E*)-1-methyl-2-butylcyclododecene (**22**) (admixed with **15**). An authentic sample of this olefin was prepared as follows. Addition of *n*-propylmagnesium bromide–copper(I) iodide to vinyl oxirane **19** produced the trans allylic alcohol **20** as the major isomer (9:1 according to ^1H NMR analysis).[8] Acetylation followed by Birch reduction afforded the trans cyclododecene **22**.

The above findings show that Wittig rearrangement of allylic ether **9** can afford varying amounts of the *E* and *Z* cyclododecenes **10** and **23** depending upon the choice of reaction conditions. In view of the low yields obtained in the absence of HMPA, the route is most suitable for the *E* isomer **10**.

With the rearrangement conditions optimized and the olefin stereochemistry firmly established, we were now in a position to examine the chirality transfer. Treatment of ether (*S*)-(+)-**9** of presumed 94% optical purity with 3 equiv of *n*-butyllithium and 5.7 equiv of HMPA in THF at −85 °C afforded the alcohol (*R*)-(+)-**10** in 51% yield. The optical purity was found to be 59% by integration of the ^{19}F NMR spectrum of the Mosher ester derivative.[9] Thus, assuming minimal loss of optical activity in the sequence **6** → **9**, we calculate an enantioselectivity of 65% for the [2,3] Wittig rearrangement of ether **9**.[13]

The configuration of the rearranged alcohol (+)-**10** was surmised from the CD spectrum of the *p*-bromobenzoate deriviative **11** as recently described by Nakanishi and Sharpless.[14] We also were able to effect kinetic resolution of the racemic alcohol **10** via Sharpless epoxidation[5] using the titanium complex derived from (+)-diethyl tartrate, titanium isopropoxide, and *tert*-butyl hydroperoxide. Interestingly, the recovered alcohol (+)-**10** showed only modest optical rotation (calculated optical purity of 15%). Examination of the epoxidized product showed it to be the homoallylic epoxide **12** rather than the expected allylic epoxide. The apparent preference for homoallylic vs. allylic epoxidation presumably stems from the greater nucleophilic reactivity of the more substituted double bond. Sharpless[15] has noted that epoxidations of homoallylic alcohols by this method proceed with lower enantioselectivity and in the opposite absolute sense from the allylic alcohol cases. The configuration shown in structure **12** is assigned accordingly. The CD spectrum of the *p*-bromobenzoate **13** confirmed the absolute configuration of the allylic carbinyl center.[14]

Nakai recently proposed a transition state model to account for threo/erythro diastereoselectivity in a number

(12) TMEDA = tetramethylethylenediamine, Dabco = 1,4-diazabicyclo[2.2.2]octane, 12-crown-4 = 1,4,7,10-tetraoxacyclododecane, HMPA = hexamethylphosphoric triamide.

(13) Under essentially identical conditions ether (+)-**9** of 94% optical purity afforded alcohol (+)-**10** of 60% and 62% optical purity in 51% and 34% yield. The enantioselectivity is calculated as the ratio of product to reactant optical purity. The appearance of weak carbonyl bands in the infrared spectra of several chromatography fractions indicates that dissociative processes may account for some or all of the racemization.[1b]

(14) Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775–3776.

(15) Sharpless, K. B. *Pure Applied Chem.* **1983**, *55*, 589–604.

of bis allylic ether rearrangements.[1] In all cases, save one, the findings could be explained by a preferred pseudoequatorial orientation of the vinyl portion of the allyl anion in a chairlike envelope arrangement of the five interacting centers. This model qualititatively accomodates our findings, as well. In Figure 3 we show a Newman projection down the forming carbon–carbon bond of Nakai's transition state. The major pathway, T_1c, from ether (*S*)-**9** to alcohol *cis*-(*R*)-**10** places the vinyl grouping in a pseudoequatorial orientation. Rearrangement of ether (*S*)-**9** to the enantiomeric alcohol *cis*-(*S*)-**10** along the analogous pathway T_2c requires a pseudoaxial orientation for this substituent. Since the developing 1,3-diaxial interaction with the allylic ring methylene substituent should strongly disfavor this pathway it is surprising to find as much as 17% of the product being formed via this transition state.[13,16]

Applying the above model to the formation of the trans cyclododecenyl alcohol **23** from ether (*S*)-**9** the prediction can be made that rearrangement will preferentially take place via pathway T_1t to give the (*S*)-alcohol. The pathway T_2t leading to the (*R*)-enantiomer suffers from the aforementioned 1,3-diaxial allyl anion–methylene interaction. It is also expected that the chiral cycloalkene moiety of **23** will possess the *R* configuration.[16] We have not been able to check these predictions owing to the low yields of olefin **23** and difficulty in separating it from the cis isomer **10**.

Experimental Section

Ethyl (*E*)-2-Methylcyclododecene-1-carboxylate (4). To a stirred, cooled (0 °C) mixture of 1.6 g (67 mmol) of sodium hydride in 35 mL of ether was added a solution of 15.0 g (59 mmol) of β-keto ester **2** in 30 mL of ether. The mixture was warmed to room temperature and a solution of 11.2 g (65 mmol) of diethyl phosphorochloridate in 20 mL of ether was added dropwise. After 2 h saturated ammonium chloride was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with sodium bicarbonate, water, and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 23 g of yellow oil. Purification by column chromatography (25% ethyl acetate–hexane) yielded 16.2 g (70%) of a pale yellow oil: IR (film) ν 2840, 1720, 1660, 1290, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 1.25 (m, O–CH_2CH_3), 1.4 (envelope, ring H), 2.4 (m, allylic H), 4.2 ppm (m, O–CH_2). This material was used without further purification.

To a stirred, cooled (0 °C) mixture of 15.2 g (80 mmol) of copper iodide in 0.55 L of ether was added dropwise 127 mL (160 mmol) of 1.25 M methyllithium in ether. After stirring at 0 °C for 10 min the solution was cooled to −78 °C and stirred for 0.5 h, and a solution of 20.9 g (54 mmol) of enol phosphate **3** in 40 mL of ether was added dropwise. Saturated ammonium chloride was added, and the mixture was warmed to room temperature and stirred overnight. The liquid layers were decanted from the undissolved copper salts and the salts were washed with ether. The organic layers were combined, washed with 10% ammonia in brine and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 15.4 g of thick opaque oil. Purification by column chromatography (15% ethyl acetate–hexane) yielded 8.09 g (59%) of ester **4**: IR (film) ν 2900, 2840, 1820, 1650, 1390, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (s, vinyl CH_3), 2.2 (m, allylic H), 2.3 (m, allylic H), 4.2 (q, J = 7 Hz, O–CH_2CH_3). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.20; H, 11.19.

(*E*)-(2-Methyl-1-cyclododecenyl)methanol (5). To a stirred, cooled (−78 °C) solution of 9.57 g (37.1 mmol) of unsaturated ester **4** in 300 mL of hexane was added dropwise 92 mL (92 mmol) of 1 M diisobutylaluminum hydride in hexane. After 2 h saturated ammonium chloride was added and the reaction mixture was warmed to room temperature. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 7.91 g (100%) of a thick yellow oil: IR (film) ν 3300, 2900, 2850, 1020, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) 1.2 (s, –OH), 1.4 (envelope, ring H), 1.8 (s, vinyl CH_3), 2.15 (m, allylic H), 4.1 ppm (s, CH_2OH). The analytical sample was purified by chromatography on silica gel. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.58; H, 12.38.

(1*S*,2*S*)-(2-Methyl-1,2-epoxycyclododecyl)methanol (6). The procedure of Sharpless was followed.[5] Titanium isopropoxide (3.49 g, 12.2 mmol) followed by 4.29 g (18.2 mmol) of (+)-diisopropyl tartrate were added dropwise to 125 mL of cooled (−20 °C) methylene chloride. The mixture was stirred for 5 min and 2.56 g (12.2 mmol) of alcohol **5** was added dropwise followed by 3.7 mL (12.2 mmol) of 3.29 M *tert*-butyl hydroperoxide in dichloroethane. After 30 min, 46 mL (30.7 mmol) of 10% aqueous tartaric acid was added. The mixture was warmed to room temperature and stirred for 1.5 h. The resultant layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 9.0 g of an opaque yellow liquid. This liquid was taken up in a solution of 1.5 g of sodium hydroxide in 400 mL of ethanol and stirred for 14 h. Water and hexane were added, the resultant layers were separated, and the aqueous layer was extracted with hexane. The hexane layers were combined, washed with 10% sodium hydroxide, water, and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 1.97 g (72%) of a beige solid: IR (film, $CDCl_3$) ν 3375, 2900, 2850, 1660, 900, 720 cm^{-1}; ^1H NMR ($CDCl_3$) 1.3 (s, CH_3) 1.4 (envelope, ring H), 3.7 ppm (m, CH_2–OH); mp 70–72 °C; $[\alpha]_D$ −9.4 (*c* 8.7, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.54; H, 12.53.

The Mosher ester derivative showed two singlets in the ^{19}F NMR spectrum at 4.53 and 4.50 ppm (relative to external trifluoroacetic acid) of integrated area 97:3.

(1*S*,2*S*)-(2-Methyl-1,2-epoxycyclododecyl)methyl Methanesulfonate (7). To a stirred, cooled (0 °C) solution of 1.8 g (8.0 mmol) of epoxy alcohol **6** in 30 mL of pyridine was added 0.93 mL (12.0 mmol) of methanesulfonyl chloride. After 2 h, the reaction mixture was poured into ice water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with copper sulfate, water, and brine, dried over potassium carbonate, and filtered. Removal of solvent under reduced pressure yielded 1.95 g (81%) of a light yellow solid: IR (film, $CDCl_3$) ν 2900, 2825, 1660, 1360, 1180, 930, 730 cm^{-1}; ^1H NMR ($CDCl_3$) 1.4 (s, CH_3), 1.45 (envelope, ring H), 3.1 (s, CH_3SO_3), 4.4 ppm (ABq, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 10 Hz); $[\alpha]_D$ +0.5 (*c* 10.7, $CHCl_3$). This material rapidly deteriorated upon storage and was therefore used directly in the next step.

(1*S*)-1-Methyl-2-methylene-1-cyclododecanol (8). To 250 mL of liquid ammonia was added a solution of 1.8 g (5.9 mmol) of epoxy mesylate **7** in 3 mL of tetrahydrofuran followed by 0.41 g (59 mmol) of lithium wire in 0.07-g increments. When the solution remained blue for 1 h, solid ammonium chloride was carefully added followed by 100 mL of hexane. The mixture was stirred overnight, water was added, the resultant layers were separated, and the aqueous layer was extracted with ether. The etheral layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by column chromatography (15% ethyl acetate–hexane) yielded 0.93 g (75%) of white solid: mp 67–72 °C; IR (film, $CDCl_3$) ν 3375, 1640, 910 cm^{-1}; ^1H NMR ($CDCl_3$) 1.3 (envelope, ring H), 1.3 (s, CH_3), 1.55 (s, –OH), 4.9, 5.2 (C=CH_2); $[\alpha]_D$ −16.9 (*c* 6.1, $CHCl_3$). Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.90; H, 12.53.

(1*S*)-1-Methyl-2-methylenecyclododecyl 2-Propenyl Ether (9). To a stirred mixture of 0.64 g (4.3 mmol) of sodium iodide and 0.34 g (14.2 mmol) of sodium hydride in 50 mL of 1,2-dimethoxyethane was added 0.59 g (2.8 mmol) of allylic alcohol (−)-**8** in 10 mL of 1,2-dimethoxyethane followed by dropwise addition of 3.5 g (29 mmol) of allyl bromide. After 2 days, the reaction was quenched through careful addition of 1:1 aqueous methanol, the resultant layers were separated, and the aqueous layer was

(16) Cf. Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew Chem., Int. Ed. Engl.* **1966**, *5*, 385–416.

extracted with ether. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.692 g (98%) of a rust colored liquid. Purification by column chromatography (hexane) afforded 0.54 g (77%) of a clear liquid: IR (film) ν 3050, 2875, 1740, 1640, 1120, 920, 900 cm^{-1}; ^1H NMR ($CDCl_3$) 1.3 (envelope, ring H), 3.7 (t, J = 5 Hz, OCH_2), 5.0, 5.1 (CH_2=CH), 5.6–6.0 (CH_2=C*H*–); $[\alpha]_D$ +35.8 (c 4.8, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.08. Found: C, 81.69; H, 11.79.

4-[(*E*)-2-Methyl-1-cyclododecen-1-yl]-1-buten-3-yl Acetate (14). To a stirred, cooled (0 °C) solution of 0.18 g (0.9 mmol) of alcohol **10** in 5 mL of distilled pyridine was added dropwise 0.7 mL (7 mmol) of acetic anhydride. After stirring at 0 °C for 1 h the solution was warmed to room temperature and stirred overnight. The reaction solution was then poured onto ice, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated copper sulfate, water, and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.22 g (88%) of a clear oil: IR (film) ν 2900, 1730, 1660, 1640, 1240, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 1.1–1.6 (envelope, ring H), 1.62 (vinyl, CH_3), 2.1 (s, acetyl CH_3), 2.0–2.5 (m, allylic H), 4.9 (m, carbinyl), 5.0–5.5, and 5.6–6.0 ppm (m, vinyl H). Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.00; H, 10.85.

(*Z*)-1-Butyl-2-methylcyclododecene (15). A. From Acetate 14. Ethylamine (ca. 60 mL) was distilled from sodium ribbon into a dry 100-mL 3-necked round botton flask. Lithium wire, 68 mg (9.7 mmol) was added followed after 0.5 h by a solution of 0.28 g (0.97 mmol) of allylic acetate **12** in 1 mL of tetrahydrofuran. After 1.5 h solid ammonium chloride was carefully added followed by ca. 25 mL of hexane. The ethylamine was allowed to evaporate, water was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with 10% hydrochloric acid, sodium bisulfite, water, and brine, dried over magnesium sulfate, and filtered. Removal of solvent at reduced pressure afforded an oil which was purified by column chromatography (silica gel, hexane) to give 0.13 g (56%) of olefin **15** as a clear liquid: ^1H NMR ($CDCl_3$) 0.7–1.0 (t, J = 6 Hz, CH_3), 1.1–1.7 (envelope, ring H), 1.6 (s, vinyl CH_3), 1.85–2.2 ppm (m, allylic H).

B. From Acetate 18. To ca. 15 mL of liquid ammonia was added 0.06 g (8.7 mmol) of lithium wire with stirring. After 30 min, a solution of 0.25 g (0.85 mmol) of allylic acetate **16** in 1 mL of tetrahydrofuran was added and stirring was continued for 45 min. Solid ammonium chloride was then carefully added followed by ca. 10 mL of hexane. The ammonia was allowed to evaporate, water was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a pale yellow liquid. Column chromatography (silica gel, hexane) yielded 0.14 g (70%) of a clear liquid: ^1H NMR ($CDCl_3$) 0.7–0.9 (envelope, CH_2CH_3), 1.0–1.6 (envelope, ring H), 1.5 (s, vinyl CH_3), 1.9–2.1 ppm (envelope, allylic H). Anal. Calcd for $C_{17}H_{32}$: C, 86.36; H, 13.64. Found: C, 86.34; H, 13.29.

(*E*)-2-Methyl-1-cyclododecenecarboxaldehyde (16). To a stirred, cooled (0 °C) solution of 0.76 g (2.0 mmol) of pyridinium dichromate in 2 mL of dimethylformamide was added 0.40 g (1.6 mmol) of allylic alcohol **5**. After 2.5 h the reaction mixture was poured into 10 mL of water, the layers were separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.404 g (100%) of a clear liquid: ^1H NMR ($CDCl_3$) 1.0–1.6 (envelope, ring H) 2.15 (s, vinyl CH_3), 2.2–2.5 (m, allylic H), and 10.0 ppm (s, CHO); MS calcd for $C_{14}H_{24}O$, m/e 208.1827; found, 208.1827.

1-[(*E*)-2-Methyl-1-cyclododecen-1-yl]-1-butanol (17). To a stirred, cooled (0 °C) solution of 0.40 g (1.6 mmol) of aldehyde **16** in 2 mL of ether was added dropwise 2.1 mL (2.4 mmol) of 1.13 M n-propylmagnesium bromide in tetrahydrofuran. After 30 min, 1 mL of aqueous ammonium chloride was added. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.50 g (105%) of a yellow oil. Purification by column chromatography (silica gel, 10% ethyl acetate–hexane) yielded 0.40 g (85%) of a clear liquid: IR (film) ν 3300, 2850, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) 0.9 (broad t, $-CH_2CH_3$), 1.2–1.6 (envelope, ring H), 1.7 (s, vinyl CH_3), 1.8–2.3 (m, allylc H), and 4.55 ppm (m, R_2CHOH); MS calcd for $C_{17}H_{32}O$, m/e 252.2453; found, 252.2454.

1-[(*E*)-2-Methyl-1-cyclododecen-1-yl]butyl Acetate (18). By the procedure described for the preparation of allylic acetate **14**, 0.33 g (1.3 mmol) of allylic alcohol **17** in 5 mL of pyridine and 1.2 mL (13 mmol) of acetic anhydride afforded 0.25 g (65%) of a clear liquid which was used with no further purification: ^1H NMR ($CDCl_3$) 0.8 (envelope, CH_3), 1.1–1.5 (envelope, ring H), 1.7 (s, vinyl CH_3), 1.95 (s, acetyl CH_3), 1.9–2.2 (envelope, allylic H), 5.6 ppm (m, R_2CHOAc). Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.26; H, 11.48.

[(*Z*)-2-Butyl-1-cyclododecen-1-yl]methanol (20). A stirred, cooled (–78 °C) mixture of 3.7 g (19.5 mmol) of copper(I) iodide and 9 mL (130 mmol) of dimethyl sulfide in 50 mL of tetrahydrofuran, under argon, was stirred for 15 min and 17.2 mL (19.4 mmol) of 1.13 M n-propylmagnesium bromide in THF was then added dropwise. After 14 min, 2.05 g (9.9 mmol) of epoxide **19** in 12 mL of tetrahydrofuran was added dropwise. The reaction was stirred for 1 h, warmed to –35 °C, and stirred for 9 h. The mixture was poured into aqueous ammonium chloride–ether and made basic with concentrated ammonium hydroxide (until the aqueous layer was blue). The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with 7% ammonia in brine, water, and brine, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 2.37 g (95%) of a viscous yellow oil. Column chromatography (silica gel, 10% ethyl acetate–hexane) gave 1.7 g (68%) of a white solid: ^1H NMR ($CDCl_3$) 0.92 (t, J = 5 Hz, CH_3), 1.1–1.6 (envelope, ring H), 2.1–2.6 (envelope, allylic H), and 4.2 ppm (ABq, J = 12 Hz, $\Delta\nu$ = 36 Hz, RCH_2OH). Anal. Calcd for $C_{17}H_{32}O$: C, 80.88; H, 12.78. Found: C, 81.04; H, 12.49.

[(*Z*)-2-Butyl-1-cyclododecen-1-yl]methyl Acetate (21). By the procedure described for the preparation of the allylic acetate **14**, 0.32 g (1.3 mmol) of allylic alcohol **20** in 8 mL of pyridine and 1.2 mL (13 mmol) of acetic anhydride afforded 0.35 g (95%) of a clear liquid which was used with no further purification: IR (neat) ν 2900, 1750, 1240, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) 1.0–1.5 (envelope, ring H), 2.0 (s, acetyl CH_3), and 4.65 ppm (ABq, J = 17 Hz, $\Delta\nu$ = 15 Hz, RCH_2OAc). Anal. Calcd for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.37; H, 11.38.

(*E*)-1-Butyl-2-methylcyclododecene (22). By the procedure described for the preparation of the alkene **15**, 0.32 g (0.8 mmol) of allylic acetate **21** in ca. 20 mL of ethylamine and 56 mg (8 mmol) of lithium wire afforded, after column chromatography (silica gel, hexane), 0.12 g (66%) of a clear liquid: IR (neat) ν 2900, 2825, 1460, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) 0.85 (distorted t, RCH_3), 1.0–1.6 (envelope, ring H), 1.7 (s, vinyl CH_3), 2.1–2.7 ppm (envelope, allylic H). Anal. Calcd for $C_{17}H_{32}$: C, 86.36; H, 13.64. Found: C, 86.10; H, 13.31.

4-[(*E*)-2-Methyl-1-cyclododecen-1-yl]-1-buten-3-ol (10). A. From Racemic Ether (±)-9. To a stirred, cooled (–85 °C) solution of 0.244 g (0.98 mmol) of the allylic ether (±)-**9** in 3 mL of tetrahydrofuran was added 1.8 mL (2.9 mmol) of 1.6 M n-butyllithium in hexane at a rate of ca. 0.09 mL/min followed by a solution of 0.95 mL (5.7 mmol) of hexamethylphosphoramide in 1 mL of tetrahydrofuran at a rate of ca. 0.05 mL/min. After 4 h, 3.6 mL (10.0 mmol) of 10% hydrochloric acid was added, the reaction mixture was warmed to room temperature, and the layers were separated. The aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.25 g (106%) of a yellow liquid. Purification by column chromatography (silica gel, 2–5% ethyl acetate–hexane) gave 0.028 g (11%) of recovered ether and 0.115 g (47%) of a clear liquid: IR (film) ν 3300, 2875, 1640, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 1.2–1.6 (ring H), 1.7 (s, vinyl CH_3), 1.8 (s, OH), 1.9–2.5 (m, allylic H), 4.2 (m, carbinyl H), 5.2 (m, terminal vinyl H), and 5.8 ppm (m, vinyl H). Several mixed fractions of unknown composition accounting for ca. 20% of the total product were also isolated.

The E/Z isomer ratio (50:1) was determined by conversion of the rearranged alcohol to the acetate (acetic anhydride, pyridine,

room temperature) followed by gas chromatographic analysis (160 °C, 6 ft, 2% Carbowax).

B. From Ether (*S*)-(+)-9. When the procedure described above was followed 0.256 g (1.0 mmol) of allylic ether (*S*)-**9** [$[\alpha]^{30}_D$ +35.8 (*c* 4.78, $CHCl_3$)], 1.9 mL (3.0 mmol) of 1.6 M *n*-butyllithium in hexane, and 0.95 mL (5.7 mmol) of hexamethylphosphoramide in 4 mL of tetrahydrofuran afforded 0.028 g (11%) of recovered ether, 0.036 g (14%) of mixed byproducts, and 0.131 g (51%) of alcohol (*R*)-(+)-**10**, a clear liquid: $[\alpha]^{30}_D$ +11.1 (*c* 3.34, $CHCl_3$); IR (film) ν 3300, 2900, 1640, 1470, 1440, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 1.1-1.7 (ring H), 1.7 (s, vinyl CH_3), 1.85 (s, OH), 2.0-2.6 (m, allylic H), 4.2 (m, carbinyl H), 5.2 (m, C=CH_2), and 5.8 ppm (m, RCH=C). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.08. Found: C, 81.51; H, 11.94.

The Mosher ester derivative showed signals at 4.64 and 4.46 ppm (relative to external trifluoroacetic acid) with integrated areas of 79:21 in the ^{19}F NMR spectrum.

Sharpless Resolution of Alcohol (*R*,*S*)-10. Following the procedure described for the preparation of epoxide **6**, 0.387 g (1.5 mmol) of the racemic alcohol (±)-**10**, 0.49 mL (1.6 mmol) of titanium isopropoxide, 0.49 mL (2.3 mmol) of (+)-diethyl tartrate, and 0.30 mL (1.0 mmol) of 3.29 M *tert*-butyl hydroperoxide in dichloroethane afforded 0.34 g (87%) of a yellow liquid. Column chromatography (silica gel, 10% ethyl acetate-hexane) afforded 0.10 g (26%) of the resolved alcohol (*R*)-(+)-**10**: $[\alpha]^{30}_D$ +2.9 (*c* 3.4, $CHCl_3$); IR (film) ν 3300, 2875, 1640, 920 cm^{-1}; ^1H NMR ($CDCl_3$) 1.2-1.7 (ring H), 1.5 (s, vinyl CH_3), 1.6 (s, -OH), 1.9-2.5 (m, allylic H), 4.2 (m, carbinyl H), 5.1 (m, C=CH_2), and 5.9 ppm (m, RC*H*=C). Continued elution afforded 0.14 g (35%) of the epoxide **12**: $[\alpha]^{30}_D$ -1.3 (*c* 5.93, $CHCl_3$); IR (film) ν 3450, 2900, 2840, 1640, 1000, and 930 cm^{-1}; ^1H NMR ($CDCl_3$) 1.2-1.8 (ring H), 1.35 (s, CH_3), 3.5 (s, OH), 4.55 (m, carbinyl H), 5.2 (m, C=CH_2), and 5.8 ppm (m, RCH=C). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.59; H, 11.10.

Acknowledgment. Support from the National Science Foundation and the National Institutes of Health (National Cancer Institute) through research grants CHE-8026013 and CA-34247 is gratefully acknowledged. We are indebted to Prof. Koji Nakanishi and Greg Verdine for determining the CD spectra of *p*-bromobenzoate (*R*)-**11** and its enantiomer at Columbia University.

Note Added in Proof. A report describing chirality transfer in the [2,3] Wittig rearrangement of (*S*),(*Z*)-1-methyl-2-butenyl 3-(trimethylsilyl)propargyl ether appeared after submission of this manuscript (Sayo, N.; Azuma, K.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 565-568). The proposed transition-state model and the absolute sense of the transfer are concordant with the present findings.

Registry No. **2**, 4017-60-1; **3**, 89462-79-3; **4**, 89462-80-6; **5**, 89462-81-7; (1*S*,2*S*)-**6**, 89462-82-8; (1*S*,2*S*)-**7**, 89462-83-9; (*S*)-**8**, 89462-84-0; (*S*)-**9**, 89462-85-1; (±)-**9**, 89462-96-4; (*R*)-**10**, 89462-86-2; (*R*,*S*)-**10**, 89497-14-3; (*R*)-**11**, 89462-87-3; **12**, 89462-97-5; **14**, 89462-88-4; **15**, 89462-89-5; **16**, 89462-90-8; **17**, 89462-91-9; **18**, 89462-92-0; **19**, 87336-89-8; **20**, 89462-93-1; **21**, 89462-94-2; **22**, 89462-95-3; diethyl phosphorochloridate, 814-49-3.

Copper Ion Promoted Esterification of *S*-2-Pyridyl Thioates and 2-Pyridyl Esters. Efficient Methods for the Preparation of Hindered Esters

Sunggak Kim* and Jae In Lee

Department of Chemistry, Korea Advanced Institute of Science & Technology, Seoul 131, Korea

Received August 24, 1983

The esterification of *S*-2-pyridyl thioates and 2-pyridyl esters with alcohols in acetonitrile is greatly facilitated by the addition of cupric bromide and copper ion is observed to catalyze the reaction. The ester formation is found to be sensitive to solvents, metal salts, and reaction temperatures. The esterification of *S*-2-pyridyl thioates is much more rapid than the esterification of 2-pyridyl esters under the reaction conditions employed. This method is exceedingly effective in the preparation of sterically hindered esters and has advantages over known methods in many respects such as high yields, the mildness of the reaction, and the rapidity of the reaction.

Esterification is an important and well-established reaction which is widely used in organic synthesis for various purposes. Although a number of useful and reliable methods for the preparation of esters have been known,[1] there are only several methods available in the literature for the preparation of hindered esters.

The preparation of hindered esters by the reaction of the mixed anhydrides of carboxylic acids using trifluoroacetic anhydride with alcohols is well-known and useful.[2] However, its synthetic application is limited due largely to the strongly acidic condition. The method using the reaction of acid chlorides with lithium alkoxides has not been a generally applicable method due to the strongly alkaline condition and limitations to acid chlorides without labile α hydrogens.[3] Recently, it has been reported that hindered esters can be prepared from acid chlorides and alcohols in the presence of an excess amount of silver cyanide in benzene or hexamethylphosphoramide.[4] This method, which proceeds under mild conditions, is useful and complementary to the methods developed previously. A great need still exists for an efficient method to prepare hindered esters in high yields under mild conditions.

There has been a continuing search for various methods to activate the carboxyl group toward facile esterification. Among many available methods, the combination of the metal ion and the thiol ester has gained a recent attention for macrolactonization.[5] The efficient synthesis of macrocyclic lactones and esters by activation of thiol esters with metal salts has been reported by Masamune.[6] However, the reaction depends critically on the structure

(1) For an excellent review, see: Haslam, E. *Tetrahedron* **1980**, *36*, 2409 and references cited theirin.
(2) Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927.
(3) Kaiser, E. M.; Woodruff, R. *J. Org. Chem.* **1970**, *35*, 1198.
(4) Takimoto, S.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2335.
(5) For reviews, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, *33*, 3041.
(6) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.

0022-3263/84/1949-1712$01.50/0