Oxyanion Orientation in Anionic Oxy-Cope Rearrangements

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Efficiency of chirality transfer in anionic oxy-Cope rearrangement depends solely on the orientational preference of the oxyanionic bond in the substrates with a single carbinol carbon chiral center. In chairlike transition-state conformations for the rearrangement of simplest substrates like anions generated from (*E*)-1-phenyl-1,5-hexadien-3-ol and (*E*)-1,5-heptadien-4-ol, the oxyanionic bond is more prone to adopt the *pseudoaxial* orientation. On the other hand, anions generated from (*E*)-2-methyl-1,5-heptadien-4-ol, (*E*)-5-*tert*-butyl-1-phenyl-1,5-hexadien-3-ol, and 4-(2′-methyl-1′-cyclohexenyl)-1-buten-3-ol undergo rearrangement via chairlike transition states in which the *pseudoequatorial* oxyanionic bond is favored. It can thus be surmized that there is a slight stereoelectronic preference for the pseudoaxial oxyanionic bond in the chairlike transition states for the rearrangement of substrates without steric constraints. Substitution at C5 of the basic 1,5-hexadien-3-ol framework of substrates, however, leads to 1,3-diaxial steric interaction in the chairlike transition states with pseudoaxial oxyanionic bond, and pseudoequatorial disposition of oxyanionic bond becomes more favorable.

Anionic oxy-Cope rearrangement[1] is now firmly established as one of the most potent and versatile tools for synthetic chemists engaged in the construction of complex organic molecules. The most remarkable feature of this anionic version of oxy-Cope rearrangement is the immense rate acceleration (10^{10-17}) relative to that of the neutral version.[2] Thus, the rearrangement reactions can be made to proceed irreversibly[3] under much milder conditions to generate new carbon skeletons. In general, they are expected to proceed via chairlike transition states analogous to the known examples for the neutral (thermal) version,[4] although there are examples in which boatlike transition states are structurally enforced.[5] Theoretical[6] and experimental[7] results agree that the anionic oxy-Cope rearrangement is characterized by highly dissociative transition states: there is only a small degree of bond formation between C1 and C6, but the C3–C4 bond dissociation is quite extensive.

If we accept the chairlike transition-state conformation in the rearrangement of the prototype substrate 1,5-hexadien-3-ol, the next logical question arises: does the oxyanionic bond prefer equatorial or axial orientation? This theoretically intriguing question should also attract the attention of synthetic chemists since in the rearrangement of 1,5-hexadien-3-ol substrates with substituents at C1 and/or C6 the efficiency of chirality transfer from the intrinsically stereogenic carbinol carbon center depends on the relative equatorial/axial preference in the chairlike transition states. A survey of anionic oxy-Cope rearrangement reactions reveals that in some systems[8] the pseudoequatorial oxyanionic bond is required in the chairlike transition states and in others[9] the chairlike conformation dictates the pseudoaxial oxyanionic bond. Most of these cases involve rather specialized types of substrates, and they do not answer the question on this fundamentally important facet of the rearrangement.

In 1990, we reported[10] the conversion of the allylic alcohol (*R*)-**1** to the aldehyde (*S*)-**2** via anionic oxy-Cope rearrangement in the enantioselective synthesis of (+)-dihydromayurone (**3**) (Scheme 1). This was the first example in which a flexible substrate with a single stereogenic center at the carbinol carbon was successfully transformed into a product retaining high enantiomeric purity: the efficiency of chirality transfer was directly translated from the 98:2 equatorial/axial oxyanionic bond preference in the rearrangement. Pronounced equatorial preference for the oxyanionic bond was explained on stereoelectronic and steric grounds. Later, Paquette and co-workers found[11] that geometrically and optically pure (3*R*,5*E*)-1,5-heptadien-3-ol (**4**) and (3*R*,5*Z*)-1,5-heptadien-3-ol (**7**) undergo anionic oxy-Cope rearrangement with a 57–61% preference for equatorial oxygen (Scheme 2). Their findings indicate that in the absence of steric constraints the chairlike transition state with a pseudoaxial oxyanionic bond is energetically comparable to the alternative conformation with a pseudoequatorially oriented oxyanionic bond. We further studied the behavior of several other substrates **10–15** (Figure 1) with a single stereogenic center in the anionic oxy-Cope rearrangement, and a better understanding of factors influencing the orientational preference of oxyanionic bond in the tran-

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(1) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 503–572. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 785–826. (c) Paquette, L. A. *Angew. Chem.* **1990**, *102*, 642; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609. (d) Paquette, L. A. *Synlett* **1990**, 67.

(2) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(3) One nonanionic example of reversible oxy-Cope rearrangement was reported: Elmore, S. W.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 319.

(4) (a) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (b) Gajewski, J. J.; Jimenez, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 468. (c) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198.

(5) (a) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107. (b) Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265. (c) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.* **1991**, *56*, 912.

(6) Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1025.

(7) Gajewski, J. J.; Gee, K. R. *J. Am. Chem. Soc.* **1991**, *113*, 967.

(8) (a) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (b) Clive, D. L. J.; Russel, G. C.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632.

(9) Koreeda, M.; Tanaka, Y.; Schwartz, A. J. *J. Org. Chem.* **1980**, *45*, 1172.

(10) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260.

(11) (a) Paquette, L. A.; Maynard, G. D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1368. (b) Paquette, L. A.; Maynard, G. D. *J. Am. Chem. Soc.* **1992**, *114*, 5018.

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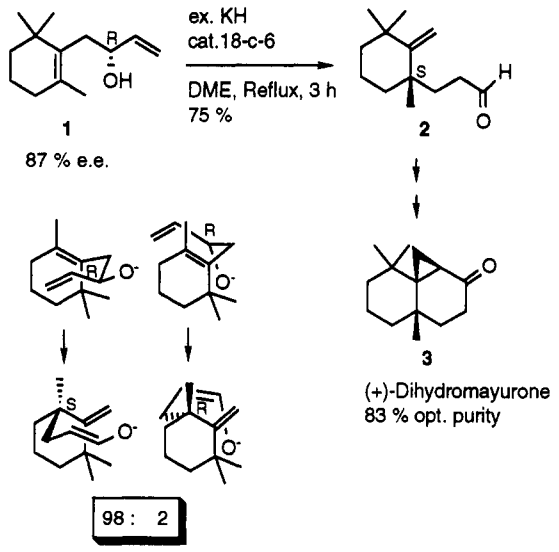
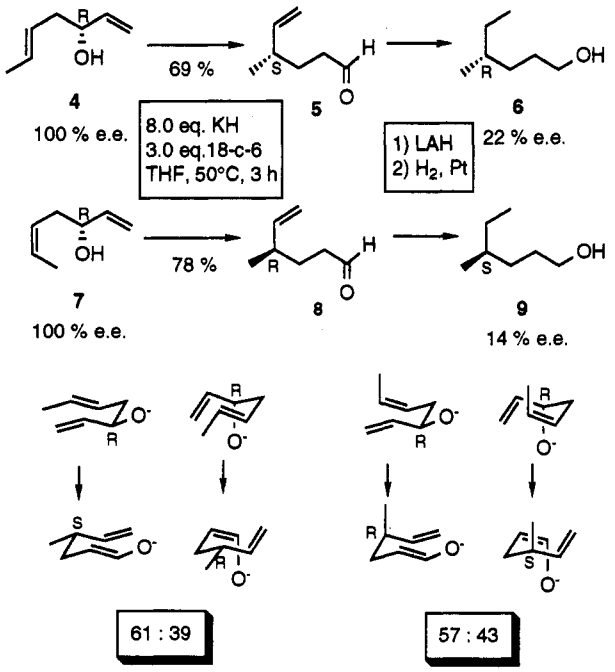
Scheme 1



Scheme 2



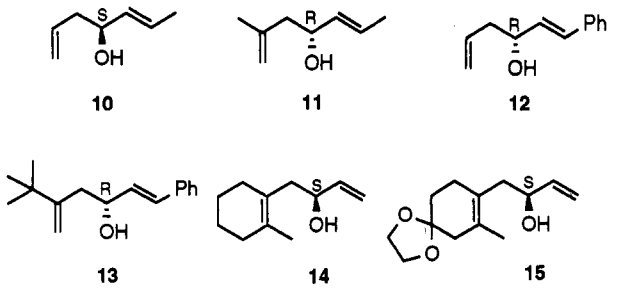
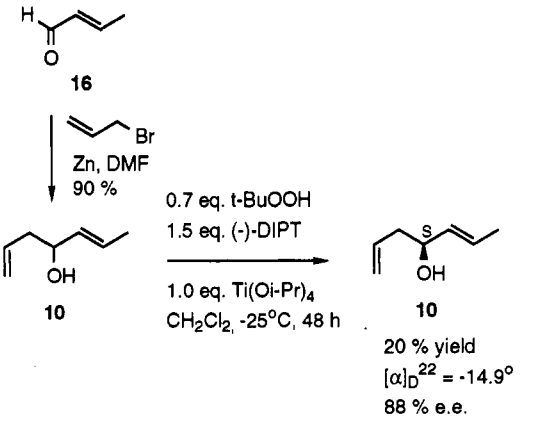
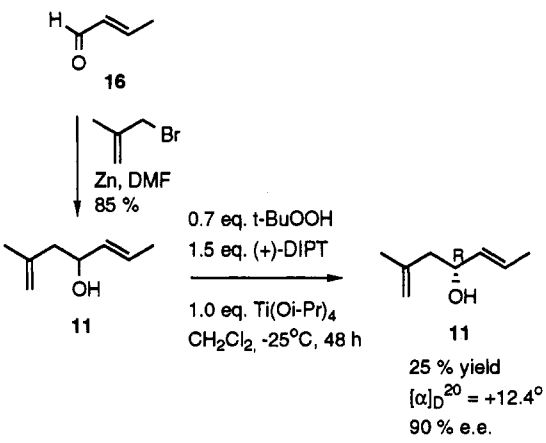


Figure 1.

Scheme 3



Scheme 4



sition states has now been achieved from the results reported here.

Results and Discussion

Synthesis of Substrates. Racemic (*E*)-1,5-heptadien-4-ol (**10**) was prepared in high yield by the reaction of crotonaldehyde (**16**) with allylzinc bromide. Subsequent kinetic resolution according to Sharpless protocol[12] using (−)-DIPT yielded enantiomerically enriched (*S*)-**10**. The absolute stereochemical assignment was based on the known stereochemical features of Sharpless kinetic resolution (Scheme 3). Enantiomeric excess of this sample (88% ee) was determined by NMR analysis of the (*S*)-*O*-acetyl mandelate (AMA) derivative:[13] in the ^{1}H-NMR spectrum of the (*S*)-AMA ester, allylic methyl proton signals appeared at δ 1.53 (94%) and δ 1.64 (6%), which also confirm the absolute stereochemical assignment.[14]

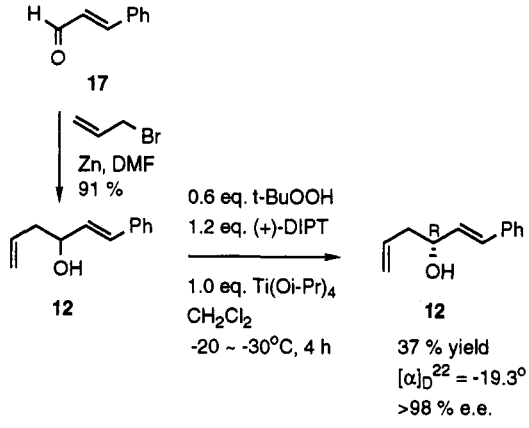
Racemic (*E*)-2-methyl-1,5-heptadien-4-ol (**11**) was synthesized from **16** and methyallyzinc bromide, and (*R*)-**11** (90% ee) was obtained by kinetic resolution mediated by (+)-DIPT (Scheme 4). The most characteristic features in the ^{1}H-NMR spectrum of the (*S*)-AMA ester were split

(12) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

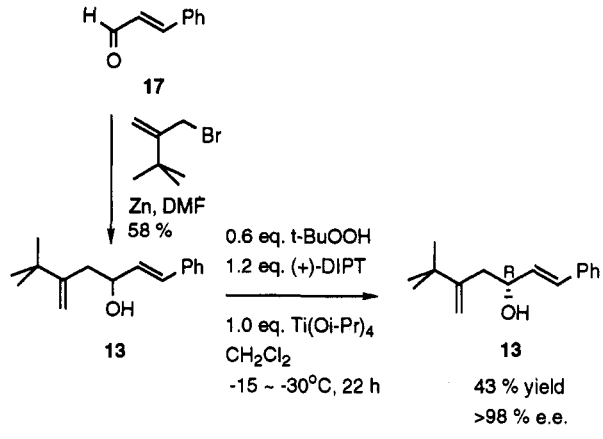
(13) For preparation of *O*-acetylmandelic acid, see: Thayer, F. K. *Organic Syntheses*; Wiley: New York, 1968; Collect. Vol. I, p 12.

(14) For details of NMR correlation rules, see: Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, pp 125–152. We used slightly modified conformational model in which the C–H bond of (*S*)-AMA is oriented antiperiplanar to the C=O bond in light of the recent crystal structure determination of an AMA derivative. See: Smith, A. B., III; Konopelski, J. P.; Wexler, B. A.; Sprengeler, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 3533. The carbinyl hydrogen of the carbinol moiety eclipses the ester carbonyl carbon. In this conformation, relatively upfield ^{1}H-NMR signals are obtained from hydrogens attached to the groups which are in the same side as the phenyl group. Identical results are obtained from this modified conformational correlation model and from the original one for *O*-methyl mandelate esters, in which the methoxy group and the carbonyl oxygen are held in an eclipsed arrangement. This correlation rule is thus very useful in confirming absolute stereochemical assignment of secondary alcohols but fails to function for primary alcohols carrying remote chiral centers.

Scheme 5



Scheme 6



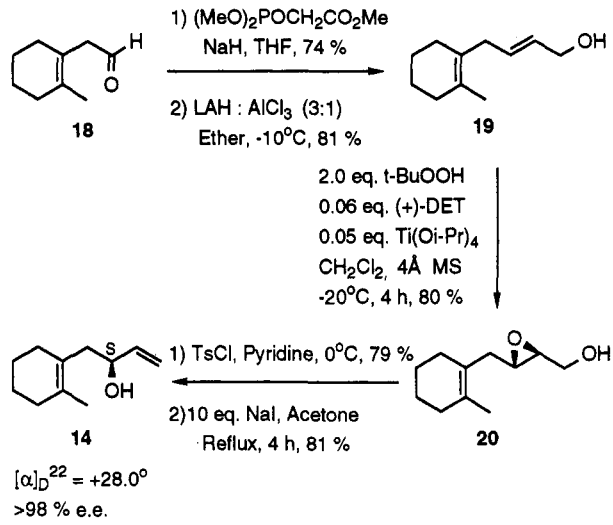
singlets for the methyl group of the isopropenyl moiety, δ 1.52 (95%) and δ 1.72 (5%). This is consistent with the pattern predicted for the (*R*)-enriched isomer by the NMR correlation rule.

Reaction of cinnamaldehyde (**17**) and allylzinc bromide yielded racemic (*E*)-1-phenyl-1,5-hexadien-3-ol (**12**), and kinetic resolution using (+)-DIPT readily afforded an enantiomerically pure sample of (*R*)-**12** (Scheme 5). The ^{1}H-NMR spectrum of the (*S*)-AMA ester showed only one doublet at δ 6.58 for the vinylic proton at Cl, and the alternative doublet at δ 6.28 was not detected.

2,3,3-Trimethyl-1-butene was reacted with *N*-bromosuccinimide in carbon tetrachloride under reflux to yield the primary bromide. This bromide was reacted with **17** in the presence of zinc dust and racemic (*E*)-5-*tert*-butyl-1-phenyl-1,5-hexadien-3-ol (**13**) was obtained. Kinetic resolution with (+)-DIPT afforded an enantiomerically pure sample of (*R*)-**13** (Scheme 6). In the ^{1}H-NMR spectrum of the (*S*)-AMA ester, the *tert*-butyl singlet signal appeared at δ 0.93 and the alternative signal at δ 1.07 was absent, confirming the assignment of the absolute stereochemistry.

The aldehyde **18**[15] served well as the starting material for the synthesis of the enantiomerically enriched allylic alcohol (*S*)-**14** (Scheme 7). Horner–Emmons reaction on **18** and reduction of the product yielded the primary allylic

Scheme 7



alcohol **19**, which was converted into the enantiomerically enriched epoxy alcohol **20** via Sharpless asymmetric epoxidation[16] mediated by (+)-DET. When the corresponding tosylate was reacted with excess sodium iodide, (*S*)-**14** was obtained directly.[17] Only one (relatively low field) signal was present in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester, and the alternative signal (0.11 ppm upfield)[18] was not detected, establishing that this was essentially enantiomerically pure sample.

Enantiomerically enriched allylic alcohol (*S*)-**15** was synthesized from the allylic alcohol **21**[19] (Scheme 8). Swern oxidation and Wittig olefination afforded the diene **22**, which was converted to the alcohol **23** via a hydroboration–oxidation sequence. The aldehyde **24**, obtained from **23** by Swern oxidation, was then used as the starting material in the established series of reactions to yield an enantiomerically enriched sample of (*S*)-**15** via the allylic alcohol **25** and the epoxy alcohol **26**. The ^{1}H-NMR spectrum of the (*S*)-AMA ester exhibited two vinylic proton signals centered at δ 5.65 (89%) and δ 5.83 (11%), confirming the absolute stereochemistry and establishing the enantiomeric purity (78% ee).

Reaction of (*S*)-10. Treatment of a sample of (*S*)-**10** (79% ee) with excess potassium hydride and 0.5 equiv of 18-c-6 in THF under reflux for 2 h produced the aldehyde **27** in 61% yield, which was reduced to 3-methyl-5-hexen-1-ol (**28**) (Scheme 9). The (*S*)-AMA ester of this sample of **28** exhibited methyl doublets at δ 0.81 (54%) and δ 0.84 (46%) in the ^{1}H-NMR spectrum, establishing the enantiomeric purity (8% ee). An unambiguous absolute stereochemical assignment was made via correlation with known (*S*)-(−)-citronellol (**29**, 60% optical purity, purchased from Aldrich). The acetate of **29** was epoxidized to afford the epoxy acetate **30**, which was converted to the allylic alcohol **31**[20] via selenohydrin synthesis, selenoxide elimination, and reprotection by TBS chloride. Ruthenium(IV) oxide cleavage[21] of **31** yielded the aldehyde **32**,

(15) Methyl 2-methylcyclohexenecarboxylate was synthesized from methyl 2-oxocyclohexanecarboxylate via known procedures. See, for example: (a) Weiler, L.; Sum, F. W. *Can. J. Chem.* **1979**, *57*, 1431. (b) Fulmer, T. D.; Bryson, T. A. *J. Org. Chem.* **1989**, *54*, 3496. The aldehyde **18** was synthesized from methyl 2-methylcyclohexenecarboxylate by LAH reduction, Swern oxidation, Wittig methoxyolefination, and acidic hydrolysis.

(16) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(17) Excess iodide obviously worked as a reducing agent in this case.

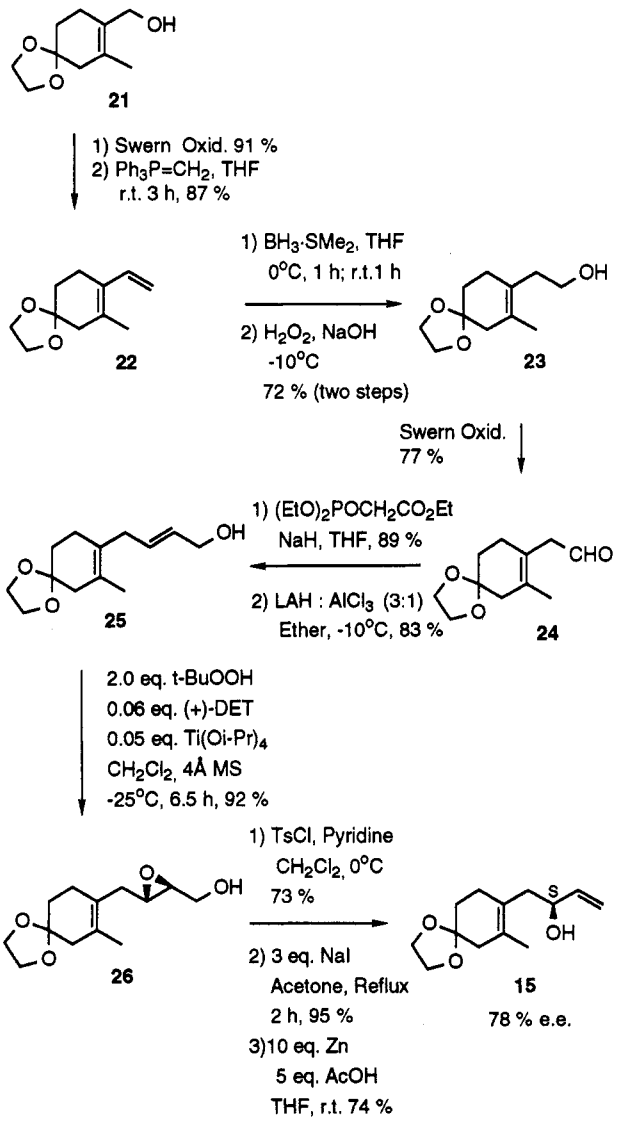
(18) Determined from the ^{19}F-NMR spectrum of the (*R*)-MTPA ester of racemic **14**.

(19) The ketal alcohol **21** was synthesized from Hageman's ester via ketal formation and LAH reduction.

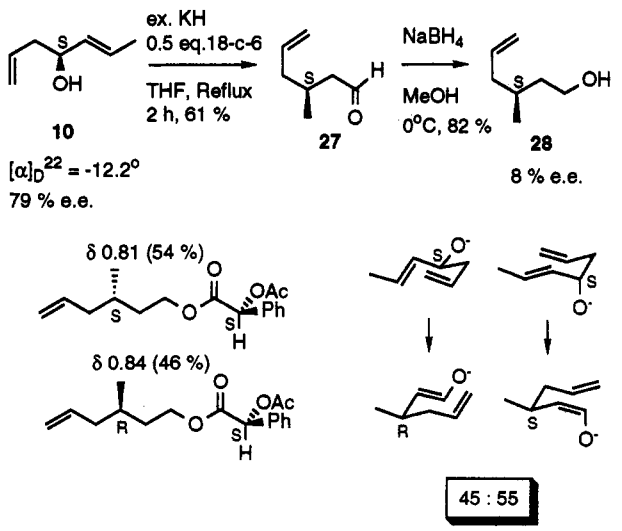
(20) Mori, K.; Sugura, T.; Uchida, M. *Tetrahedron* **1978**, *34*, 3119.

(21) Carlsen, P. M.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

Scheme 8

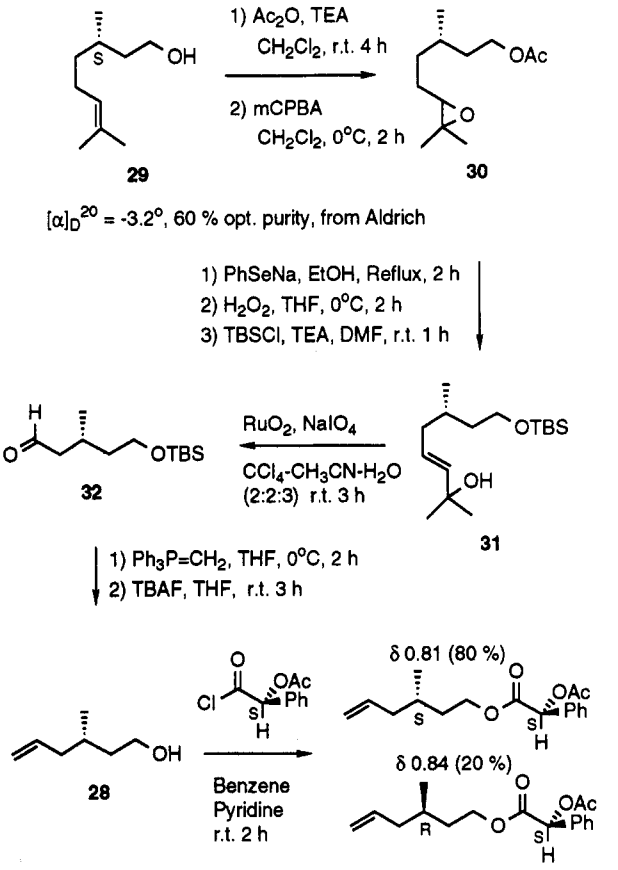


Scheme 9

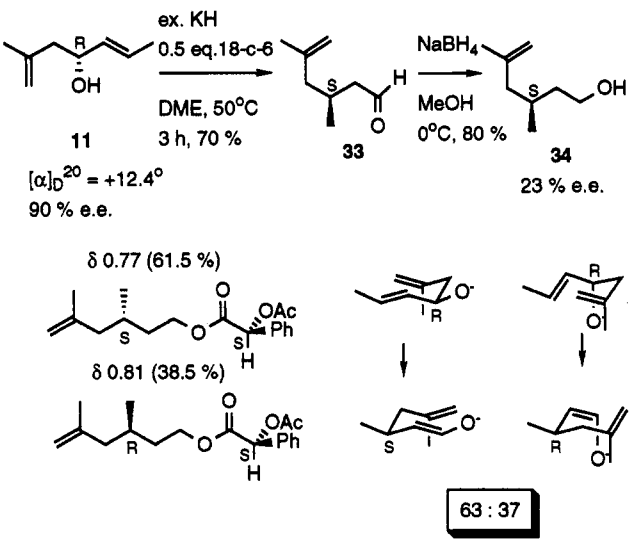


from which the alcohol **28** was synthesized by Wittig olefination and deprotection. In the ^{1}H-NMR spectrum of the (*S*)-AMA ester of this sample of the alcohol **28**, two doublets at δ 0.81 (80%) and δ 0.84 (20%) were present (Scheme 10). Thus, it follows that the original sample of the alcohol **28** is enriched with the (*S*)-isomer, which in

Scheme 10



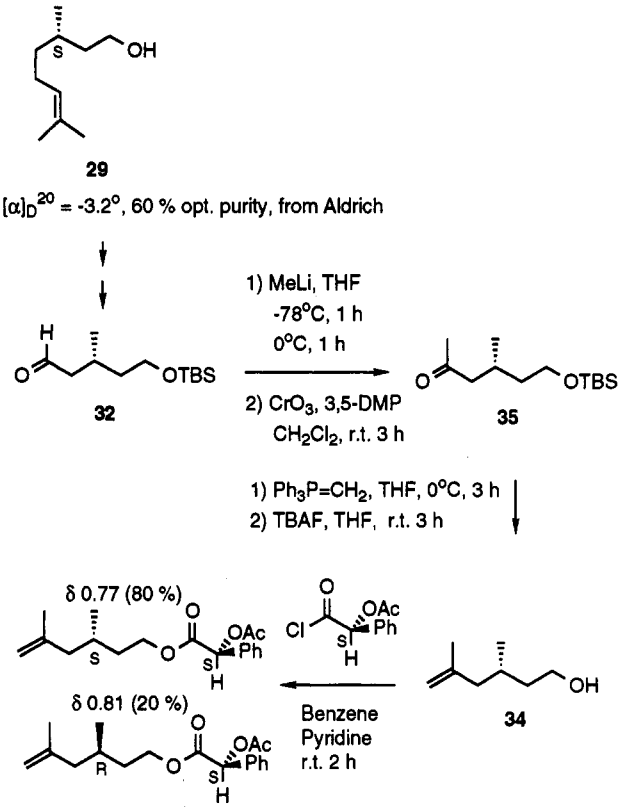
Scheme 11



turn requires that the aldehyde (*S*)-**27** (8% ee) is produced from the rearrangement. A simple calculation leads to the conclusion that there was 45:55 equatorial/axial oxyanionic bond orientation in the chairlike transition state for the rearrangement of (*S*)-**10**.

Reaction of (*R*)-11. A DME solution of (*R*)-**11** (90% ee) was heated for 3 h at 50 °C in the presence of excess potassium hydride and 0.5 equiv of 18-c-6. The aldehyde **33** was obtained in 70% yield, and 3,5-dimethyl-5-hexen-1-ol (**34**) was synthesized by sodium borohydride reduction (Scheme 11). In the ^{1}H-NMR spectrum of the (*S*)-AMA ester, two methyl doublets were evident at δ 0.77 (61.5%) and δ 0.81 (38.5%), which established the enantiomeric purity (23% ee). Absolute stereochemical assignment was

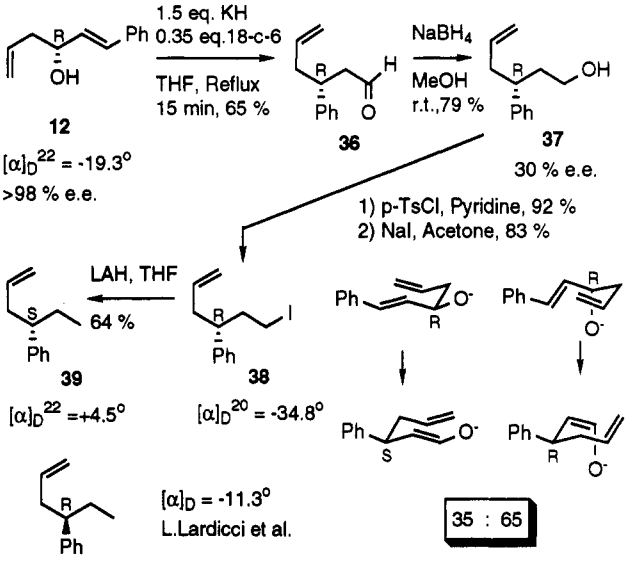
Scheme 12



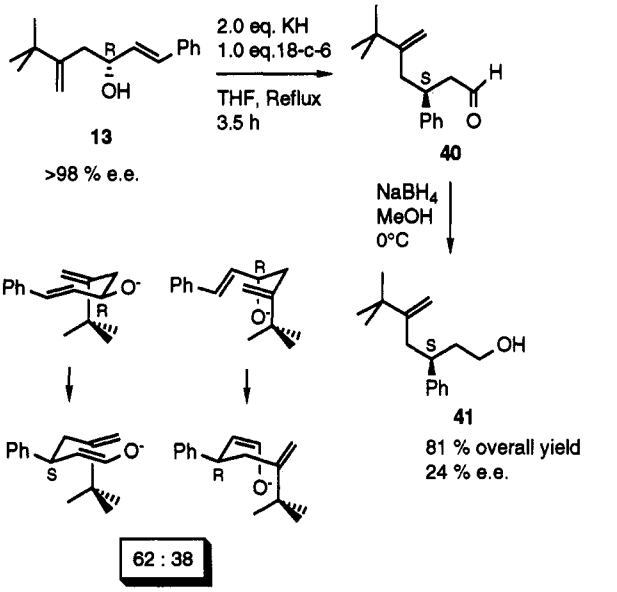
carried out again by correlation with (*S*)-(−)-citronellol. Thus, the intermediate **32** was reacted with methyllithium, and the product was oxidized to give the ketone **35**. Wittig olefination and deprotection led to the preparation of **34**, of which (*S*)-AMA ester exhibited methyl doublets at δ 0.77 (80%) and δ 0.81 (20%) in the ^{1}H-NMR spectrum (Scheme 12). The original sample of **34** was evidently enriched with the (*S*)-isomer, and it is clear that the anionic oxy-Cope rearrangement of (*R*)-**11** (90% ee) led to the production of (*S*)-**33** (23% ee). In this case, equatorial/axial ratio of 63:37 can be calculated for the transition-state orientation of the oxyanionic bond.

Reaction of (*R*)-12. A sample of enantiomerically pure (*R*)-**12** was dissolved in THF containing 1.5 equiv of potassium hydride and 0.35 equiv of 18-c-6, and the suspension was heated under reflux for 15 min. 3-Phenyl-5-hexenal (**36**) was isolated in 65% yield, which was converted to the 3-phenyl-5-hexen-1-ol (**37**) by borohydride reduction. This sample of **37** was converted to the iodide **38** which in turn was transformed into a dextrorotory sample of 4-phenyl-1-hexene (**39**) via lithium aluminum hydride reduction. Since the levorotarory 4-phenyl-1-hexene is known to have the (*R*) configuration,[22] the sample synthesized was enriched with the (*S*)-isomer, which requires that the original sample of the aldehyde **36** was enriched with the (*R*)-isomer. Since the ^{19}F-NMR spectrum of the (*R*)-MTPA ester of **37** did not exhibit split signals, the enantiomeric purity (30% ee) of **37** was determined via conversion to **42** (*vide infra*), and it was concluded that there is a 35:65 equatorial/axial oxygen preference in the chairlike transition state for the rearrangement of (*R*)-**12** (Scheme 13).[23]

Scheme 13



Scheme 14

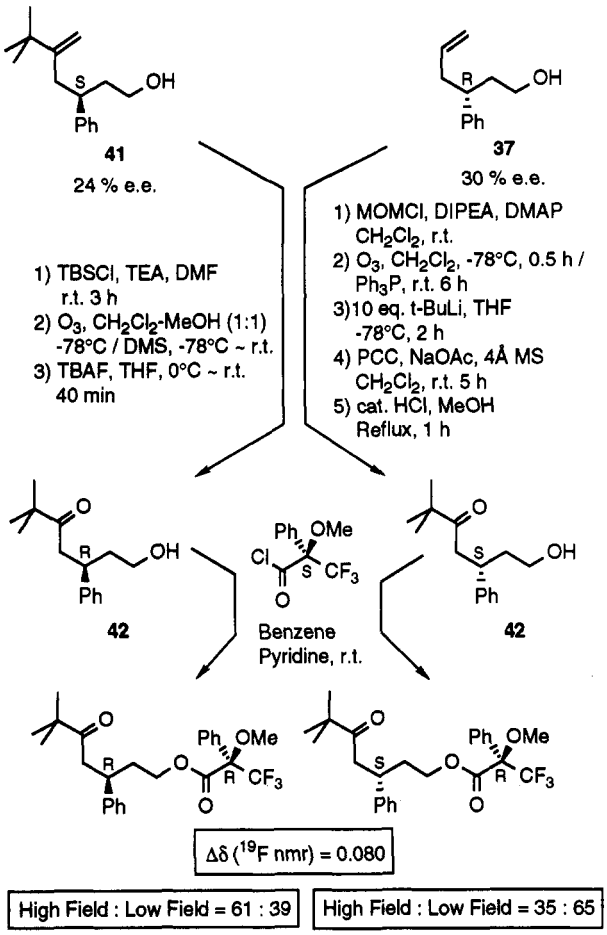


Reaction of (*R*)-13. A sample of enantiomerically pure (*R*)-**13** was dissolved in THF containing 2.0 equiv of potassium hydride and 1.0 equiv of 18-c-6, and the solution was heated under reflux for 5 h to yield 5-*tert*-butyl-3-phenyl-5-hexenal (**40**), which was promptly converted to 5-*tert*-butyl-3-phenyl-5-hexen-1-ol (**41**) by borohydride reduction. This sample of **41** was converted into the corresponding (*R*)-MTPA ester, which exhibited two signals separated by 0.101 ppm (high field:low field = 62:38) in the ^{19}F-NMR spectrum, from which the enantiomeric purity (24% ee) was calculated (Scheme 14). The sample of **41** obtained here was converted into the TBS ether, which was subjected to ozonolysis conditions. Fluoride deprotection led to the formation of the keto alcohol **42**, of which the (*R*)-MTPA ester exhibited two ^{19}F-NMR signals separated by 0.080 ppm (high field:low field = 61:

(22) (a) Lardicci, L.; Menicagli, R.; Salvadori, P. *Gazz. Chim. Ital.* **1968**, *98*, 738. (b) Menicagli, R.; Lardicci, L. *Chem. and Ind.* **1971**, *25*, 1490.

(23) The rearrangement could also be carried out in benzene. In this case, more than 1 equiv of 18-c-6 was used and the reaction proceeded smoothly at room temperature to yield the aldehyde **36** (83% yield in 2 h). But the efficiency of chirality transfer did not depend on the solvents used: the sample of the iodide **38** obtained from **36** this time had a specific rotation (−35.8°) which was very close to the value already obtained (−34.8°).

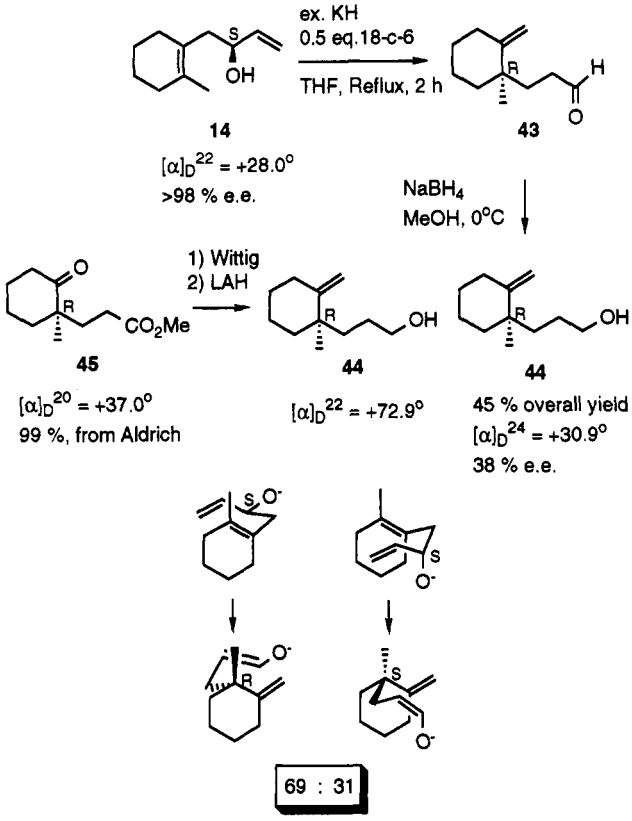
Scheme 15



39). For comparison, a sample of (*S*)-enriched **42** was synthesized from (*R*)-**37** which was obtained from (*R*)-**12** (*vide supra*). The MOM ether of (*R*)-**37** was subjected to ozonolysis, t-BuLi addition, PCC oxidation, and acidic hydrolysis reactions leading to a sample of (*S*)-enriched **42**. Its (*R*)-MTPA ester exhibited two ^{19}F-NMR signals as above but in an opposite ratio (high field:low field = 35:65) (Scheme 15). Clearly, (*R*)-**42** was obtained from (*S*)-**41**, and (*S*)-**40** was the product of anionic oxy-Cope rearrangement of (*R*)-**13**. It is concluded that there was 62:38 equatorial/axial oxyanionic bond preference in the chairlike transition state for the rearrangement of (*R*)-**13**.

Reaction of (*S*)-14. A THF solution of enantiomerically pure sample of (*S*)-**14** containing excess potassium hydride and 0.5 equiv of 18-c-6 was heated under reflux for 2 h. The product aldehyde **43** was quickly reduced to the dextrorotatory alcohol **44** in 45% overall yield. The enantiomeric purity of this sample (38% ee) was determined by analyzing the ^{19}F-NMR spectrum of its (*R*)-MTPA ester: two signals were present separated by 0.05 ppm (high field:low field = 31:69). The absolute stereochemical determination was carried out by correlation with commercially available (*R*)-(+)-keto ester **45** (99%, purchased from Aldrich). Wittig olefination of (*R*)-**45** and subsequent lithium aluminum hydride reduction yielded (*R*)-**44**, which was dextrorotatory. Thus, the original sample of the alcohol **44** was enriched with the (*R*)-isomer and (*R*)-isomer enriched sample of the aldehyde **43** was produced from (*S*)-**14**. Routine calculation leads to a 69:31 equatorial/axial oxyanionic bond orientation ratio in the transition state for the rearrangement of (*S*)-**14** (Scheme 16).

Scheme 16

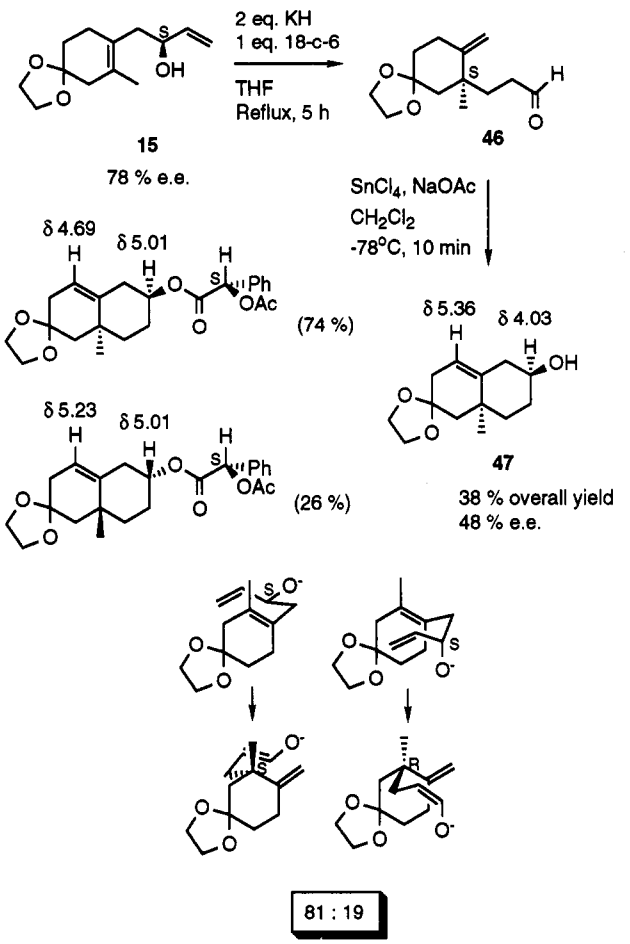


Reaction of (*S*)-15. A sample of (*S*)-**15** (78% ee) was dissolved in THF, and the solution was heated under reflux for 5 h after addition of 2 equiv of potassium hydride and 1 equiv of 18-c-6. The aldehyde **46** obtained was relatively unstable and reacted immediately with stannic chloride in dichloromethane at −78 °C for 10 min to yield the bicyclic ketal alcohol **47** (Scheme 17). This ketal alcohol **47** exhibited ^{1}H-NMR spectral features reminiscent of those of 3-epicholesterol (**49**) rather than those of cholesterol (**48**), establishing the relative stereochemistry. In the ^{1}H-NMR spectrum of the (*S*)-AMA ester of **47**, two vinylic proton signals at δ 4.69 (74%) and δ 5.23 (26%) were clearly seen, and the enantiomeric purity (48% ee) could be determined with ease. Absolute stereochemical assignment was possible by comparing with 3-epicholesterol derivatives. In the event, 3-epicholesterol (**49**), synthesized from cholesterol (**48**) via Mitsunobu reaction and hydrolysis, was converted to the (*S*)-AMA ester, which exhibited the vinylic proton signal at δ 5.29 (Scheme 18). Thus, it can be safely concluded that the original sample of the ketal alcohol **47** was enriched with the isomer which is enantiomeric with the corresponding part of 3-epicholesterol, and the original rearrangement product aldehyde **46** must be enriched with the (*S*)-isomer. A simple calculation leads to an 81:19 ratio for equatorial/axial orientation of oxyanionic bond in the chairlike transition state.

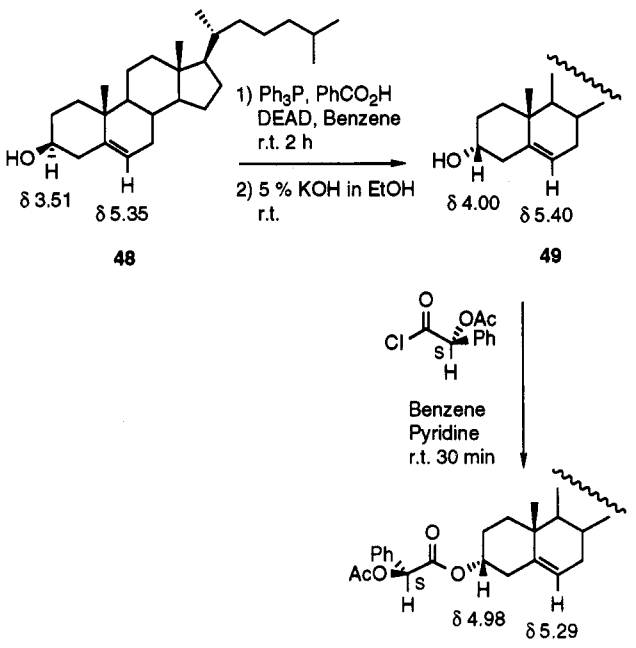
Discussion

Recently, reports on the detailed stereochemical consequenses of anionic oxy-Cope rearrangement of various substrates appeared in the literature. Aside from the examples stated in the introduction, they all deal with substrates which possess two or more chiral centers, and the fundamental question on the equatorial/axial pref-

Scheme 17



Scheme 18



erence of oxyanionic bond in the chairlike transition state can hardly be answered even after careful analysis of the opposing or reinforcing factors.

Stereochemical discussions are absent in some earlier examples with secondary alcohols.[24] In a fascinating study on the rearrangement of diastereomers of 5-(5-fluoroadamant-2-ylidene)-4-hydroxy-4-phenyl-1-pentene,[25] le Noble concluded that the preferred site of the phenyl group in the chair transition states is the quasiequatorial one (and hence the quasiaxial site for the oxide anion) and that the electronically preferred face of the adamantyl terminus is that syn to the fluorine. These preferences amount to factors of 2.75 and 1.54, respectively. It would be difficult to transpose the results of these particular tertiary alcohols for prediction on the prototype secondary allylvinylcarbinol system. This is an example in which π-facial selectivity on the double bond at the vinyl part of the substrate was clarified. π-Facial selectivity in regard to the double bond at the allyl part of the substrate was studied in detail by Paquette[11] using secondary allyl vinyl alcohols fused with 4-*tert*-butylcyclohexene, norbornene, and 1,7,7-trimethylnorbornene. In these cases, equatorial oxyanionic bond orientation appears to be favored, and substrates with the structure which can satisfy the usual axial bond formation (for 4-*tert*-butylcyclohexene system), exo bond formation (for norbornene system), and endo bond formation (for 1,7,7-trimethylnorbornene system) with equatorial oxyanionic bond tend to rearrange in much better stereoselectivity. Acyclic diastereocontrol and asymmetric transmission in anionic oxy-Cope rearrangement of stereochemically-defined 3-methyl-1,5-heptadien-4-ols were recently reported by Nakai.[26] If an alkyl substituent were added to the position adjacent to the hydroxyl-bearing carbon in the *erythro* configuration, the oxyanion substituent could be directed to the pseudoequatorial position in the associated transition states by virtue of the equatorial preference for the added alkyl group. Their results also stipulate that (*Z*)-alkyl substitution at the vinyl terminus stabilizes chairlike transition states with pseudoequatorial oxyanionic bond since in the alternative conformation there should be steric crowding between pseudoaxial oxide anion and the alkyl substituent: (*Z*)-*erythro*-3-methyl-1,5-heptadien-4-ol was thus the isomer which rearranged with highest stereoselectivity (Scheme 19).

The most salient feature of the present study is that chairlike transition states with pseudoaxial oxyanionic bond are favored in the rearrangement of simplest substrates, (*E*)-1,5-heptadien-4-ol (**10**) and (*E*)-1-phenyl-1,5-hexadien-3-ol (**12**). Alkyl substitution at C5 of the basic 1,5-hexadien-3-ol skeleton then reverses the trend, and substrates like (*E*)-2-methyl-1,5-heptadien-4-ol (**11**) and (*E*)-5-*tert*-butyl-1-phenyl-1,5-hexadien-3-ol (**13**) are more apt to rearrange via transition states with a pseudoequatorial oxyanionic bond. When the results for the ring-fused substrates like **14** and **15** are compared with the previous one for **1**, one can see the trend more clearly: with the bigger substituents at C5, the chairlike transition states with the equatorial oxyanionic bond become more favorable.

It is now possible to address factors governing the stereochemical outcome of anionic oxy-Cope rearrangement of acyclic substrates.

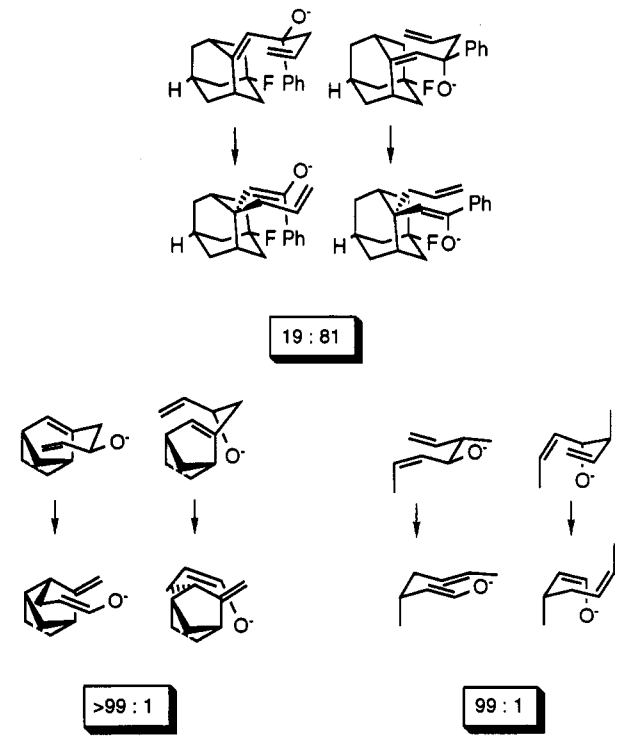
(1) There is a moderate stereoelectronic bias for the pseudoaxial oxyanionic bond in the chairlike transition

(24) (a) Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *80*, 4719. (b) Truesdale, L. K.; Swanson, D.; Sun, R. C. *Tetrahedron Lett.* **1985**, *26*, 5009. (c) Enholm, E. J.; Satici, H.; Prasad, G. *J. Org. Chem.* **1990**, *55*, 324.

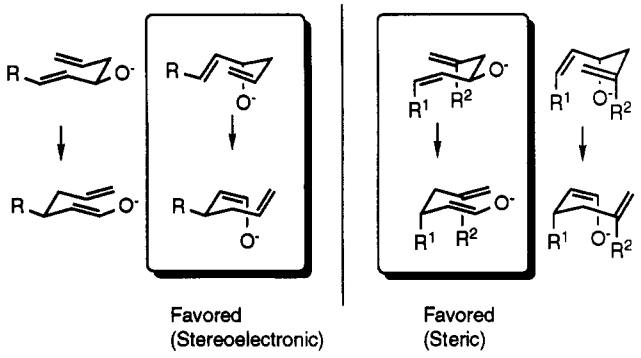
(25) (a) Lin, M.-H.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 997. (b) Lin, M.-H.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1990**, *55*, 3597.

(26) (a) Tomooka, K.; Wei, S.-Y.; Nakai, T. *Chem. Lett.* **1991**, 43. (b) Wei, S.-Y.; Tomooka, K.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 5973.

Scheme 19



Scheme 20



states for the rearrangement of substrates with (*E*)-alkyl and -aryl substituents at C1 of the 1,5-hexadien-3-ol system.

(2) Chairlike transition states with pseudoequatorial oxyanionic bond become more favorable upon (*Z*)-alkyl substitution at C1 and alkyl substitution at C5 of the acyclic 1,5-hexadien-3-ol system as these substituents will generate significant steric congestion in the transition states with pseudoaxial oxyanionic bond. Very efficient chirality transfer via transition states with pseudoequatorial oxyanionic bond is possible with substrates carrying sterically-demanding groups on those sites.

(3) As expected, alkyl substituents at C4 tend to be oriented pseudoequatorially in the absence of overriding steric effects specified in 2. When various substituents are introduced at double bond sites (C1, 2, 5, and 6) for induction of π-facial differentiation, the expected π-facial stereoselection is manifested in conjunction with the steric effects specified in 2.

The above analysis is graphically demonstrated in Scheme 20. The steric factors mentioned above are not difficult to understand. The most fascinating part of the result is the stereoelectronic bias for the pseudoaxial oxyanionic bond in the rearrangement of **10** and **12**. It is now clear that efficient chirality transfer in the rearrangement of **1**[10] via the transition state with the pseudoequatorial oxyanionic bond derives from steric effects overriding modest stereoelectronic bias.

As mentioned earlier, theoretical studies on these rearrangements propose highly dissociative transition states with the negative charge primarily on the oxygen atom.[6] The chairlike transition state with a pseudoaxial oxyanionic bond may then be described by an s-cis acrolein anion radical moiety interacting with an allyl radical on the way to a (*Z*)-enolate of the product aldehyde. The n electrons on the oxygen atom are known to facilitate homolytic cleavage of the adjacent bond,[27] and they may also better promote bond formation at the allylic site via syn conformation. The "syn effect" is a well-documented phenomenon.[28] The known thermodynamic preference[28f,29] for (*Z*)-enolates for aldehydes (and ketones) compared to (*E*) counterparts may also be used in explaining this intriguing stereoelectronic effect.

Conclusion

There appears to be a modest stereoelectronic bias for pseudoaxial oxyanionic bond in the chairlike transition states of anionic oxy-Cope rearrangement of acyclic 1,5-hexadien-3-ol systems with an (*E*)-1-alkyl or aryl substituent. Chairlike transition states with a pseudoequatorial oxyanionic bond are more favorable in the rearrangement of substrates with a (*Z*)-1- or -5-alkyl substituent as steric effects become more important.

Experimental Section

NMR spectra were obtained on Varian EM-360 (60 MHz), Bruker AC-80 (80 MHz), Varian VXR-200 (200 MHz), and JEOL SX-500 (500 MHz) spectrometers. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated and coupling constants as hertz. IR spectra were taken on a Perkin-Elmer Model 782 spectrometer. Mass spectra were measured on a JEOL JMS GSX-300 spectrometer. Optical rotation data were obtained on a JASCO DIP360 polarimeter with the Na D line.

The progress of reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under UV254 light and/or charring after dipping the TLC plate into vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated sulfuric acid in 300 mL of methanol). Column chromatography was performed on silica gel (Merck 7734 or 9385 Kiesel gel 60) using hexane/ethyl acetate (v/v) unless otherwise noted.

Titanium(IV) isopropoxide, (+)-diethyl L-tartrate, (+)-diisopropyl L-tartrate, and (−)-diisopropyl D-tartrate were purchased from Aldrich. *tert*-Butyl hydroperoxide (3.0 M in isooctane) was purchased from Aldrich and used as a solution in isooctane after azeotropic removal of water.

(*E*)-1,5-Heptadien-4-ol (10). To a stirred solution of crotonaldehyde (3.57 g, 50.9 mmol) and allyl bromide (8.0 g, 66 mmol) in 50 mL of DMF was added zinc powder (5.0 g, 76 mmol) at

(27) (a) Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3319. (b) Steigerwald, M. L.; Goddard, W. W., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994.

(28) For examples of possible homoaromatic stabilization of the syn configuration, see: (a) Cremer, D. *J. Am. Chem. Soc.* **1979**, *101*, 7199. (b) Block, E.; Penn, R. E.; Bazzi, A. A. *Tetrahedron Lett.* **1981**, *22*, 29. (c) Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.-A.; Wall, A. *J. Am. Chem. Soc.* **1986**, *108*, 4568. For different interpretations, see below and references cited therein: (d) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426. (e) Larson, J. R.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1978**, *100*, 5713. (f) Bond, D.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1003.

(29) Spears, G. W.; Caufield, C. E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 1226.

room temperature. An exothermic reaction started within 10 min and was allowed to proceed for 30 min. The reaction mixture was poured into a saturated NH_4Cl solution and extracted with ether (50 mL × 2). The combined organic layer was washed with 2 N HCl, water, and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by distillation under reduced pressure to give the secondary allylic alcohol **10** (5.14 g, 90% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.62 (d, 3H, J = 5.1 Hz), 2.09–2.29 (m, 3H), 4.02 (q, 1H, J = 5.9 Hz), 4.93 (m, 1H), 5.11 (m, 1H), 5.45–6.01 (m, 3H); IR (neat) 3100–3600, 3080, 2910, 1675, 1640, 1440, 1030, 960, 910 cm^{-1}.

(*E*)-2-Methyl-1,5-heptadien-4-ol (11). The reaction of crotonaldehyde and methallyl bromide by the sample procedure as that for **10** afforded the secondary allylic alcohol **11** in 85% yield. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.65–1.78 (m, 7H), 2.22 (d, 2H, J = 6.3 Hz), 4.20 (q, 1H, J = 6.4 Hz), 4.78–4.87 (m, 2H), 5.33–5.88 (m, 2H).

(*E*)-1-Phenyl-1,5-heptadien-3-ol (12). The reaction of cinnamaldehyde and allyl bromide by the same procedure as that for **10** gave the alcohol **12** in 91% yield. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.77 (s, 1H), 2.31–2.49 (m, 2H), 4.34 (q, 1H, J = 5.8 Hz), 5.04–5.29 (m, 2H), 5.62–6.72 (m, 3H), 7.20–7.40 (m, 5H).

(*E*)-5-*tert*-Butyl-1-phenyl-1,5-hexadien-3-ol (13). In a 50-mL two-necked round-bottom flask fitted with a reflux condenser were placed 2,3,3-trimethyl-1-butene (1.6 g, 0.016 mmol), 30 mL of CCl_4, NBS (2.9 g, 0.016 mmol), and a catalytic amount of benzoyl peroxide. The solution was heated under reflux for 6 h under nitrogen atmosphere. Succinimide was filtered off from the cold reaction mixture and washed with CCl_4. The combined CCl_4 solution was washed with aqueous $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting bromide (2.1 g, 72% yield) was used directly for the reaction with cinnamaldehyde.

Cinnamaldehyde was reacted with allylic bromide obtained above by the same procedure as above to afford the alcohol **13** in 58% yield. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.10 (s, 9H), 2.01 (br s, 1H), 2.31–2.35 (m, 1H), 2.41 (s, 1H), 4.49 (q, 1H, J = 7.4 Hz), 4.90 (d, 1H, J = 1.0 Hz), 5.07 (s, 1H), 6.23 (dd, 1H, J = 16 and 5.8 Hz), 6.65 (d, 1H, J = 16 Hz), 7.19–7.45 (m, 5H). MS m/z (EI, relative intensity): 230 (M^+, 4), 212 (14), 197 (14), 156 (11), 155 (42), 154 (12), 153 (14), 133 (85), 128 (15), 115 (37), 105 (14), 91 (100), 77 (27), 57 (22), 55 (24), 41 (20).

(*S*)-10 via Sharpless Kinetic Resolution. A solution of titanium(IV) tetraisopropoxide (6.0 mL, 20 mmol) and (−)-diisopropyl D-tartrate (6.3 mL, 30 mmol) in 200 mL of dry CH_2Cl_2 was cooled to −25 °C under nitrogen. After being stirred for 10 min, the racemic alcohol **10** (2.24 g, 20.0 mmol) in 5 mL of CH_2Cl_2 was slowly added. The reaction mixture was stirred for 30 min, and 3.0 M TBHP in isooctane (4.7 mL, 14 mmol) was slowly added. The resulting mixture was stirred at −25 °C for 48 h, and the reaction was quenched with 100 mL of water. The reaction mixture was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. Flash silica gel chromatography (4:1 pentane/ether eluant) afforded the unreacted allylic alcohol (*S*)-**10** (448 mg, 20% recovered): $[\alpha]^{22}_D$ = −14.9° (c = 0.71, CH_2Cl_2).

The enantiomeric excess was determined to be 88% by comparing the relative areas of the methyl peaks at δ 1.53 (94%) and δ 1.64 (6%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

(*R*)-11. (+)-Diisopropyl L-tartrate was used in the standard kinetic resolution procedure to recover 25% of (*R*)-**11**. $[\alpha]^{20}_D$ = +12.4° (c = 0.22, CH_2Cl_2).

The enantiomeric excess was determined to be 90% by comparing the relative areas of the methyl peaks at δ 1.72 (5%) and δ 1.52 (95%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

(*R*)-12. (+)-Diisopropyl L-tartrate was used to recover 37% of (*R*)-**12**. $[\alpha]^{22}_D$ = −19.3° (c = 1.33, ether).

The enantiomeric excess was determined to be over 98% by comparing the relative areas of the vinyl peaks at δ 6.58 (>99%) and δ 6.28 (<1%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

(*R*)-13. (+)-Diisopropyl L-tartrate was used to recover 43% of (*R*)-**13**.

The enantiomeric excess was determined to be over 98% by comparing the relative areas of the *tert*-butyl [illegible] (>99%) and δ 1.07 (<1%) in the ^{1}H-NMR spec[illegible] AMA ester.

4-(2′-Methyl-1′-cyclohexenyl)-2-buten-1-ol [illegible] phosphonoacetate (2.78 g, 9.75 mmol) was added dropwise to a slurry of 60% NaH (9.75 mmol) in 20 mL of THF at room temperature. The resulting solution was stirred for 1 h, and a solution of the aldehyde **18** (900 mg, 6.51 mmol) in 2 mL of THF was added at room temperature. The resulting pale yellow solution was stirred for 1 h, poured into 20 mL of saturated NH_4Cl solution, and extracted with ethyl acetate. The combined extract was washed with water and brine. After evaporation of the solvent, flash chromatography (20:1 Hex/EtOAc) afforded the α,β-unsaturated ester (936 mg, 74% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.53–1.60 (m, 7H), 1.94 (br s, 4H), 2.86 (dd, 2H, J = 6.4 and 1.6 Hz), 3.72 (s, 3H), 5.77 (dt, 1H, J = 15.5 and 1.6 Hz), 6.91 (dt, 1H, J = 15.5 and 6.4 Hz). IR (neat): 2900, 2810, 1715, 1640, 1425, 1320, 1260 cm^{-1}.

A two-necked round-bottom flask was fitted with a reflux condenser connected to a nitrogen line. In this flask were placed LAH (191 mg, 5.03 mmol) and $AlCl_3$ (224 mg, 1.68 mmol) in 20 mL of dry ether. After the mixture was stirred for 30 min at −10 °C, the α,β-unsaturated ester (700 mg, 3.36 mmol) was added slowly with vigorous stirring. The resulting mixture was stirred for 1 h, quenched with ice–water, and extracted with ether after addition of 2 N HCl solution. The combined organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, flash chromatography (5:1 Hex/EtOAc) afforded the allylic alcohol **19** (450 mg, 81% yield). ^{1}H-NMR (60 MHz, $CDCl_3$): δ 1.28–1.94 (m, 11H), 2.70–2.77 (m, 2H), 2.94 (s, 1H), 4.00–4.07 (m, 2H), 5.58–5.70 (m, 2H).

Epoxy Alcohol 20. An oven-dried two-necked round-bottom flask was charged with 100 mg of powdered, activated 4-Å molecular sieves and 1.5 mL of dry CH_2Cl_2 under nitrogen. The flask was cooled to −20 °C, and (+)-diethyl tartrate (30 mg, 1.14 mmol) and titanium(IV) isopropoxide (34 mg, 0.12 mmol) were added sequentially with stirring. The reaction mixture was stirred at −25 °C as 3.0 M TBHP in isooctane (4.8 mmol) was added through the septum. The resulting mixture was stirred for 30 min at −25 °C. The allylic alcohol **19** (400 mg, 2.4 mmol) in 1.5 mL of CH_2Cl_2 was then added dropwise through the syringe at −25 °C. The mixture was stirred for 4 h at −20 °C, allowed to warm to room temperature, and quenched with 1 mL of water. Hydrolysis of tartrate was effected by adding 0.5 mL of a 30% aqueous solution of NaOH saturated with NaCl. After 30 min of vigorous stirring, 30 mL of CH_2Cl_2 was added. The aqueous layer was extracted three times, and the combined extract was concentrated. Flash chromatography (6:1 Hex/EtOAc) afforded the epoxy alcohol **20** (351 mg, 80% yield). ^{1}H-NMR (60 MHz, $CDCl_3$): δ 1.51–2.24 (m, 11H), 2.75–2.94 (m, 2H), 3.08–3.29 (m, 2H), 3.49–3.73 (m, 2H).

(*S*)-4-(2′-Methyl-1′-cyclohexenyl)-1-buten-3-ol (14). *p*-TsCl (535 mg, 2.80 mmol) was added portionwise to a stirred and ice-cooled solution of the epoxy alcohol **20** (340 mg, 1.80 mmol) in 5 mL of pyridine. The mixture was left to stand overnight at 0–5 °C and then poured into ice–water and extracted with ether. The ether extract was washed with water, aqueous $CuSO_4$, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give crude product which was pure enough for the next step.

To the crude product in 20 mL of acetone was added NaI (2.7 g, 18 mmol) and the mixture was stirred and heated under reflux for 4 h. It was concentrated, diluted with water, and extracted with ether. The organic layer was washed with aqueous $Na_2S_2O_3$ solution, aqueous $NaHCO_3$ solution, and brine and then dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (6:1 Hex/EtOAc) afforded the secondary allylic alcohol **14** (198 mg, 64% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.54–1.72 (m, 4H), 1.66 (s, 3H), 1.97–2.40 (m, 6H), 4.25 (q, 1H, J = 6.6 Hz), 5.00–5.36 (m, 2H), 5.71–6.12 (ddd, 1H, J = 17, 10, and 5.6 Hz). $[\alpha]^{22}_D$ = +28.0° (c = 0.30, MeOH).

The enantiomeric excess was determined to be over 98% by comparing the relative areas of two peaks (>99:1) at 4.42 and 4.31 ppm (relative to internal trifluoroacetic acid) in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester.

Diene 22. In a 50-mL two-necked round-bottom flask fitted with a nitrogen balloon was placed 15 mL of CH_2Cl_2. It was

cooled to −78 °C, and then oxalyl chloride (0.89 mL, 7.4 nmmol) and DMSO (1.6 mL, 15 mmol) were added. After the mixture was stirred for 5 min, the alcohol **21** (1.18 g, 6.41 mmol) in 5 mL of CH_2Cl_2 of was added. It was further stirred for 15 min, and Et_3N (12.7 mL, 64.1 mmol) was added slowly. After 5 min, the cooling bath was removed. The reaction mixture was warmed to about 0 °C, and 6.3 mL of water was added. It was extracted with ether, washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (7:1 Hex/EtOAc) afforded the corresponding aldehyde (1.07 g, 91% yield). ^{1}H-NMR (60 MHz, CCl_4): δ 1.52–2.64 (m, 9H), 4.0 (s, 4H), 10.2 (s, 1H).

In a 250-mL two-necked round-bottom flask were placed Ph_3PCH_3I (5.59 g, 13.8 mmol) and 80 mL of THF under nitrogen. It was cooled to 0 °C, and 2.4 M n-BuLi (5.5 mL, 13.2 mmol) was added. The mixture was warmed to room temperature and stirred for 30 min. Then the aldehyde obtained above (5.59 g, 12.6 mmol) in 20 mL of THF was added slowly, and the resulting reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by adding water dropwise, and the mixture was poured into water and extracted with ether. The extract was washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (10:1 Hex/EtOAc) afforded the diene **22** (1.97 g, 87% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.78 (s, 3H), 1.70–1.87 (m, 2H), 2.24–2.35 (m, 4H), 3.98 (s, 4H), 4.99 (d, 1H, J = 10.9 Hz), 5.12 (d, 1H, J = 17.4 Hz), 6.80 (dd, 1H, J = 17.4 and 10.9 Hz).

Primary Alcohol 23. To the solution of the diene **22** (663 mg, 3.68 mmol) in 5 mL of THF at 0 °C was added 10 M BH_3·SMe_2 solution (0.4 mL, 4.0 mmol) slowly. It was stirred for 1 h at 0 °C and for 1 h at room temperature, and then 0.08 mL of EtOH was added at 0 °C. After the mixture was cooled to −10 °C, 3 N NaOH solution (1.4 mL) and 30% aqueous H_2O_2 (1.4 mL) were added. The resulting reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with ether, and the extract was washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (4:1 Hex/EtOAc) afforded the alcohol **23** (525 mg, 72% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.64–2.39 (m, 12H), 3.63 (t, 2H, J = 6.7 Hz), 3.94 (s, 4H).

Allylic Alcohol 25. Horner–Emmons reaction of the aldehyde **24** afforded the conjugate ester in 89% yield. ^{1}H-NMR (60 MHz, CCl_4): δ 1.27 (t, 3H, J = 9.3 Hz), 1.63–2.34 (m, 9H), 2.90 (d, 2H, J = 7.7 Hz), 3.90 (s, 4H), 4.20 (q, 2H, J = 9.3 Hz), 5.52–5.95 (m, 1H), 6.40–7.06 (m, 1H).

The reduction of the above ester by the same procedure used in the formation of the alcohol **19** afforded the alcohol **25** in 83% yield from the ester. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.63 (s, 3H), 1.72–1.78 (m, 2H), 2.04–2.20 (m, 4H), 2.77 (br d, 2H, J = 2.3 Hz), 3.97 (s, 4H), 4.04–4.12 (m, 2H), 5.57–5.67 (m, 2H).

Epoxy Alcohol 26. The alcohol was obtained by the same Sharpless epoxidation procedure as in the case of **20** in 92% yield from the allylic alcohol **25**. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.65–1.82 (m, 6H), 2.04–2.33 (m, 6H), 2.98 (m, 2H), 3.68 (br s, 1H), 3.83 (br s, 1H), 3.97 (s, 4H).

(*S*)-15. *p*-TsCl (145 mg, 0.759 mmol) was added to the solution of the epoxy alcohol **26** (152 mg, 0.633 mmol) and pyridine (5 mL) in 10 mL of CH_2Cl_2 at 0 °C. The resulting mixture was stored in the refrigerator overnight. It was poured into ice–water and extracted with ether. The ether extract was washed with saturated $CuSO_4$ solution, water, and brine, dried over $MgSO_4$, and concentrated in vacuo.

The suspension of the crude tosylate obtained above (182 mg, 0.462 mmol) and NaI (208 mg, 1.39 mmol) in 15 mL of acetone was heated under reflux for 2 h. After evaporation of most of acetone, the residue was poured into $Na_2S_2O_3$ solution and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave the nearly pure epoxy iodide, which was reacted with zinc powder and acetic acid without purification.

Acetic acid (freshly distilled from $KMnO_4$, 0.027 mL, 0.48 mmol) in 0.4 mL of THF was added to the purified zinc powder (63 mg, 0.96 mmol). After the mixture was stirred for 10 min, the iodide (34 mg, 0.096 mmol) in 1 mL of THF was added. After the mixture was vigorously stirred for 30 min, ether was added, and the zinc was filtered. The filtered organic solution was washed with aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (4:1 Hex/EtOAc eluant) afforded the (*S*)-enriched allylic alcohol **15** (16 mg, 74% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.67–2.57 (m, 12H), 3.96 (s, 4H), 4.25 (m, 1H), 5.20–5.34 (m, 2H), 5.92 (ddd, J = 17, 10, and 5.6 Hz). IR (neat): 3100–3660, 2900, 1635, 1430, 1360, 1250, 1110, 1080, 1060, 1030 cm^{-1}. MS m/z (EI, relative intensity): 224 (M^+, 9), 209 (11), 206 (23), 168 (88), 167 (40), 153 (27), 123 (22), 109 (16), 99 (72), 87 (19), 86 (100), 55 (29), 41 (22).

The enantiomeric excess was determined to be 78% by comparing the relative areas of the vinyl peaks at δ 5.65 (89%) and δ 5.38 (11%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

Anionic Oxy-Cope Rearrangement of (*S*)-10. Excess KH in a mineral oil suspension was washed with dry THF (1.0 mL × 3). The allylic alcohol (*S*)-**10** (320 mg, 2.85 mmol) in 10 mL of THF was added dropwise. 18-Crown-6 (378 mg, 1.43 mmol) in 1 mL of THF was added. The mixture was heated under reflux for 2 h, cooled to −78 °C, and quenched by rapid injection of 0.5 mL of MeOH. The resulting slurry was immediately poured into a mixture of 30 mL of ether and 5 mL of saturated NH_4Cl solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product **27** was relatively unstable and sensitive to heat and directly used in the next step.

3-Methyl-5-hexen-1-ol (28). To the crude aldehyde **27** in 10 mL of MeOH was added excess $NaBH_4$ at 0 °C. After the mixture was stirred for 1 h, water (10 mL) was added dropwise, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated NH_4Cl solution and brine. The crude product was purified by column chromatography to give the alcohol **28** (169 mg, 52% overall yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.88 (d, 3H, J = 6.0 Hz), 1.19–2.09 (m, 5H), 1.75 (s, 1H), 3.64 (t, 2H, J = 6.6 Hz), 4.82–5.10 (m, 2H), 5.51–6.02 (m, 1H). IR (neat): 3340, 3070, 2950, 2920, 1620, 1415, 1330 cm^{-1}.

The enantiomeric excess was determined to be 8% by comparing the relative areas of the vinyl peaks at δ 0.81 (54%) and δ 0.84 (46%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

(*S*)-Epoxycitronellyl Acetate (30). To a mixture of (*S*)-citronellol **29** (2.0 g, 13 mmol, $[\alpha]^{20}_D$ = −3.2°, 60% optical purity) and 2.0 mL of TEA in 20 mL of CH_2Cl_2, was added 4.0 mL of acetic anhydride. The mixture was stirred for 4 h at room temperature, poured into 50 mL of ice–water, and extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl, water, saturated $NaHCO_3$ solution, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (8:1 Hex/EtOAc) to yield the acetate (2.18 g, 86% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.92 (d, 3H, J = 5.9 Hz), 1.04–2.12 (m, 13H), 2.03 (s, 3H), 4.10 (t, 2H, J = 6.6 Hz), 5.00–5.12 (m, 1H).

m-CPBA (11.9 mmol, 80% purity) was added portionwise to the ice-cooled solution of (*S*)-citronellyl acetate (1.98 g, 9.90 mmol) in 20 mL of CH_2Cl_2 at 0 °C while stirring. The reaction mixture was stirred for 2 h at 0 °C and extracted with CH_2Cl_2 after quenching the reaction with water. The organic layer was washed with 10% $NaHSO_3$ solution, 10% $NaHCO_3$ solution, and brine. It was dried over $MgSO_4$, and the residue resulted from evaporation of the solvent was purified by column chromatography to afford the epoxide **30** (1.82 g, 85% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.95 (d, 3H, J = 6.0 Hz), 1.18 (s, 3H), 1.20 (s, 3H), 1.45 (br s, 7H), 1.96 (s, 3H), 2.05 (t, 1H, J = 4.0 Hz), 4.05 (t, 2H, J = 6.0 Hz). IR (neat): 2960, 2930, 2880, 1745, 1460, 1385, 1375, 1250, 1060, 1040 cm^{-1}.

(*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyloct-3-en-2-ol (31). A solution of PhSeNa was prepared by the addition of $NaBH_4$ (0.40 g) to a suspension of diphenyl diselenide (1.45 g) in 15 mL of EtOH under nitrogen, and the epoxide **30** (1.50 g, 7.0 mmol) in 2 mL of EtOH was added. The reaction mixture was stirred and heated under reflux for 2 h. After cooling and dilution with 10 mL of THF, 28% H_2O_2 (7 mL) was added dropwise to the stirred and cooled mixture during 1 h below 0 °C. The stirring was continued for 1 h at 0 °C. Then the mixture was diluted with water and extracted with ether. The extracted organic layer was washed with $NaHCO_3$ solution and brine and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, column chromatography (3:1 Hex/EtOAc) gave

the deacetylated diol (784 mg, 65% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.89 (d, 3H, J = 5.9 Hz), 1.27–1.71 (m, 3H), 1.29 (s, 6H), 1.90–2.03 (m, 2H), 2.94 (br s, 2H), 3.62 (t, 2H, J = 6.6 Hz), 5.53–5.63 (m, 2H). IR (neat): 3360, 2980, 2930, 1060 cm^{-1}.

To a solution of the diol (700 mg, 4.06 mmol) in DMF (10 mL) were added 2 mL of TEA, TBSCl (918 mg, 6.09 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred for 1 h at room temperature. It was diluted with 50 mL of ether, washed with water, saturated NH_4Cl solution, and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (4:1 Hex/EtOAc) yielding the alcohol **31** (1.10 g, 95% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.85 (s, 9H), 0.87 (s, 3H), 1.26 (s, 6H), 1.45 (s, 1H), 1.20–2.03 (m, 5H), 3.60 (t, 2H, J = 6.6 Hz), 5.53–5.58 (m, 2H).

(*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3-methylpentanal (32). A flask was charged with 3.0 mL of CCl_4, 3.0 mL of acetonitrile, and 4.5 mL of water, TBS protected alcohol **31** (1.30 g, 6.08 mmol), and $NaIO_4$. To this solution, was added $RuO_2 \cdot H_2O$ (4 mg, 0.03 mmol), and the resulting mixture was stirred vigorously for 3 h at room temperature. Fifty mL of CH_2Cl_2 was added, and the mixture was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated. The resulting residue was filtered through a Celite pad with ether, and the filtrate was concentrated. The crude product was passed through a short silica gel column (6:1 Hex/EtOAc) to give the aldehyde **32** (136 mg, 42% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.87 (s, 9H), 0.96 (d, 3H, J = 6.7 Hz), 1.24–1.60 (m, 3H), 2.27–2.35 (m, 2H), 3.64 (t, 2H, J = 6.3 Hz), 9.73 (t, 1H, J = 2.3 Hz).

(*S*)-3-Methyl-5-hexen-1-ol (28). To a suspension of methyltriphenylphosphonium iodide in 10 mL of THF was added n-BuLi (1.01 mmol) with stirring under nitrogen at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The aldehyde **32** (80 mg, 0.35 mmol) was added to the reaction mixture, and it was further stirred for 2 h at 0 °C. The reaction was quenched with saturated NH_4Cl solution. The reaction mixture was extracted with ethyl acetate, and the combined extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (12:1 Hex/EtOAc), giving the TBS-ether (59 mg, 80% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 0.89 (d, 3H, J = 6.6 Hz), 1.26–2.11 (m, 5H), 3.64 (t, 2H, J = 6.7 Hz), 4.85–5.10 (m, 2H), 5.54–5.92 (m, 1H).

The TBS-protected ether (50 mg, 0.24 mmol) was treated with tetra-*n*-butylammonium fluoride (0.5 mL, 1.0 M in THF) for 3 h at room temperature. Water was added, and the crude product was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography (4:1 Hex/EtOAc) afforded the alcohol **28** (24 mg, 90% yield).

The enantiomeric excess was determined to be 60% by comparing the relative areas of the methyl peaks at δ 0.81 (80%) and δ 0.84 (20%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

Anionic Oxy-Cope Rearrangement of (*R*)-11. Excess KH in mineral oil suspension was washed with dry DME (1.0 mL × 3). The allylic alcohol (*R*)-**11** (60 mg, 4.8 mmol) in 10 mL of DME was added dropwise. 18-Crown-6 (2.37 mmol, 2.4 mmol) in 1 mL of DME was added. The mixture was heated to 50 °C for 3 h, cooled to −78 °C, and quenched with 0.5 mL of MeOH via rapid injection. The resulting slurry was immediately poured into a mixture of ether and saturated NH_4Cl solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude sample of the aldehyde **33** thus obtained was relatively unstable and sensitive to heat and was directly used in the next step.

3,5-Dimethyl-5-hexen-1-ol (34). The aldehyde **33** was reduced and purified by the same procedure as that of aldehyde **27**. The primary alcohol **34** was obtained in 56% yield from the alcohol (*R*)-**11**. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.88 (d, 3H, J = 6.1 Hz), 1.45–2.04 (m, 6H), 1.70 (s, 3H), 3.68 (t, 2H, J = 6.5 Hz), 4.67–4.77 (m, 2H). IR (neat): 3340, 3080, 2960, 2930, 1650, 1450, 1380, 1060 cm^{-1}. The enantiomeric excess was determined to be 23% by comparing the relative areas of the methyl peaks at δ 0.77 (61.5%) and δ 0.81 (38.5%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

(*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-4-methylhexan-2-one (35). To a solution of the aldehyde **32** (150 mg, 0.65 mmol) in 10 mL of THF was added MeLi (0.7 mL, 0.98 mmol; 1.4 M in ether) at −78 °C. The mixture was stirred for 1 h at −78 °C and warmed to 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched with saturated NH_4Cl solution. The reaction mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by silica gel column chromatography (6:1 Hex/EtOAc) to give the corresponding alcohol (132 mg, 82% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.87 (s, 9H), 0.81–0.93 (m, 3H), 1.15 (d, 3H, J = 6.1 Hz), 1.26–1.58 (m, 5H), 1.65 (s, 1H), 3.63 (t, 2H, J = 6.6 Hz), 3.73–4.02 (m, 1H).

To a solution of 3,5-DMP (340 mg, 3.54 mmol, 6.0 equiv) in 5 mL of CH_2Cl_2 was added CrO_3 (354 mg, 3.54 mmol, 6.0 equiv) at room temperature. After being stirred for 10 min, the alcohol obtained from above (145 mg, 0.59 mmol) in 1 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 3 h at room temperature and filtered through Celite. The filtrate was concentrated, and crude isolate was passed through a plug of silica gel giving the ketone **35** (108 mg, 75% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 0.91 (d, 3H, J = 6.1 Hz), 1.39–1.59 (m, 3H), 2.11 (s, 3H), 2.16–2.65 (m, 2H), 3.64 (t, 2H, J = 6.5 Hz).

(*S*)-3,5-Dimethyl-5-hexen-1-ol (34). The alcohol **34** was obtained by the same Wittig reaction and deprotection procedure as used for **28** in 66% overall yield from **35**.

The enantiomeric excess was determined to be 60% by comparing the relative areas of the methyl peaks at δ 0.77 (80%) and δ 0.81 (20%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester.

Anionic Oxy-Cope Rearrangement of (*R*)-12. To a 250-mL two-necked round-bottom flask was loaded KH (700 mg; 35% dispersion in oil) under nitrogen flushing. KH was washed twice with dry pentane under nitrogen. The excess pentane was removed in vacuo. After 100 mL of dry THF was added, the alcohol (*R*)-**12** (648 mg, 3.93 mmol) diluted in 10 mL of dry THF was added to the gray suspension with vigorous stirring. 18-Crown-6 (300 mg) was quickly added to the reaction mixture. The color of the solution turned brown. The temperature of the solution was immediately raised to reflux. After being refluxed for 15 min, the reaction mixture was cooled to room temperature. The reaction was quenched by adding the solution to ice-cooled saturated NH_4Cl solution. The mixture was extracted with ether three times, and the extract was washed with brine. After being dried over anhydrous Na_2SO_4, it was concentrated under vacuum. The residue was purified by column chromatography to give the aldehyde **36** (445 mg, 65% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 2.30–2.48 (m, 2H), 2.67–2.88 (m, 2H), 3.13–3.38 (m, 1H), 4.90–5.09 (m, 2H), 5.43–5.93 (m, 1H), 7.22–7.36 (m, 5H), 9.86 (t, 1H, J = 1.9 Hz).

3-Phenyl-5-hexen-1-ol (37). The aldehyde **36** was reduced, and the product **37** was purified by the same procedure as used for **27**. The primary alcohol **37** was obtained in 79% yield. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.36 (s, 1H), 1.72–2.16 (m, 2H), 2.28–2.46 (m, 2H), 2.63–2.90 (m, 1H), 3.41–3.60 (m, 2H), 4.84–5.08 (m, 2H), 5.44–5.94 (m, 1H), 7.05–7.39 (m, 5H).

The enantiomeric excess was determined to be 30% via conversion to **42** (*vide infra*).

6-Iodo-4-phenyl-1-hexene (38). The alcohol **37** (262 mg, 149 mmol) was dissolved in 3 mL of dry pyridine. *p*-TsCl (340 mg, 179 mmol) was slowly poured into the solution, and it was stirred for 1 h at 0 °C and then stored in a refrigerator overnight. After 30 mL of CH_2Cl_2 was added, it was washed with 2 N HCl and saturated $CuSO_4$ solution. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the crude tosylate (453 mg, 92% yield).

NaI (620 mg, 4.11 mmol) was added to the solution of the tosylate (453 mg, 1.37 mmol) in 20 mL of acetone. The mixture was heated under reflux for 3 h. After addition of 10 mL of water, acetone was removed in vacuo. The residue was extracted with EtOAc, and the extract was washed with saturated $Na_2S_2O_3$ solution and brine. It was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was separated by column chromatography to give the iodide **38** (326 mg, 83% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.94–2.46 (m, 4H), 2.62–

3.14 (m, 3H), 4.87–5.07 (m, 2H), 5.43–5.84 (m, 1H), 6.99–7.43 (m, 5H). $[\alpha]^{20}_D$ = −34.8° (c = 1.76, hexane).

4-Phenyl-1-hexene (39). The solution of LAH in THF was prepared in the following manner. LAH (3.0 g, 79 mmol) was added to 50 mL of THF (freshly distilled over Na and benzophenone), and the mixture was stirred vigorously for 2 h at room temperature under dry nitrogen atmosphere. The resulting solution was filtered through a Kramer filter containing a pad of Celite under slightly positive nitrogen pressure. The solution of the iodide **38** (320 mg, 1, 12 mmol) in 50 mL of THF was added dropwise to the prepared LAH–THF solution (3 mL) at 0 °C. It was stirred for 30 min at room temperature and carefully quenched with ice–water. The mixture was extracted with ether, and the organic layer was washed with brine. The extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (pentane) to give colorless 4-phenyl-1-hexene (**39**) (114 mg, 64% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.77 (t, 3H, J = 7.1 Hz), 1.43–1.70 (m, 2H), 2.26–2.59 (m, 3H), 4.81–5.06 (m, 2H), 5.43–5.85 (m, 1H), 7.07–7.37 (m, 5H). $[\alpha]^{23}_D$ = +4.5° (c = 0.67, heptane).

Anionic Oxy-Cope Rearrangement of (*R*)-13. In a 50-mL two-necked round-bottom flask fitted with a reflux condenser was placed 35% KH (574 mg, 5.0 mmol) under nitrogen. It was washed with 5 mL of THF three times, and 19 mL of THF, 18-crown-6 (661 mg, 2.5 mmol) in 1 mL of THF, and the alcohol (*R*)-**13** (577 mg, 2.5 mmol) in 5 mL of THF were added. The solution turned dark brown. It was refluxed for 3.5 h. The reaction was quenched with MeOH at −78 °C. After the addition of water, the organic product was extracted with ether, and the extract was washed with NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The product aldehyde **40** was not purified further and directly used in the next step.

Primary Alcohol 41. The crude aldehyde **40** resulting from the anionic oxy-Cope rearrangement of alcohol (*R*)-**13** was reduced and purified by the same procedure as that for the aldehyde **27**. The primary alcohol **41** was obtained in 81% overall yield from (*R*)-**13**. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.52–2.20 (m, 2H), 2.37 (d, 2H, J = 7.6 Hz), 2.83–3.11 (m, 1H), 3.40–3.57 (m, 2H), 4.79 (d, 2H, J = 17.9 Hz), 7.13–7.35 (m, 5H); MS *m/z* (EI, relative intensity) 232 (M^+, 1), 214 (1), 187 (8), 175 (6), 157 (3), 143 (2), 135 (18), 117 (17), 105 (100), 104 (8), 91 (54), 77 (8), 57 (7), 55 (6), 41 (12).

The enantiomeric excess was determined to be 24% by comparing the relative areas (62:38 = high field:low field, Δ = 0.101 ppm) in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester.

7-Hydroxy-2,2-dimethyl-5-phenyl-3-heptanone (42). To a solution of the above alcohol **41** (142 mg, 0.611 mmol) in 2 mL of DMF were added TBSCl (230 mg, 1.52 mmol), 0.7 mL of triethylamine, and a catalytic amount of DMAP. It was stirred for 3 h at room temperature. The reaction was quenched with water, and ether was added to the reaction mixture. The ether layer was separated from water, and the aqueous layer was extracted with ether. The combined ether extract was washed with brine and dried over anhydrous $MgSO_4$. Flash chromatography (10:1 Hex/EtOAc) afforded the TBS–ether (211 mg, ca. 100% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.88 (s, 9H), 1.03 (s, 9H), 1.62–2.14 (m, 2H), 2.36 (d, 2H, J = 7.4 Hz), 2.96–3.12 (m, 1H), 3.33–3.53 (m, 2H), 4.78 (d, 2H, J = 17.2 Hz), 7.11–7.37 (m, 5H).

To a 50-mL two-necked round-bottom flask fitted with a bubbler and a drying tube were added 15 mL of MeOH, 15 mL of CH_2Cl_2, and the TBS ether (520 mg, 1.50 mmol) obtained above. The solution was treated with ozone for 1 h at −78 °C, and then excess DMS was added. After the addition of water, MeOH was evaporated under reduced pressure. The organic products were extracted with ether. The ether extract was washed with NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (7:1 Hex/EtOAc) afforded the ketone (426 mg, 82% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.39 (s, 6H), 0.93 (s, 9H), 1.07 (s, 9H), 1.75–2.03 (m, 2H), 2.81 (dd, 2H, J = 6.9 and 2.8 Hz), 3.26–3.60 (m, 1H), 3.48 (t, 2H, J = 6.8 Hz), 7.18–7.37 (m, 5H).

To a solution of the ketone (140 mg, 0.40 mmol) in 15 mL of THF was added 1.0 M THF solution of TBAF (1.80 mL, 0.80 mmol) at 0 °C. The reaction mixture was stirred for 40 min at room temperature. The reaction was quenched with water, and the reaction mixture was extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5:1 Hex/EtOAc) afforded the alcohol **42** (92 mg, 98% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.57 (br s, 1H), 1.72–1.97 (m, 2H), 2.81 (d, 2H, J = 7.1 Hz), 3.24–3.58 (m, 1H, CH), 3.50 (t, 2H, J = 6.4 Hz), 7.23 (br s, 5H).

The enantiomeric excess was determined to be 22% by comparing the relative areas (61:39 = high field:low field, Δ = 0.080 ppm) in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester.

7-Hydroxy-2,2-dimethyl-5-phenyl-3-heptanone (42) from 37. To a solution of the (*R*)-enriched alcohol **37** (450 mg, 2.55 mmol) which was obtained from anionic oxy-Cope rearrangement of alcohol (*R*)-**12** in 30 mL of CH_2Cl_2 were added diisopropylethylamine (0.89 mL, 5.11 mmol), MOMCl (0.29 mL, 3.83 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred for 5 h at room temperature. The solution was washed with 2 N HCl solution, $NaHCO_3$ solution, and brine and concentrated under reduced pressure. Flash chromatography (10:1 Hex/EtOAc) afforded the MOM ether (460 mg, 82% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.56–2.09 (m, 2H), 2.26–2.46 (m, 2H), 2.64–2.82 (m, 1H), 3.30 (s, 3H), 3.24–3.46 (m, 2H), 4.53 (s, 2H), 4.83–5.08 (m, 2H), 5.44–5.85 (m, 1H), 7.09–7.34 (m, 5H).

To a 100-mL two-necked round-bottom flask fitted with a bubbler and a drying tube were added 40 mL of CH_2Cl_2 and the olefin (418 mg, 1.90 mmol). It was treated with ozone for 30 min at −78 °C and warmed to room temperature. Triphenylphosphine (500 mg, 1.09 mmol) was added to the reaction mixture at room temperature, and it was stirred for 6 h. After the removal of CH_2Cl_2 under reduced pressure, flash chromatography (6:1 Hex/EtOAc) afforded the aldehyde (418 mg, 99% yield). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.81–2.09 (m, 2H), 2.76 (dd, 2H, J = 7.4 and 2.0 Hz), 3.32 (s, 3H), 3.27–3.48 (m, 3H), 4.54 (s, 1H), 4.55 (s, 1H), 7.19–7.36 (m, 5H), 9.67 (t, 1H, J = 2.0 Hz).

In a 100-mL two-necked round-bottom flask were placed 20 mL of THF and a 1.7 M pentane solution of *t*-BuLi (6.6 mL, 11 mmol) under nitrogen. The above aldehyde (252 mg, 1.13 mmol) in 50 mL of THF was added dropwise at −78 °C. After being stirred for 2 h at −78 °C, the reaction was quenched with NH_4Cl solution at −78 °C. The reaction mixture was extracted with ether, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (4:1 Hex/EtOAc) afforded the secondary alcohol (257 mg, 80% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.79 (s, 9H), 1.54–1.94 (m, 4H), 2.80–3.16 (m, 1H), 3.31 (s, 3H), 3.28–3.45 (m, 3H), 4.53 (s, 2H), 7.19–7.36 (m, 5H).

To the solution of the secondary alcohol (180 mg, 0.642 mmol) in 20 mL of CH_2Cl_2, were added PCC (277 mg, 1.28 mmol) mixed with powdered 4-Å molecular sieve and a small amount of NaOAc. It was stirred for 5 h. The reaction mixture was filtered through a silica gel pad, and the collected organic solution was concentrated under reduced pressure. Flash chromatography (6:1 Hex/EtOAc) afforded the ketone (139 mg, 78% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.61–2.04 (m, 2H), 2.74 (d, 1H, J = 1.7 Hz), 2.83 (d, 1H, J = 0.8 Hz), 3.27 (s, 3H), 3.20–3.44 (m, 3H), 4.52 (s, 2H), 7.12–7.26 (m, 5H).

Three drops of concentrated HCl were added to the solution of the above ketone (80 mg, 0.29 mmol) in 10 mL of MeOH. It was heated under reflux for 1 h. After the addition of $NaHCO_3$ solution to the reaction mixture, MeOH was evaporated under reduced pressure. The organic products were extracted with ether. The ether solution was washed with $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5:1 Hex/EtOAc) afforded the (*S*)-enriched alcohol **42** (52 mg, 77% yield).

The enantiomeric excess was determined to be 30% by comparing the relative areas (35:65 = high field:low field, Δ = 0.080 ppm) in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester.

Anionic Oxy-Cope Rearrangement of (*S*)-14. Excess KH in mineral oil was washed with dry THF three times under nitrogen. The alcohol (*S*)-**14** (50 mg, 0.30 mmol) in 10 mL of THF and 18-crown-6 (40 mg, 0.15 mmol) in 1 mL of THF were added at room temperature. The mixture was heated under reflux for 2 h, and the reaction was quenched with MeOH and water at −78 °C. The ether extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude

product was used directly in the next step. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.93 (s, 3H), 1.13–1.54 (m, 8H), 1.74–2.36 (m, 4H), 4.53–4.67 (m, 2H), 9.69 (t, 1H, J = 1.5 Hz).

3-(1′-Methyl-2′-methylenecyclohexyl)propan-1-ol (44). The aldehyde **43** was reduced and purified by the same procedure as used for the aldehyde **27**. The primary alcohol **44** was obtained in 45% overall yield from the alcohol (*S*)-**14**. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.13–1.76 (m, 10H), 1.59 (s, 1H), 2.04–2.18 (m, 2H), 3.57 (t, 2H, J = 6.0 Hz), 4.56 (d, 1H, J = 2.0 Hz), 4.68 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 154.78, 106.66, 63.49, 45.29, 40.37, 33.11, 33.00, 28.36, 27.27, 25.36, 21.82. $[\alpha]^{24}_D$ = +30.9° (c = 0.11, MeOH).

The enantiomeric excess was determined to be 38% by comparing the relative areas of the peaks (69:31) at 4.39 and 4.34 ppm (relative to internal trifluoroacetic acid) in the ^{19}F-NMR spectrum of the (*R*)-MTPA ester.

(*R*)-3-(1′-Methyl-2′-methylenecyclohexyl)propan-1-ol (44). To a suspension of methyltriphenylphosphonium iodide (610 mg, 1.5 mmol) in 10 mL of THF was added *n*-BuLi (1.50 mmol; 2.5 M in hexane) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 1 h and recooled to 0 °C, and the keto ester **45** (200 mg, 1 mmol, 99% optical purity, $[\alpha]^{20}_D$ = +37.0° (c = 3.0, EtOH)) was added over 5 min. The mixture was once again allowed to warm to room temperature and stirred for 12 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The extract was washed with saturated NH_4Cl solution and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (30:1 Hex/EtOAc eluant) to give the ester (102 mg, 52% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.47–1.54 (m, 8H), 2.06–2.17 (m, 4H), 3.63 (s, 3H), 4.58 (d, 1H, J = 1.9 Hz), 4.71 (m, 1H); $[\alpha]^{25}_D$ = +42.1° (c = 1.5, MeOH).

A two-necked round-bottom flask was fitted with a reflux condenser connected to a drying tube. In this flask was placed LAH (23 mg, 0.61 mmol) in 10 mL of dry ether. The ester (80 mg, 0.47 mmol) was added slowly with vigorous stirring at 0 °C. The resulting mixture was stirred for 1 h at room temperature and extracted with ethyl acetate after the addition of ice–water to quench the reaction. The extract was washed with 2 N HCl, water, saturated $NaHCO_3$ solution, and brine and dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography to give the optically pure alcohol **44** (56 mg, 80% yield). $[\alpha]^{22}_D$ = +72.9° (c = 0.56, MeOH).

Anionic Oxy-Cope Rearrangement of (*S*)-15. The aldehyde **46** was formed by the same procedure as used for the production of the aldehyde **40** from (*R*)-**13** except for 5 h of refluxing time in 64% yield. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.58–2.38 (m, 10H), 3.92 (s, 4H), 4.69 (br s, 1H), 4.83 (br s, 1H), 9.72 (t, 1H, J = 1.8 Hz). IR (neat): 2940, 1720, 1640, 1450, 1360, 1275, 1185, 1120, 1095, 1040 cm^{-1}.

Bicyclic Ketal Alcohol 47. To the cooled CH_2Cl_2 solution (7 mL) of the aldehyde **46** (74 mg, 0.33 mmol) and NaOAc (27 mg, 0.33 mmol) was introduced a CH_2Cl_2 solution (3 mL) of $SnCl_4$ (0.066 mL, 0.56 mmol) at −78 °C. It was stirred for 10 min at that temperature and quenched with water. After the reaction mixture was warmed to around 0 °C, it was poured into water and extracted with ether. The combined organic layer was washed with aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5:1 Hex/EtOAc) afforded the alcohol **47** (44 mg, 59% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.25–2.70 (m, 11H), 3.94 (s, 4H), 3.95 (m, 1H), 5.36 (m, 1H). MS: m/z (EI, relative intensity) 224 (M^+, 4), 147 (3), 138 (9), 120 (50), 105 (35), 92 (12), 91 (19), 87 (100), 86 (67), 79 (20), 77 (15), 55 (14), 43 (13), 41 (12).

The enantiomeric excess was determined to be 48% by comparing the relative areas of the vinyl peaks at δ 4.69 (74%) and δ 5.23 (26%) in the ^{1}H-NMR spectrum of the (*S*)-AMA ester of **47**.

3-Epicholesterol (49). Benzoic acid (134 mg, 1.1 mmol) in 2 mL of benzene and DEAD (192 mg, 1.1 mmol) in 2 mL of benzene were added to a solution of the cholesterol **48** (387 mg, 1.0 mmol) and Ph_3P (289 mg, 1.1 mmol) in 5 mL of benzene at room temperature. After the reaction was completed, 10 mL of water was added. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (15:1 Hex/EtOAc) afforded the 3-epicholesteryl benzoate (419 mg, 86% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.52–2.90 (m, 43H), 4.75 (m, 1H), 5.37 (m, 1H), 7.25–7.60 (m, 5H).

3-Epicholesteryl benzoate (419 mg, 0.86 mmol) was hydrolyzed with 10 mL of 5% KOH and 10 mL of EtOH at room temperature. After the reaction was completed, EtOH was removed under reduced pressure. The product was extracted with ether, and the extract was washed with aqueous NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (7:1 Hex/EtOAc) afforded 3-epicholesterol (**49**) (160 mg, 48% yield). ^{1}H-NMR (80 MHz, $CDCl_3$): δ 0.68–2.80 (m, 44H), 4.0 (m, 1H), 5.40 (m, 1H).

The vinyl peak appeared at δ 5.29 in the ^{1}H-NMR spectrum of the (*S*)-AMA ester of 3-epicholesterol (**49**).

General Experimental Procedure for the Preparation of the MTPA Ester. Oxalyl chloride (0.7 mL, 8 mmol) was added to (*R*)-(+)-MTPA acid (86 mg, 0.4 mmol), and the mixture was stirred for 4 h. The excess oxalyl chloride was removed in vacuo, and 0.7 mL of benzene was added. A solution of alcohol (0.08 mmol) and dry pyridine (0.1 mL) in 0.8 mL of benzene was added, and the mixture was stirred for 30 min before being poured into 10 mL of water. The aqueous layer was extracted with ether. The extract was washed with aqueous $CuSO_4$ solution and brine, dried, and evaporated. The product was separated by column chromatography on silica gel.

General Experimental Procedure for the Preparation of the *O*-Acetyl Mandelate. In a 10-mL round-bottom flask were placed (*S*)-(+)-mandelic acid (59 mg, 0.4 mmol) and acetyl chloride (0.6 mL, 8 mmol). As soon as a clear solution resulted, the excess acetyl chloride was removed under reduced pressure. To the crude *O*-acetylmandelic acid was added oxalyl chloride (0.7 mL, 8 mmol). It was stirred for 1 h, and the residual oxalyl chloride was thoroughly evaporated under vacuo. The resulting *O*-acetylmandelyl chloride was diluted with 0.7 mL of benzene, and a solution of the alcohol **13** (20 mg, 0.08 mmol) and dry pyridine (0.1 mL) in 0.8 mL of benzene was added to it. The reaction mixture turned opaque at once. After 30 min or longer, the reaction was quenched with water. The aqueous solution was extracted with ether, and the combined extract was washed with aqueous $CuSO_4$ solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (9:1 Hex/EtOAc) afforded the *O*-acetylmandelate (31 mg, 90% yield).

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Supplementary Material Available: ^{1}H NMR spectra of the substrates **10-15**, the products **28, 34, 37, 41, 44,** and **47**, their derivatives used for the determination of enantiomeric excess, and intermediates in the transformations **19, 20, 22, 26, 31, 32, 35, 36, 38, 39, 46,** and **49** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.