An Asymmetric Synthesis of (+)-Grandisol, a Constituent of the Aggregation Pheromone of the Cotton Boll Weevil, via a Kinetic Resolution

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A novel approach to the asymmetric synthesis of (+)-grandisol, (1*R*,2*S*)-isopropenyl-1-methylcyclobutaneethanol, involves the use of catalytic kinetic resolution of a primary allylic alcohol, [(1*RS*,5*SR*)-5-methylbicyclo[3.2.0]hept-2-en-2-yl] methanol. The allylic alcohol is prepared in four steps from simple achiral materials involving the use of a modified Shapiro reaction. The resolved alcohol (95% ee) is then reduced in two steps to the corresponding methyl alkene, (1*S*,5*R*)-2,5-dimethylbicyclo[3.2.0]hept-2-ene. This alkene is converted to (+)-grandisol (95% ee), in three steps, by modified literature procedures.

The ability to prepare enantiomerically enriched organic compounds by the use of catalytic amounts of enantiopure material is of paramount importance in asymmetric synthesis. Furthermore, the continual development of new techniques and strategies means that older synthetic problems can be solved in new and better ways. One such molecule which has been used often in this context is (+)-grandisol **1**. Grandisol **1** is the principle component of the aggregation pheromone of the male cotton boll weevil, *Anthonomus grandis* Boheman.[1] It has been a popular molecule for synthesis, both as a synthetic challenge or as a tool to investigate the properties of the naturally occurring pheromone. The cotton boll weevil is a serious pest of cotton crops in the United States and Central America.[1] There are a number of ways of making the required enantiomer of grandisol.[2,3] Few of these are by asymmetric synthesis, and those that are, mostly employ a stoichiometric amount of a chiral auxiliary to induce asymmetry.[4] All require the extensive separation of diastereomers. The construction of the four-membered ring, in an enantioselective manner from achiral starting materials, would be the ideal approach to a catalytic asymmetric synthesis of grandisol, but to date, experiments with that approach in mind have not been very successful.[5] Although less satisfactory in concept, but perhaps nevertheless more successful in practice, is to consider a kinetic resolution of a preformed cyclobutane intermediate. If the intermediate is efficiently synthesized, if the kinetic resolution is effective and catalytic in resolving agent, and if the synthesis can be completed without the need for separating diastereomers, then overall the process may be a useful endeavor. Furthermore, there is no doubt that such pursuits can be important in pedagogy for the insights they provide. With these ideas in mind we set out to explore this approach, and herein we describe the details of a new asymmetric synthesis of grandisol, which was reported earlier as a preliminary communication,[6] whereby grandisol **1** can be synthesized in 8% overall yield and 95% ee in 10 steps from achiral materials. This synthesis uses a kinetic resolution of a primary allylic alcohol by a Sharpless asymmetric epoxidation reaction as the source of chirality. To our knowledge this is the first time such a resolution has been used in the synthesis of a natural product. As far as we are aware this is the shortest route for the formation of optically active grandisol from achiral materials, and it employs only a catalytic amount of enantiopure reagents.

Syntheses of racemic grandisol **1** of particular pertinence to our route to the optically active pheromone are those of Rosini.[7−9] It was recognized that *cis*-(±)-2,5-dimethylbicyclo[3.2.0]hept-2-ene **2** constitutes a key intermediate for an efficient synthesis of the natural product because (±)-grandisol **1** could be formed in three steps from this bicyclic alkene **2**.[8] We recognized that enantiomerically enriched alkene **2** should be available from the optically active allylic alcohol **3** and that, in principle, the nonracemic alcohol could be obtained from a kinetic resolution of the primary allylic alcohol **3** by the Sharpless asymmetric epoxidation reaction. The use of the Sharpless asymmetric epoxidation reaction is well-known for the kinetic resolution of secondary alcohols where the stereogenic center bears the hydroxyl group. However, there are few reported kinetic resolutions of primary allylic alcohols by this method, and most of these do not yield the starting material with high enantiopurity in reasonable yield.[10] Inspection of a molecular model

* As Dr. D. P. G. Hamon has retired, any correspondence concerning this paper should be addressed to Dr. K. L. Tuck.

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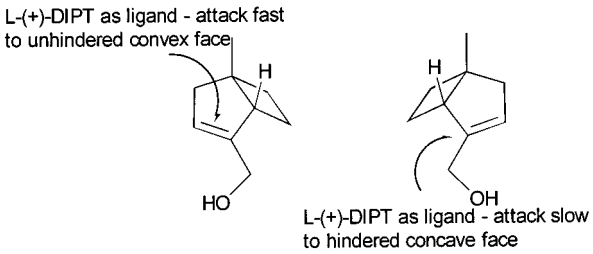


Figure 1. The proposed kinetic resolution of the allylic alcohol **3** by the Sharpless asymmetric epoxidation reaction.

reveals that the allylic alcohol **3** has an open accessible convex face and also a much more hindered concave face. From the Sharpless mnemonic, L-(+)-diisopropyl tartrate (L-(+)-DIPT) should attack preferentially one enantiomer of the racemate, as shown (Figure 1), and leave the other enantiomer of the allylic alcohol in high enantiomeric purity. It was of interest therefore to see if the Sharpless asymmetric epoxidation reaction could be used effectively for a kinetic resolution in a molecule where the chiral center is remote from the hydroxyl.[10,11] However, since a kinetic resolution must necessarily waste at least half of the material it was necessary to prepare the racemic key intermediate in as efficient a route as possible.

The Synthesis of the Racemic Key Allylic Alcohol. Initially it was thought that this key intermediate might be formed via an epoxide **5** or **6** in three steps from the ketone, 3-methyl-2-cyclopentenone. It is known that the bicyclic ketone **4** is available in high yield via a [2 + 2] photocycloaddition reaction on 3-methyl-2-cyclopentenone.[12] Addition of sulfoxonium or sulfonium ylides to the ketone should give the epoxide **5** and/or **6**. Treatment of the epoxide **5** and/or **6** with a nonnucleophilic amide base might then give the required racemic allylic alcohol **3**.

Commercially available[13] 3-methyl-2-cyclopentenone was contaminated with up to 5% acetonyl acetone (as determined by ^{1}H and ^{13}C NMR spectra), and this caused complications with the purification of the bicyclic ketone **4**. This contamination was avoided by the synthesis of 3-methyl-2-cyclopentenone from acetonyl acetone by reaction with aqueous potassium hydroxide.[14]

The photochemical [2 + 2] cycloaddition reaction of 3-methyl-2-cyclpentenone with ethylene then gave the bicyclic ketone **4**. Comparison of the ^{1}H NMR signals for this product corresponded to the literature values quoted for a spectrum obtained at a lower field strength. Due to the complexity of the signals at 300 MHz, it was not clear if the product was the desired *cis*-isomer or a mixture of isomers. In particular the lower peak assignable to a CH next to a carbonyl appeared as a doublet of doublet of doublets. This was not consistent with the methine proton in **4** but might correspond to overlapping signals of this methine proton if both the *cis* and *trans* compounds were present in equal amounts. In syntheses of caryophyllene and caryophyllene alcohol a mixture of *cis* and *trans* isomers are formed during [2 + 2] cycloaddition reactions of cyclohexenones with ethylene.[15,16] Therefore, it was of interest to see if similar chemistry with the cyclopentenone pertained.

Exchange of the acidic protons, in the bicyclic ketone **4**, by deuterium (D_2O, $^-$OD) gave the deuterated compound from which it could be determined which proton resonances, in the ^{1}H NMR spectrum, were due to those adjacent to the carbonyl group. The ^{1}H NMR spectrum of the bicyclic ketone **4** at 600 MHz also clarified the situation somewhat. By the use of HETCOR and COSY spectra, the ^{1}H NMR spectrum of the bicyclic ketone could be fully assigned (see Experimental Section and Supporting Information). In particular the peak at δ 2.25 was shown to be due to one proton of the methylene group adjacent to the carbonyl group. The ^{13}C NMR spectrum showed only eight resonances, and there was only one sharp signal for a methyl group in the ^{1}H NMR. Consequently, only one isomer of the bicyclic ketone **4** had formed directly, and it was the previously reported thermodynamically more stable *cis*-isomer.[12]

Formation of two epoxides was possible upon reaction of the ketone **4** with either dimethylsulfoxonium methylide ($((CH_3)_3OS^+I^-)$) or dimethylsulfonium methylide ($((CH_3)_3S^+I^-)$). From previous work,[17] it is known that addition of the stabilized ylide, dimethylsulfoxonium methylide, to a ketone is reversible, whereas addition of the nonstabilized ylide, dimethylsulfonium methylide, is irreversible. Therefore, it is expected that the two reagents would give different ratios of products. In the case of the stabilized ylide, the ratio of the epoxides obtained should be dependent on the relative energies of the transition states of the second step. However, when the first step in the reaction is nonreversible, as in the case with the nonstabilized ylide, the product formed should reflect the ease of approach of the reagent. Since the concave face is subject to greater steric hindrance than the convex face, this should favor formation of the epoxide shown (Figure 2).

Reaction of the bicyclic ketone **4** with dimethylsulfoxonium methylide (reversible addition) gave two epoxides **5** and **6** in the ratio 4.3:5.7. Reaction of the bicyclic ketone with dimethylsulfonium methylide (irreversible addition) gave only one epoxide **5**.

To confirm the stereochemistry of the epoxides, they were formed in a different way. A Wittig reaction between methylenetriphenylphosphorane and the bicyclic ketone **4** gave the known[7] volatile alkene **7**. Addition of *m*CPBA to this alkene **7** in a buffered solution gave the two epoxides **5** and **6**. In this kinetically controlled reaction, attack should come preferentially from the convex face to give the epoxide **6** with the oxygen *cis* to the methyl group as the major product. At −5 °C the two epoxides **5** and **6** are formed in the ratio 2:8, at −12 °C a 1:9 ratio of epoxides resulted. The major product formed was the same as the major product formed from the stabilized ylide reaction i.e., **6**, whereas the minor product was the same as the product from the reaction of the nonstabilized ylide, i.e., **5**.

There are numerous examples of base-induced isomerization of epoxides to give allylic alcohols,[18] but there are

(10) Principles of Asymmetric Synthesis; Gawlwy, R. E., Aubé, J., Eds.; Elselvier Science: New York, 1996; p 331.

(11) A primary alcohol exhibiting planar chirality has been resolved in this manner and used in a synthesis of betweenanenes. Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 3360−62.

(12) Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. *Org. Synth.* **1984**, *62*, 118−124.

(13) Sigma Aldrich Chemical Co., Sydney, Australia.

(14) Bagnell, L.; Bliese, M.; Cablewski, T.; Strauss, C. R.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 921−25.

(15) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485−92.

(16) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5733−35.

(17) Johnson, C. R.; Schroeck, C. W.; Shankin J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424−31.

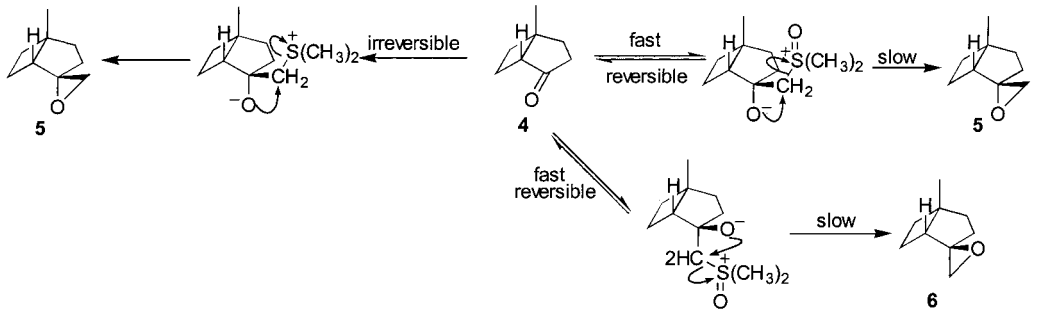
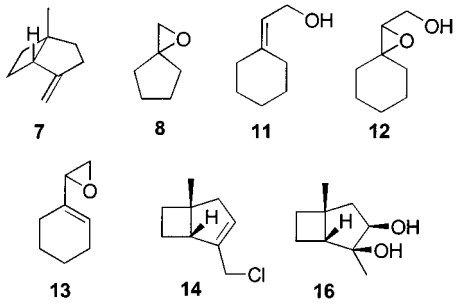


Figure 2. Reaction of the stabilized and nonstabilized ylides with the bicyclic ketone **4**.

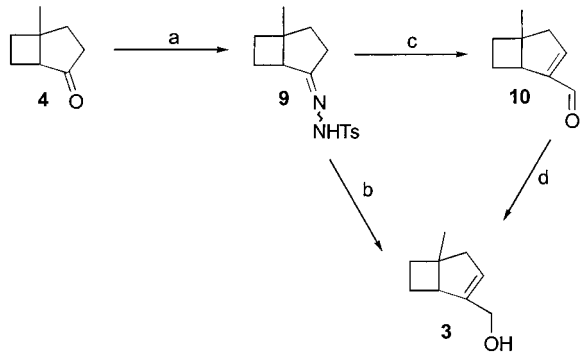
few examples of this reaction on terminal epoxides. Nevertheless, the reaction of β-pinene oxide with lithium diethylamide in ether to give, in 81% yield, the corresponding allylic alcohol, provides a precedent.[19]

Reaction of a mixture of the epoxides **5** and **6** with several nonnucleophilic amide bases ($LiNEt_2$; $LiNEt_2$, HMPA; LDA, HMPA) gave very poor yields of the desired allylic alcohol **3** with a 2% yield the highest obtained, most of the product was intractable material. More extensive experiments on a model epoxide **8** (^{n}BuLi, DBU, and tBuOK), did not give the expected allylic alcohol. An alternative approach was reaction of a mixture of epoxides **5** and **6** with the reagent trimethylsilyl trifluoromethanesulfonate (TMSOTf).[20,21] Several different variations of this reaction were explored in which the solvent and the temperature were changed. However, the best yield of the allylic alcohol **3** obtained was only 27%, and this was not sufficiently high for the preparation of an intermediate in a multistep synthesis.



A different approach to the synthesis of the allylic alcohol **3** was pursued. There are examples in the literature of the use of modified Shapiro reactions[22−27] where the vinyl anion generated reacts with either DMF or formaldehyde as the electrophile to produce α,β-unsaturated aldehydes or allylic alcohols, respectively.

Scheme 1[a]



[a] Conditions: (a) NH_2NHTs, MeOH. (b) (1) ^{n}BuLi, TMEDA. (2) CH_2O. (3) H_3O^+. (c) (1) ^{n}BuLi, TMEDA. (2) DMF. (3) H_3O^+. (d) $NaBH_4/CeCl_3$.

The ketone **4** was converted to the tosyl hydrazone **9** in a 90% yield (Scheme 1). Treatment of the tosyl hydrazone **9** with 3 equiv of *n*BuLi, followed by reaction of the intermediate alkenyl anion with gaseous formaldehyde, gave the required allylic alcohol **3** in only a 5% yield. Better results are achieved when the electrophile is DMF. The reaction proceeds to give the crude unsaturated aldehyde **10** in a good yield after workup, if strict adherence to the conditions carefully detailed in the Experimental Section are followed. The crude aldehyde **10** is reduced immediately with sodium borohydride and ceric chloride, and the desired allylic alcohol **3** is obtained in a 75% overall yield from the bicyclic ketone **4**. Thus, a high yielding four-step synthesis of the key allylic alcohol **3** from 3-methylcyclopentenone is available, without the need for chromatographic purification.

The Kinetic Resolution. Sharpless has noted that the kinetic resolution of allylic alcohols by the AE reaction is adversely affected by the presence of water, and he has published extensive experimental details for the procedures.[28] The reaction reported here is extremely sensitive to the presence of water, and we found it necessary to practice the AE reaction first on the achiral model compound **11**, and this led to the discovery of an interesting secondary reaction. The allylic alcohol **11** was prepared from the corresponding α,β-unsaturated ester by a $LiAlH_4$ reduction.[29,30]

The general literature procedure[28] with L-(+)-DIPT was followed but with the following adaptations. When the

(18) For a review on base-induced isomerization reactions, see: Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345−441.
(19) Hill, R. K.; Morgan, J. W.; Shetty, R. V.; Synerholm, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 4201−06. Since this work was completed, a further example has appeared: Leonard, J.; Bennett, L.; Mahmood, A. *Tetrahedron Lett.* **1999**, *40*, 3965−68.
(20) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738−39.
(21) Murata, S.; Suzuki, M.; Noyori, R., J. *Tetrahedron* **1981**, *37*, 3899−3910.
(22) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734−35.
(23) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55−59.
(24) Chamberlin, A. R.; Bond, F. T. *Synthesis* **1979**, 44−45.
(25) Stemke, J. E.; Chamberlin, A. R.; Bond, F. T. *Tetrahedron Lett.* **1976**, *34*, 2947−50.
(26) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, 1811−14.
(27) Traas, P. C.; Boelens, H.; Takken, H. J. *Tetrahedron Lett.* **1976**, *26*, 2287−88.
(28) Gao, Y.; Hanson, R. A.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−80.
(29) Wadsworth, W. S *Org. React.* **1977**, *25*, 73−253.
(30) Ellis, M. K.; Golding, B. T. *Org. Synth.* **1984**, *63*, 140−46.

aliquots are removed and quenched with ferrous sulfate and citric acid as described, two things are important. First, it is better to use CH_2Cl_2 as the solvent, as the allylic alcohol **11** is not extracted efficiently with ether. Second, the product should be extracted immediately, as the epoxy alcohol **12** undergoes a slow reaction with ferrous sulfate and citric acid (but not citric acid alone). The product of this rearrangement is the epoxy alkene **13**, which arises presumably from a Lewis-acid-catalyzed Payne rearrangement[31] followed by dehydration of the resultant tertiary alcohol.[32]

Even after the epoxidation reaction of the allylic alcohol **11** had been mastered, the kinetic resolution reaction of the key intermediate **3** still gave inconsistent results. It was found necessary to introduce a slight modification to the reported standard procedure to ensure reproducible removal of all water. It was also found that it is better to limit the amount of *tert*-butyl hydroperoxide added to the reaction vessel and allow the reaction to proceed for an adequate length of time, as this avoids the risk that water can be introduced when the progress of the reaction is followed by GC. A small portion of the reaction mixture is worked up in the described manner to determine the exact percentage of the allylic alcohol remaining.

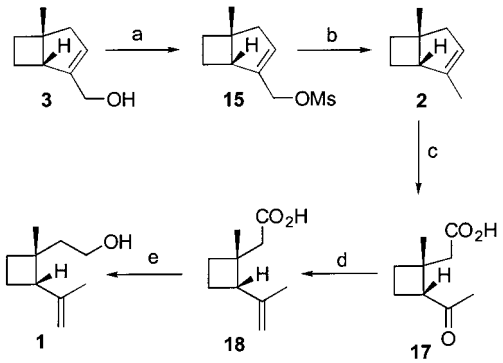
Before the asymmetric epoxidation reaction was attempted on the key allylic alcohol **3**, a method was needed for the determination of the enantiomeric enrichment of this key intermediate. This was not straightforward. No useful separation was seen with NMR experiments on the alcohol or derived acetate with the chiral shift reagent $Eu(hfc)_3$. The diastereomeric urethanes derived from (S)-(−)-α-methylbenzyl isocyanate gave no useful separation by either chromatography or NMR. Partial, but incomplete separation, of the alcohol enantiomers was found on chiral GC.[33] Eventually it was discovered that an analysis could be made by ^{1}H NMR at 600 MHz on the derived Mosher ester of the alcohol. The most reliable region for analysis was for the resonances for the CH_2 group bearing the COR group.[34] In the spectrum for the diastereomeric Mosher ester, derived from the racemic allylic alcohol, this region consisted of overlapping AB quartets, for the diastereotopic protons. One peak from each diastereomer separated from all other signals. These peaks did not represent the same part in each AB quartet, and so a correction factor was obtained by integration of these peaks in the spectrum. In this way an estimate for the enantiomeric excess achieved in the kinetic resolution could be made. In the ester from the racemic alcohol the peaks at 4.93 and 4.88 are in the ratio of 1:2, which is close to the theoretical value calculated for the intensities of these peaks. Confirmation of this interpretation for this part of the spectrum was obtained later when samples of each optically enriched enantiomer were obtained by the use of L-(+)-DIPT and D-(−)-DET in separate kinetic resolution experiments. The AB quartet regions of the ^{1}H NMR spectra (600 MHz) of the Mosher esters from the racemic and two enriched samples of the enantiomers confirmed the interpretation. (Reproduction of these regions and those for the methoxy resonances in the ^{1}H NMR spectra are provided as Supporting Information.)

Table 1. Kinetic Resolution Results at Various Temperatures

temp (°C)	% conversion	enantiomeric excess, %[a]	% of **3** recovered[c]
−20	80	>98[b]	18
−40	60	95	30
−60	55	90	34

[a] The enantiomeric excess of the allylic alcohol was determined by conversion to the corresponding Mosher esters. [b] Only one enantiomer detected by ^{1}H NMR spectroscopy. [c] Refers to the yield of **3** obtained after purification by flash chromatography.

Scheme 2[a]



[a] Conditions: (a) $(MeSO_2)_2O$, Et_3N, CH_2Cl_2. (b) $LiAlH_4$, THF. (c) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, tBuOH, H_2O. (d) Ph_3PCH_2I, n-BuLi, THF. (e) $LiAlH_4$, THF.

Kinetic resolutions of the allylic alcohol **3** with L-(+)-DIPT under the modified conditions gave the results shown in Table 1. The absolute configuration for the resolved allylic alcohol was assumed from the Sharpless mnemonic and confirmed by the eventual synthesis of (+)-grandisol **1** of known configuration.

Reaction of the allylic alcohol **3** with methanesulfonyl chloride gave a poor yield of the unstable allylic chloride **14**, formed by subsequent nucleophilic substitution by chloride anion on the mesylate **15**. This problem is avoided by the use of methanesulfonic anhydride.[35] The mesylate **15** is obtained in a 78% yield after purification (Scheme 2).

Reduction of the optically active and racemic mesylates **15**, separately with lithium aluminum hydride in THF, gave exclusively the corresponding endocyclic alkene **2**, with no exocyclic alkene **7** detected by ^{1}H NMR spectroscopy.

To ensure that the method used to estimate the ee of the allylic alcohol was reliable, a determination of the ee of a sample of this alkene was made in the following way. The optically active alkene **2**, prepared from allylic alcohol estimated to be 85% ee, was treated according to the Sharpless dihydroxylation procedure[36] with the achiral ligand quinuclidine. The resultant diol **16** was then converted to the mono Mosher's ester. The ^{1}H NMR (300 MHz) of the diastereomeric mixture of mono esters obtained from the racemic diol showed two doublet of

(31) Payne, G. B. *J. Am. Chem. Soc.* **1962**, *27*, 2819−3822. We are not aware of any reports of a Lewis-acid-catalyzed Payne rearrangement.

(32) Due to the instability of the olefin, microanalyses was not attempted, and HR MS is not available in these laboratories.

(33) SGE Cydex-*β*, 25m × 0.22m. We would like to thank Dr M. G. Banwell, A. N. U., Canberra, for chiral GC experiments.

(34) Almost complete separation of the methoxy signals is also observed, but as this region could be contaminated with reagent signals, it was used only for confirmation.

(35) Owen, L. N.; Whitelaw, S. P. *J. Am. Chem. Soc.* **1953**, *75*, 3723−23.

(36) VanNieuwenhze, M. S., Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864−65.

doublets at δ 5.44 and 5.38 consistent with the protons on the carbons bearing the ester groups. By integration of each of these two doublet of doublets, for the enriched sample an enantiomeric excess of 86% is obtained. This established the reliability of our initial method and was not used further.

The synthesis of (+)-grandisol **1** was completed by a combination of previously described chemistry. Thus on a larger scale, the volatile alkene **2a** was prepared via the mesylate **15a**, from allylic alcohol **3a** of a 94% ee. Then, without complete isolation from the solvent, it was treated with $RuCl_3/NaIO_4$ under essentially the same conditions as those reported by Rosini[9] except that the reaction was heated at 40 °C for 15 h. The crude optically active ketoacid **17a** was obtained in a 54% yield from the mesylate **15a**. Because the ketoacid **17a** has a tendency to epimerize it was not purified but was treated immediately by the procedure of Webster,[37] with methylenetriphenylphosphorane to give the optically active olefinic acid **18a** in a 62% yield (76% for the racemate **18r**). Reduction of this acid gave, in a 95% yield, (+)-grandisol **1a**.[37] The enantiopurity of grandisol **1a** was established as 95% ee, by conversion to the Mosher ester followed by integration of the methyl resonances in the ^{1}H NMR (600 MHz) spectum.[38]

In conclusion, therefore, we have developed a 10-step asymmetric synthesis of the pheromone **1a**, in an 8% overall yield from achiral starting material **4**. In principle, by sacrificing the yield of the allylic alcohol **3a** in the kinetic resolution, the ee could be made even higher. Furthermore the chemistry explored in connection with this synthesis appears to have revealed a Lewis-acid-catalyzed Payne rearrangement, of the hydroxy-epoxide **12**, for which we know of no precedent.

Experimental Section

General Procedure. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 200, 300, or 600 MHz spectrometer. MS and GC-MS were recorded at an ionization energy of 70 eV. Elemental analyses were carried out at the University of Otago, Dunedin, New Zealand. Accurate mass determinations (LI-MIS) were made at the University of Tasmania, Australia. GC analyses were carried out on a DANI 8510 Gas Chromatograph with a SGE S.C. O.T 50m OV101 column. Flash chromatography was performed with Merck Kieselgel 60 (230−400 mesh ASTM). TLC was performed using Merck silica gel (60 F-254) plates which were visualized either with UV light (254 nm) or by immersion in acidic ammonium molybdate solution. Organic solutions were dried over Na_2SO_4. Other anhydrous solvents and reagents were prepared according to standard laboratory procedures.[39]

(1*SR*,5*SR*)-5-Methylbicyclo[3.2.0]heptan-2-one 4. Compound **4** was synthesized following the method of Cargill[12] except the apparatus was modified by an external jacket of stainless steel rather than glass and enclosed with a nylon socket. [*CAUTION*: With this apparatus it is an important fire safety requirement to ensure that an atmosphere of CO_2 blankets the whole apparatus whenever this 1000 W lamp is turned on. This can be achieved by building walls high enough around the "dry ice" acetone bath to ensure the escaping CO_2 forms a blanket thereby excluding air.] The *title compound* was obtained as a colorless liquid (19.0 g, 77%). ^{1}H NMR (600 MHz):[40] δ 1.26 (3H, s, CH_3), 1.55−1.80 (2H, complex, $H4_a$, $H6_a$), 1.82−1.95 (2H, complex, $H4_b$, $H7_a$), 2.0−2.1 (1H, multiplet, $H7_b$), 2.25−2.42 (3H, complex, H1, $H3_a$, $H6_b$), 2.68 (1H, dt, J = 9.0, 11.0, 18.5 Hz, $H3_b$). δ_C and DEPT (50 MHz): 18.7 (CH_2), 25.8 (CH_3), 30.6 (CH_2), 35.4 (CH_2), 38.3 (CH_2), 42.5 (q), 50.2 (CH), 222.5 (CO). NMR data was consistent with the literature.[41,42]

A Mixture of 3-Dideuterated (1*SR*,5*SR*)-5-Methylbicyclo[3.2.0]heptan-2-one, 3,3-Dideuterated (1*SR*,5*SR*)-5-Methylbicyclo[3.2.0]heptan-2-one, and 1,3,3-Trideuterated (1*SR*,5*SR*)-5-Methylbicyclo[3.2.0]heptan-2-one. A solution of (1*SR*,5*SR*)-5-methylbicyclo[3.2.0]heptan-2-one **4** (121 mg, 0.98 mmol), K_2CO_3 (738 mg, 5.34 mmol), and D_2O (5 mL, 273 mmol) in anhydrous THF (13 mL) were refluxed for 15 h under nitrogen. Et_2O was added to the cooled solution, and the reaction was washed with water. The organic phase was dried, and solvent was removed in vacuo to give a mixture of the mono-, di-, and tri-deuterio species as a colorless liquid (105 mg, 85%). δ_H (300 MHz): 1.29 (s, 3H, CH_3), 1.55−2.0 (complex, 5H, H4, $H6_a$, H7), 2.23−2.35 (complex, $1^1/_2$H, $^1/_2$H1 and $H6_b$). δ_C (50 MHz): 18.7, 25.8, 30.6, 35.4, 38.3 (t), 42.5, 50.2, 222.5. m/z revealed the molecular ions ($M^{+\bullet}$) 127:126:125:124 in the ratio of 3.8:24:3.5:1.

(1*SR*,2*RS*,5*SR*)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane 5 and (1*SR*,2*SR*,5*SR*)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane 6. (a) With Trimethylsulfoxonium Iodide and NaH. To anhydrous, degassed DMSO (7 mL) was added sodium hydride (dispersion, oil removed) (123 mg, 5.11 mmol). The flask, under a nitrogen atmosphere, was fitted with a gooch tube containing trimethylsulfoxonium iodide (1.21 g, 5.51 mmol). Sulfoxonium iodide was added portionwise over 10 min. After the reaction mixture had stirred at ambient temperature for 30 min (1*SR*,5*SR*)-5-methylbicyclo[3.2.0]heptan-2-one **4** (502 mg, 4.04 mmol) was added dropwise over 5 min. The reaction mixture stirred at ambient temperature for 15 min and then heated at 55 °C for 2 h. After being cooled to ambient temperature, the reaction mixture was poured into cold water and then extracted with Et_2O. The combined organic phases were washed with water and sat. $NaCl_{(aq)}$. The organic phases were dried, and solvent was removed by distillation at atmospheric pressure. An evaporative distillation (kugelrohr), 70 °C/760 mmHg, gave the *title compounds* as a colorless liquid (421 mg, 75%). ^{1}H NMR showed the presence of the two epoxides in a 43:57 ratio (*endo*-**5**:*exo*-**6**). The data for these compounds **5** and **6** is detailed below for the individual compounds. Accurate mass spectrum: (MH^+) calcd 139.112, found 139.112.

(b) With Trimethylsulfonium Iodide and NaH. Sodium hydride (dispersion, oil removed) (323 mg, 13.4 mmol) was added to anhydrous DMSO (4 mL) under a nitrogen atmosphere. The reaction mixture heated to 72 °C, whereupon hydrogen was given off. THF (8 mL) was added and the solution subsequently cooled to 0 °C. Trimethylsulfonium iodide (1.66 g, 6.31 mmol) dissolved in DMSO (10 mL) was added over 3 min, and the mixture was stirred for a further minute when (1*SR*,5*SR*)-5-methylbicyclo[3.2.0]heptan-2-one **4** (610 mg, 4.92 mmol) was added dropwise. After a further 10 min at 0 °C, the ice bath was removed and solution stirred at ambient temperature for 2.5 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried, and solvent was removed in vacuo. An evaporative distillation (kugelrohr) (150 °C/ 880 mmHg) gave the *endo* epoxide **5** as a colorless liquid (466 mg, 68%). δ_H (600 MHz):[40] 1.26 (s, 3H, CH_3), 1.50 (td, J = 7.2, 12.6 Hz, 1H, $H4_a$), 1.67 (complex, 2H, $H4_b$ and $H3_a$), 1.82 (complex, 2H, $H6_a$ and $H7_a$), 1.94 (complex, 2H, H1 and $H6_b$), 2.06 (m, 1H, $H7_b$), 2.45 (td, J = 7.2, 13.2 Hz, 1H, $H3_b$), 2.73 (dd, J = 0.8, 5.4 Hz, 1H, H1′), 2.82 (d, J = 5.4 Hz, 1H, H1′). δ_C[43] (50 MHz): 15.7 (CH_2, C7), 26.6 (CH_3),

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30.3 (CH_2, C6), 31.6 (CH_2, C3), 37.7 (CH_2, C4), 44.3 (q), 45.1 (CH, C1), 57.0 (CH_2, C1′), 67.2 (q). *m/z*: 138($M^{+\bullet}$, 30%), 55(100).

(1*SR*,5*SR*)-5-Methyl-2-methylenebicyclo[3.2.0]heptane 7. Compound **7** has been previously prepared by Rosini, by an alternative procedure.[7] To a solution of methyltriphenylphosphonium iodide (4.23 g, 10.5 mmol) in Et_2O (25 mL), under a nitrogen atmosphere, was added, over 5 min, *t*-BuOK (1.62 g, 14.5 mmol). The mixture was stirred at ambient temperature for 20 min, the yellow reaction mixture was cooled to 0 °C, and (1*SR*,5*SR*)-5-methylbicyclo[3.2.0]-heptan-2-one **4** (1.10 g, 8.94 mmol) was added dropwise. After being stirred for 15 h at ambient temperature, the still-yellow solution was filtered through Celite, and solvent was removed at atmospheric pressure. An evaporative distillation (kugelrohr) 760 mm/60 °C gave the title compound as a colorless liquid (436 mg, 40%). δ_H (200 MHz): 1.20 (s, 3H), 1.2−2.0 (complex, 5H), 2.30 (complex, 2H), 2.42 (dm, 1H, 16.6 Hz), 2.75 (m, 1H), 4.66 (br s, 1H), 4.76 (br s, 1H). δ_C (50 MHz): 22.0, 26.4, 30.2, 33.2, 40.2, 45.8, 48.7, 104.3, 158.5. Analysis and HR MS were not obtained.

(1*SR*,2*RS*,5*SR*)-5-Methyl-2-methylene oxide bicyclo-[3.2.0]heptane 5 and (1*SR*,2*SR*,5*SR*)-5-Methyl-2-methylene oxide bicyclo[3.2.0]heptane 6. The alkene **7** (30 mg, 0.25 mmol) was added to the two-phase solution of Et_2O (3 mL) and 0.68 M $NaHCO_{3(aq)}$ (3 mL). After the mixture was cooled to −5 °C, *m*CPBA (90% *m*CPBA, 71 mg, ∼0.37 mmol) was added portionwise over 15 min. The mixture was then allowed to stir at ambient temperature for 15 h. CH_2Cl_2 (20 mL) and water (10 mL) were added, the organic phase was separated, this was washed successively with 1 M $NaOH_{(aq)}$ and water and dried, and the solvent was removed in vacuo to give the title compounds (21 mg, 60%). ^{1}H NMR showed the presence of the two epoxides in a 20:80 ratio (*endo*-**5**:*exo*-**6**). The major signals were for the isomer **6**. δ_H (600 MHz): 1.20 (s, 3H, CH_3), 1.5−2.2 (complex, 8H, H1, $H3_a$, H4, H6, H7), 2.56 (td, J = 7.8, 13.8 Hz, 1H, $H3_b$), 2.70 (d, J = 4.5 Hz, 1H, H1′), 2.79 (d, J = 4.5 Hz, 1H, H1′). δ_C (50 MHz): 17.5, 26.4, 29.6, 32.7, 38.9, 45.3, 47.9, 48.5, 69.4.

Attempted Formation of [(1*RS*,5*SR*)-5-Methylbicyclo-[3.2.0]hept-2-en-2-yl]methanol 3. To a solution of CH_2Cl_2 (1.5 mL), DBU (0.2 mL), and *endo*-epoxide **5** (99 mg, 0.72 mmol) was added TMSOTf (0.2 mL). The solution was stirred for 15 h under a nitrogen atmosphere and at ambient temperature, 15% $HCl_{(aq)}$ (5 mL) and CH_2Cl_2 (10 mL) were added, and the aqueous layer was separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with sat. $NaCl_{(aq)}$ (10 mL) and dried, and solvent was removed in vacuo. Flash chromatography (CH_2-Cl_2/hexanes 15/85 v/v) gave the title compound as a colorless liquid (27 mg, 27%). ^{1}H NMR data was identical with that obtained later for the alcohol **3**.

A Mixture of *E* and *Z* Isomers of *N*′-1-[(1*SR*,5*SR*)-5-Methylbicyclo[3.2.0]hep-2-yliden]-4-methyl-1-toluenesulfonoylhydrazone 9. Tosylhydrazine (3.53 g, 18.9 mmol) was added to 60% $MeOH_{(aq)}$ (46 mL) heated to 60 °C. (1*SR*,5*SR*)-Methylbicyclo[3.2.0]heptan-2-one **4** (2.33 g, 18.8 mmol) was then added dropwise to the clear solution. The reaction mixture was immediately stored at 5 °C for 15 h. The resultant white crystals were filtered, washed with 60% $MeOH_{(aq)}$, and air-dried for 10 min. The title compound was obtained as white crystals (4.91 g, 89%), mp 174−176 °C. ^{1}H NMR revealed a 1:1 mixture of isomers. δ_H (200 MHz): 1.21 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.42 (br s, 6H, Ar−CH_3), 1.35−2.9 (m, 18H, ring protons), 4.06 (br s, 2H, NH), 7.30 (dm, J = 8.0 Hz, 4H, Ar), 7.82 (d, J = 8.0 Hz, 4H, Ar). δ_C (50 MHz): 18.6, 21.4, 21.5, 25.3, 25.5, 27.9, 29.8, 30.0, 33.2, 36.7, 37.3, 42.1, 44.1, 45.9, 48.0, 127.9, 129.5, 135.6, 143.58, 171.4, 172.3. υ_{max}: 3297, 3220 (2 peaks, NH) cm^{-1}. *m/z*: 293 ($M^{+\bullet}$,100%), 137 (94). Anal. Calcd for $C_{15}H_{20}O_2SN$: C, 61.61; H, 6.89. Found: C, 61.48; H, 7.03.

[(1*RS*,5*SR*)-5-Methylbicyclo[3.2.0]hept-2-en-2-yl]methanol 3. Formation of the Aldehyde 10. [CAUTION: Nitrogen is produced in this reaction and allowance must be made for its escape. Do not use a sealed system.]

A suspension of the tosylhydrazone **9** (1.04 g, 3.59 mmol) and TMEDA (15 mL) was cooled to −78 °C, under a nitrogen atmosphere. A solution of ^{n}BuLi (2.3 M, 4.6 mL, 10.58 mmol) was added dropwise to the frozen suspension, and the solution generated was kept at −78 °C for 15 min and then allowed to warm to ambient temperature, whereupon it turned a dark red color. This solution was stirred for a further 5 h, it was cooled to 0 °C, DMF (0.4 mL, 5.18 mmol) was added, and the solution was stirred at ambient temperature overnight. It was then poured into 7.5% $HCl_{(aq)}$ (60 mL) and extracted with CH_2-Cl_2 (4 × 40 mL). The combined organic phases were washed with sat. $NaCl_{(aq)}$ (40 mL) and dried, and solvent was removed in vacuo. The crude material was used directly in the next reaction. A small portion was purified by flash chromatography (CH_2Cl_2) to give a pure sample for spectroscopic analysis. δ_H (300 MHz): 1.30 (s, 3H), 1.6−2.1 (m, 3H), 2.2−2.6 (m, 3H), 3.02 (br d, 1H, J = 8.2 Hz), 6.87 (br s, 1H), 9.78 (s, 1H). δ_C (75 MHz): 23.4, 24.6, 33.0, 44.4, 46.9, 47.9, 150.8, 152.6, 190.1. υ_{max}(neat): 1680(s) cm^{-1}. *m/z*: 136($M^{+\bullet}$, 11%), 79(100).

Reduction of the Aldehyde 10. To the crude aldehyde **10** (∼2 g, max. 3.5 mmol) dissolved in MeOH (15 mL) was added ceric chloride (0.1 mL), and the reaction vessel placed under a nitrogen atmosphere. Solid $NaBH_4$ (201 mg, 5.32 mmol) was added with stirring over 10 min, and after 4 h the solution was diluted with CH_2Cl_2 and washed with 7.5% $HCl_{(aq)}$. The aqueous phase was further extracted with CH_2-Cl_2. The combined organic extracts were washed with sat. $NaCl_{(aq)}$ and dried, and solvent was removed in vacuo. Flash chromatography (CH_2Cl_2) gave the title compound (477 mg, 83% over two steps). δ_H (600 MHz):[40] 1.27 (s, 3H, CH_3), 1.69 (m, 1H, $H7_a$), 1.79 (m, 1H, $H6_a$), 1.94 (m, 1H, $H6_b$), 2.1−2.3 (complex, 3H, H4, $H7_b$), 2.74 (d, J = 7.8 Hz, 1H, H1), 4.12 (AB quartet, J = 15.5 Hz, 1H, $H1_a$′), 4.20 (AB quartet, J = 15.5 Hz, 1H, $H1_b$′), 5.62 (s, 1H, H3). δ_C and DEPT (75 MHz): 23.2 (CH_2), 25.0 (CH), 33.2 (CH_2), 44.4 (q), 47.2 (CH_2), 50.1 (CH_3), 60.5 (CH_2), 125.0 (CH), 146.9 (q).M/z: 138($M^{+\bullet}$, 15%), 95(100). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.20 Found: C, 78.19; H, 9.96.

1-Oxaspiro[2.5]oct-2-ylmethanol 12 from Sharpless Asymmetric Epoxidation Reaction. Formation of 2-(1-Cyclohexenyl)oxirane 13. Following the procedure of Sharpless,[28] an anhydrous flask was flushed with nitrogen and charged with *n*-decane (40 μL), (L)-(+)-DIPT (27 mg, 0.12 mmol), activated powdered 4 Å sieves (38 mg), and a solution of the alcohol **11** (100 mg, 0.80 mmol) in anhydrous CH_2Cl_2 (2 mL), previously dried over 3 Å sieves for 1 h. The flask was cooled to −20 °C, titanium(IV) isopropoxide (0.35 mL, 0.08 mmol) was added, and the solution was stirred at −20 °C for 1 h. The flask was then cooled to −40 °C, and *tert*-butyl hydroperoxide solution (0.15 mL of a 4.2 M CH_2Cl_2 solution, 0.63 mmol), previously dried[19] and then freshly dried over freshly activated 3 Å sieves for 15 min, was added. At timed intervals, aliquots (0.1 mL) of the reaction mixture were taken (with an oven dried syringe) and quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), CH_2Cl_2 (0.1 mL) was added, and the organic layer was separated. The organic layer was then analyzed by GLC (150 °C) for the remaining allylic alcohol relative to the internal standard *n*-decane. After the reaction was complete, it was quenched with a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL) and then left for 15 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic phases were washed with sat. $NaCl_{(aq)}$ and dried, and solvent was removed in vacuo. Flash chromatography (hexanes/EtOAc, 70/30 v/v) did not give the expected product but a colorless liquid identified as 2-(1-cyclohexenyl)oxirane[32] **13** (47%). δ_H (200 MHz): 1.5 (complex, 4H), 1.8 (complex, 4H), 3.4−3.7 (AB of ABX, 2H), 3.9−4.1 (X of ABX, 1H), 5.66 (br s, 1H). δ_C (150 MHz): 22.4, 22.5, 24.8, 24.9, 65.4, 76.2, 123.9, 136.7. GC/MS: 124 (M^+, 65%), 95 (100).

Formation of 1-Oxaspiro[2.5]oct-2-ylmethanol 12. The above procedure was repeated with the following quantities: *n*-decane (40 μL), (L)-(+)-DIPT (24 mg, 0.10 mmol), activated powdered 4 Å sieves (33 mg), a solution of the alcohol **11** (102

mg, 0.81 mmol) in anhydrous CH_2Cl_2 (2 mL), titanium(IV) isopropoxide (0.35 mL, 0.08 mmol), and *tert*-butyl hydroperoxide solution (0.16 mL of a 3.8 M CH_2Cl_2 solution, 0.61 mmol). At timed intervals, aliquots (0.1 mL) of the reaction mixture were taken (with an oven dried syringe) and quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), CH_2Cl_2 (0.1 mL) was added, and the organic layer was separated. After the reaction was complete, it was quenched with sodium thiosulfate (5 mL) and then left for 2 days (for comparison with the above $FeSO_4$ solution). Upon workup and flash chromatography (hexanes/EtOAc, 70/30 v/v) the title compound was obtained as a colorless oil (52 mg, 45%) with no rearranged epoxide **13** present in the ^{1}H NMR spectrum. δ_H (300 MHz): 1.5−1.8 (complex, 10H, methylene envelope), 2.2 (br s, 1H, OH), 2.9−3.1 (X portion of ABX, 1H), 3.6−4.0 (AB of ABX, 2H).

Mosher Ester of the Racemic Allylic Alcohol 3r: [(1*SR*,2*RS*,5*SR*)-5-Methylbicyclo[3.2.0]hep-2-en-yl]methyl (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. According to the procedure of Hassner,[44] a solution of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (26 mg, 0.11 mmol), DCC (19 mg, 0.090m mmol), the racemic alcohol **3r** (14 mg, 0.102 mmol), and DMAP (2 mg, 0.019 mmol) in CH_2Cl_2 (0.7 mL) were allowed to stand at ambient temperature until esterification was complete. *N*,*N*-Dicyclohexylurea was filtered, the filtrate washed with water, 5% citric acid solution, and again with water and dried, and the solvent was evaporated in vacuo. Flash chromatography (hexanes/EtOAc,[45] 95/5, v/v) as an eluant gave the corresponding Mosher ester as a colorless oil (15 mg, 55%). The diastereomers could not be distinguished in the ^{1}H NMR spectrum at 200 MHz. From the ^{1}H NMR spectrum (600 MHz) of the products from the racemic and optically active alcohols it was possible to assign the following data. Diastereomer A δ_H (600 MHz): 1.27 (s, 3H), 1.3−2.0 (complex, 3H), 2.24 (m, 3H), 2.62 (m, 1H), 3.55 (br s, 3H), (AB quartet, one centered at 4.84, 1H and the other at 4.91, 1H), 5.69 (br s, 1H), 7.35−7.55 (m, 5H). Diastereomer B δ_H (600 MHz): 1.24 (s, 3H), 1.3−2.0 (complex, 3H), 2.24 (m, 3H), 2.62 (m, 1H), 3.56 (br s, 3H), (AB quartet, one centered at 4.84, 1H and the other at 4.89, 1H), 5.70 (br s, 1H), 7.35−7.55 (m, 5H).

Kinetic Resolution of [(1*RS*,5*SR*)-5-Methylbicyclo-[3.2.0]hept-2-en-2-yl]methanol 3. In general, these reactions were run as follows although the scale, number of aliquots, and the time of quenching were varied throughout the studies.

A solution of L-(+)-DIPT (295 mg, 1.26 mmol), titanium isopropoxide (196 mg, 0.69 mmol), freshly activated powdered 4 Å sieves (337 mg), and freshly distilled anhydrous CH_2Cl_2 (4 mL) were combined, put under a small pressure of dry nitrogen, and cooled to −15 °C. *tert*-Butyl hydroperoxide (1.1 mL, 5.9 M, 6.4 mmol), previously dried[19] and then freshly dried over freshly activated 3 Å sieves for 15 min, was added, and the solution was then cooled to −40 °C and aged at −40 °C for 2 h. Then a solution of *n*-decane (0.4 mL) and the allylic alcohol **3** (1.63 g, 11.8 mmol) in CH_2Cl_2 (5 mL), which had been drying over freshly activated 3 Å sieves for 15 min, were added, the sieves were washed with additional CH_2Cl_2 (2 mL), and the washings were also added to the reaction mixture. [A T_o GLC sample had been taken from the *n*-decane and allylic alcohol solution before it was added to the reaction mixture.] After the reaction had been stirred at −40 °C for 15 h, an aliquot (0.1 mL) was removed (with an oven dried syringe) and quenched with 0.1 mL of a solution of $FeSO_4$ (1.6 g/5 mL) and citric acid (0.5 g/5 mL), CH_2Cl_2 (0.1 mL) was added, and the organic layer was separated. GLC showed that the reaction had gone to 59% completion. Sodium thiosulfate (3 mL) was added, and the reaction mixture was allowed to warm to ambient temperature. CH_2Cl_2 was added, and the organic phase was separated. The aqueous phase was re-extracted with CH_2Cl_2. The combined organic phases were washed with sat. $NaCl_{(aq)}$ and dried, and solvent was removed in vacuo. Flash chromatography (hexanes/EtOAc 85/15 v/v) gave the (1*R*,5*S*) allylic alcohol as a colorless oil (490 mg, 31% recovery). δ_H (300 MHz): 1.27 (s, 3H, CH_3), 1.35−2.5 (m, 6H, ring protons), 2.75 (br d, J = 5.6 Hz, 1H, H4), 4.20 (AB quartet, 2H, H1′), 5.62 (br s, 1H, H3). $[\alpha]^{20}_D = -1.77 \pm 0.2$ (c = 1.5 CH_2Cl_2). The ee was calculated to be 94 ± 2% by conversion to the corresponding Mosher ester, diastereomer B above.

In a similar manner by the use of D-(−)-DET, but by letting the reaction go to 85% conversion, the other enantiomer was obtained. Conversion to the corresponding Mosher ester gave mainly diastereomer.

Racemic 15r and [(1*R*,5*S*)-5-Methylbicyclo[3.2.0]hept-2-en-2-yl]methyl methanesulfonate 15a. Methanesulfonic anhydride[35] (846 mg, 4.85 mmol) was added portionwise to a solution of the allylic alcohol **3** (438 mg, 3.17 mmol) and triethylamine (1 mL) in CH_2Cl_2 (4 mL) and cooled to 0 °C, and the mixture was stirred at ambient temperature for 2.5 h before the solution was diluted with CH_2Cl_2 and washed with 15% $HCl_{(aq)}$. The aqueous phase was re-extracted with CH_2Cl_2. The combined organic layers were washed with sat. $NaCl_{(aq)}$ and dried, and solvent was removed in vacuo. Purification by flash chromatography (hexanes/EtOAc 75/15 v/v) gave **15r** as a colorless oil (543 mg, 78%). δ_H (300 MHz): 1.29 (s, 3H, CH_3), 1.4−2.0 (m, 3H, ring protons), 2.33 (m, 3H, ring protons), 2.78 (m, 1H, allylic proton), 3.00 (s, 3H, O_2S-CH_3), 4.79 (s, 2H, H1′), 5.85 (br s, 1H, H3). δ_C (75 MHz): 23.2, 25.0, 33.1, 37.8, 44.6, 47.4, 50.2, 67.5, 132.2, 140.2. υ_{max}(neat): 2869(s), 1425(s), 1253(s) cm^{-1}. *m*/*z*: 217 (MH^+, 6%), 95 (83), 79 (100).

The above procedure was repeated with methanesulfonic anhydride[35] (629 mg, 3.60 mmol), the allylic alcohol **3a** (471 mg, 3.40 mmol), triethylamine (0.5 mL), and CH_2Cl_2 (4 mL). After purification, **15a** was obtained as a colorless oil (583 mg, 78%). ^{1}H NMR data of **15a** were identical with those of **15r**.

Racemic 2r and (1*S*,5*R*)-2,5-Dimethylbicyclo[3.2.0]-hept-2-ene 2a. A suspension of $LiAlH_4$ (122 mg, 3.21 mmol) and THF (3 mL), under a nitrogen atmosphere, was cooled to 0 °C. A solution of the mesylate **15r** (350 mg, 1.60 mmol) in THF (3 mL) was cautiously added, and the solution was stirred at ambient temperature for 15 h. The solution was carefully quenched with water and then poured into water. The solution was extracted with CH_2Cl_2. The combined organic layers were washed with water and sat. $NaCl_{(aq)}$ and then dried, and solvent was removed by distillation at atmospheric pressure. The racemic alkene **2r** was obtained as a clear oil, with some solvent impurity (450 mg). It was used crude in the next reaction. δ_H (300 MHz): 1.25 (s, 3H), 1.4−2.0 (m, 3H), 1.71 (br s, 3H), 2.10 (m, 3H), 2.55 (m, 1H), 5.28 (br s, 1H). δ_C (75 MHz): 14.5, 22.9, 25.1, 33.2, 44.4, 47.6, 53.6, 124.2, 143.1. Resonances for THF and CH_2Cl_2 were also present. GC-MS: 123 (MH^+, 32%), 79 (100). ^{1}H NMR and ^{13}C data corresponded with the literature values.[7,9]

The above procedure was repeated with $LiAlH_4$ (146 mg, 3.84 mmol), THF (4 mL), and the mesylate **15a** (583 mg, 2.66 mmol) in THF (3 mL). After solvent was removed by distillation at atmospheric pressure, **2a** was obtained as a clear oil, with some solvent impurity. It was used crude in the next reaction. The ^{1}H NMR spectrum was the same as that for **2r**.

Racemic 16r and (1*R*,2*S*,3*R*,5*R*)-2,5-Dimethylbicyclo-[3.2.0]heptane-2,3-diol 16a. Following the procedure of Sharpless,[36] a 25-mL round-bottom flask was charged with *t*BuOH (1.5 mL) and water (1.5 mL). Potassium carbonate (134 mg, 0.97 mmol), potassium ferricyanide (369 mg, 1.12 mmol), quinuclidine hydrochloride (1 mg, 0.01 mmol), 4% $OsO_{4(aq)}$ (0.02 mL, 0.8 mg, 0.003 mmol), and methane sulfonamide (30 mg, 0.31 mL) were then added. To the well-stirred solution was added alkene **2r** (35 mg, 0.29 mmol). Once the reaction was complete (15 h), solid sodium sulfite (430 mg, 3.41 mmol) was added and the solution stirred at ambient temperature for 30 min. CH_2Cl_2 was added to the reaction mixture, and after separation of the layers, the aqueous phase was further

(43) DEPT and (H, C) COSY experiments were used to assign the resonances.

(44) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475−78.

(45) In the preparation of Mosher esters for optical purity measurements, purification by chromatography was performed with a short column and care was taken so as to avoid possible fractionation of diastereomers.

extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the diol **16r** and the ligand. The crude product was purified by flash chromatography (hexanes/EtOAc 70/30 v/v) to afford the 1,2-diol **16r** as white crystals (15 mg, 60%). Mp 66−67 °C. δ_H (300 MHz): 1.20 (s, 3H), 1.22 (s, 3H), 1.4−2.2 (m, 7H), 4.19 (dd, 1H, J = 7.0, 10.5 Hz). δ_C (75 MHz): 16.5, 20.1, 28.2, 30.9, 40.4, 46.5, 52.8, 77.9, 80.6. υ_{max}($CDCl_3$): 3608 (b, OH), 3432 (b, OH), cm^{-1}. m/z: 156 (MH^+,1%), 67 (25), 43 (100).

The general procedure (above) was repeated with potassium carbonate (124 mg, 0.89 mmol), potassium ferricyanide (303 mg, 0.92 mmol), quinuclidine hydrochloride (2.3 mg, 0.03 mmol), *t*BuOH (2 mL), H_2O (2 mL), 4% $OsO_{4(aq)}$ (0.05 mL, 2.0 mg, 0.007 mmol), and (1*SR*,5*RS*)-2,5-dimethylbicyclo[3.2.0]-hept-2-ene **2a** (20 mg, 0.16 mmol). The ^{1}H NMR spectrum was the same as that for **16r**.

Mono-Mosher Ester of the Racemic Diol 16r and the Optically Active Diol 16a: (1*R*,3*R*,4*S*,5*R*)-4-Hydroxy-1,4-dimethylbicyclo[3.2.0]hep-3-yl (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The general procedure for Mosher ester formation[44] was repeated with the following reagents. Diol **16r** (8 mg, 0.05 mmol), DMAP (2 mg, 0.01 mmol), DCC (23 mg, 0.11 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (23 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL). The corresponding mono-Mosher ester was obtained as a colorless oil (16 mg, 85%). From the ^{1}H NMR spectra of the products from the racemic and optically active diols it was possible to assign the following data. Diastereomer A: δ_H (600 MHz): 1.20 (s, 3H), 1.27 (s, 3H), 1.1−2.2 (complex, 7H), 3.55 (br s, 3H), 5.38 (dd, 1H, J = 7.0, 11.0 Hz), 7.35−7.55 (m, 5H). Diastereomer B: δ_H (600 MHz): 1.10 (s, 3H), 1.25 (s, 3H) 1.1−2.2 (complex, 7H), 3.57 (br s, 3H), 5.44 (dd, 1H, J = 6.5, 11 Hz), 7.35−7.55 (m, 5H).

The above procedure was repeated with the enantiomerically enriched diol **16a**, 85% ee (5 mg, 0.03 mmol), DMAP (2 mg, 0.02 mmol), DCC (13 mg, 0.06 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (13 mg, 0.06 mmol), and CH_2Cl_2 (0.5 mL) and gave the corresponding optically active Mosher ester, mainly diastereomer B (8 mg, 63%). The ee was found to be 86 ± 3% by integration of the pair of dd at δ 5.38 and 5.44.

Mosher Ester of Racemic Grandisol 1r and Optically Active Grandisol 1a: 1-[(1*R*)-2-{2-[1*R*,2*S*)-2-Isopropenyl-1-methylcyclobutyl]ethoxy}-1-methoxy-1-(trifluoromethyl)-2-propenyl]benzene. The general procedure for Mosher formation[44] was repeated with the following reagents: racemic grandisol **1r** (8 mg, 0.05 mmol), DMAP (1 mg, 0.01 mmol), DCC (14 mg, 0.07 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (18 mg, 0.08 mmol), and CH_2Cl_2 (0.5 mL). The corresponding Mosher ester was obtained as a colorless oil (12 mg, ∼65%). From the ^{1}H NMR spectrum of the products from the racemic and optically active esters it was possible to assign the following data.

Diastereomer A: δ_H (600 MHz): 1.14 (s, 3H), 1.64 (s, 3H), 1.45−1.65 (complex, 3H), 1.75−2.0 (complex, 3H), 2.58 (t, 1H, J = 9.0 Hz), 3.55 (br s, 3H), 4.37 (m, 2H), 4.64 (br s, 1H), 4.84 (br s, 1H), 7.35−7.55 (m, 5H). Diastereomer B: δ_H (600 MHz): 1.15 (s, 3H), 1.65 (s, 3H) 1.45−1.65 (complex, 3H), 1.75−2.0 (complex, 3H), 2.58 (t, 1H, J = 9.0 Hz), 3.55 (br s, 3H), 4.37 (m, 2H), 4.64 (br s, 1H), 4.84 (br s, 1H), 7.35−7.55 (m, 5H).

The above procedure was repeated with the following reagents; grandisol **1a** (7 mg, 0.04 mmol), DMAP (5 mg, 0.04 mmol), DCC (20 mg, 0.10 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (20 mg, 0.09 mmol), and CH_2Cl_2 (0.5 mL). The corresponding Mosher ester was obtained as a colorless oil, mainly diastereomer B (11 mg, ∼70%). Due to the closeness of the resonances the ee were calculated by cutting and weighing the methyl resonances at ∼δ 1.15. The ee was found to be 94 ± 2%.

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Supporting Information Available: Experimental details for the synthesis of the compounds **17a**, **17r**, **18a**, **18r**, **1a**, and **1r**. (H,H) COSY and (H,C) COSY spectra of the ketone **4**, the epoxide **5**, and the alcohol **3**. A ^{1}H NMR spectra of the diastereotopic protons of the Mosher esters from the racemic and two enriched samples of the enantiomers of the alcohol **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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