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A cyclopropanol approach to the synthesis of both enantiomers of the C13–C21 fragment of epothilones

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Dedicated to Professor Jacques Salaün on the occasion of his 70th birthday

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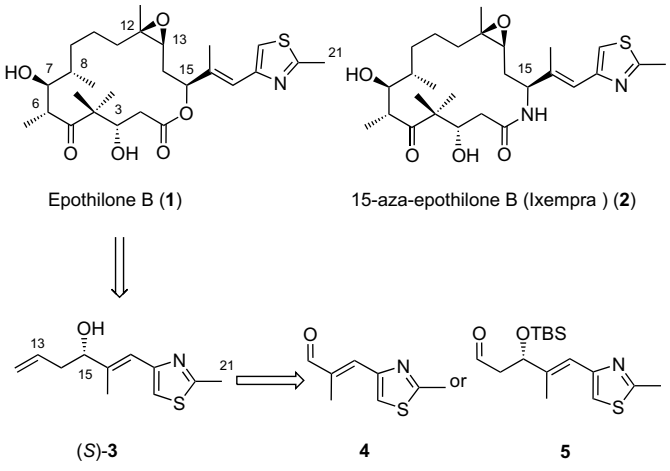
ABSTRACT

Efficient syntheses of both enantiomers of the C13–C21 fragment of epothilone molecules have been performed by use of enantiomeric oxiranyl-substituted cyclopropylsulfonates as key intermediates. The latter were obtained by the cyclopropanation of easily available (*R*)-methyl 2,3-*O*-isopropylideneglycerate and subsequent manipulation of the functional groups. Asymmetric allylation of 1-formylcyclopropyl pivalate led to an alternative precursor of the target compounds with moderate enantioselectivity.

1. Introduction

Epothilones are bioactive macrocyclic natural products with potent antitumour properties. These compounds were isolated from extracts of the cellulose-degrading myxobacterium *Sorangium cellulosum*[1,2] and in the last decade they have served as lead structures for the development of anticancer agents.[3] Several epothilones, including epothilone B **1**, are currently in clinical trials and the 15-aza analogue of epothilone B **2** (brand name: Ixempra) has recently obtained FDA approval as an anticancer drug.[4] Since epothilone analogues possessing improved therapeutic properties have been obtained efficiently by total synthesis, elaboration of convenient procedures for their preparation has practical interest. Among the synthetic approaches to the epothilones, macrolactonization and ring-closing olefin metathesis strategies have been applied most frequently and both of these strategies allow the efficient use of the thiazole-containing fragment (*S*)-**3** as an advanced intermediate.[5] The latter has been prepared by asymmetric allylation of the thiazole-containing α,β-unsaturated aldehyde **4**, in accordance with Brown and Keck procedures,[5a–d] olefination of TBS-protected hydroxyaldehyde precursor **5**[5e] and enantioselective enzymatic resolution of allylic alcohol **3**[5f] or other precursors.[5g,h] To our knowledge, there are no published details on the preparation of compound (*S*)-**3** or (*R*)-**3** from natural chiral precursors (Scheme 1).

In continuation of our efforts on the development of cyclopropanol methodology for the synthesis of natural products, we have recently reported the preparation of the C13–C21 epothilone fragment **6** by the appropriate transformation of the ester groups in



Scheme 1.

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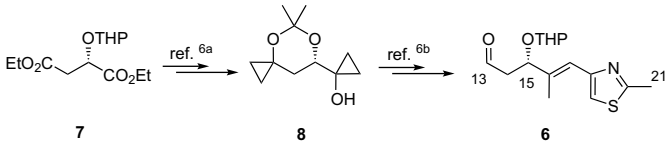
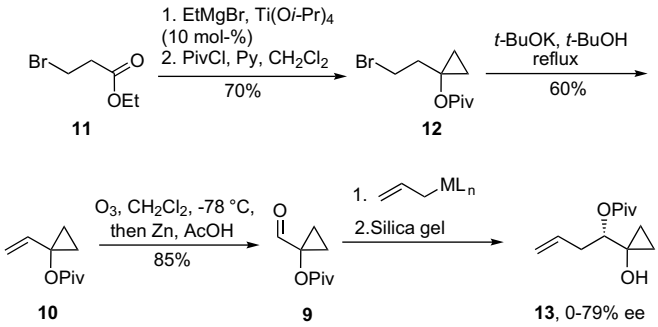


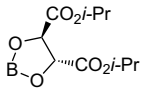
Scheme 2.

THP-protected (*S*)-diethyl malate **7** via the key bis-cyclopropanol derivative **8** (Scheme 2).[6] The homoallylic alcohol (*S*)-**3** can be prepared by Wittig olefination of aldehyde **6**[5e] and subsequent deprotection of the hydroxyl group. However, the preparation of enantiomeric alcohol (*R*)-**3** by this pathway requires the use of the corresponding derivatives of the rather expensive (*R*)-malic acid. Since homoallylic alcohol (*R*)-**3** could be employed for the preparation of (*S*)-15-aza-epothilones via inversion at the C15 center with nitrogen-based nucleophiles,[7] we were interested in elaboration of the cyclopropanol approach to the syntheses of both enantiomers of the C13–C21 epothilone fragments (*S*)-**3** and (*R*)-**3**.

2. Results and discussion

At first, asymmetric allylation of 1-formylcyclopropyl pivalate **9** as a possible key step for the preparation of homoallylic alcohols (*S*)-**3** and (*R*)-**3** was studied. Aldehyde **9** was obtained by reductive ozonolysis of 1-vinylcyclopropanol **10**, prepared in turn using the approach to vinylcyclopropanols elaborated earlier by Salaün et al.[8] The titanium(IV)-catalyzed cyclopropanation of ethyl-3-bromopropionate[9] **11** with ethylmagnesium bromide, followed by esterification and dehydrobromination of **12** with potassium *tert*-butoxide, gave vinylcyclopropanol derivative **10** in 42% overall yield. Aldehyde **9** was prepared by reductive ozonolysis of vinylcyclopropanol derivative **10** and subjected to asymmetric allylation with Keck, Roush and Brown reagents.[10–12] The allylation of **9** with allyltri-*n*-butylstannane in the presence of the (*S*)-BINOL enantiodirecting ligand,[10] proceeded slowly to give racemic homoallylic alcohol derivative **13**. Better results were obtained with allylboron reagents. Aldehyde **9** reacted with diisopropyl (*R*,*R*)-tartrate-modified allylboronate **14**[11] and (+)-diisopinocamphenyl-derived allylborane **15**[12] to form **13** with 50% and 79% ee, respectively (Scheme 3).



ML_n	Yields **13**, %	*ee*, %
$SnBu_3$[a]	-[b]	0
 **14**	51	50
(+)-$B(Ipc)_2$ **15**	52	79

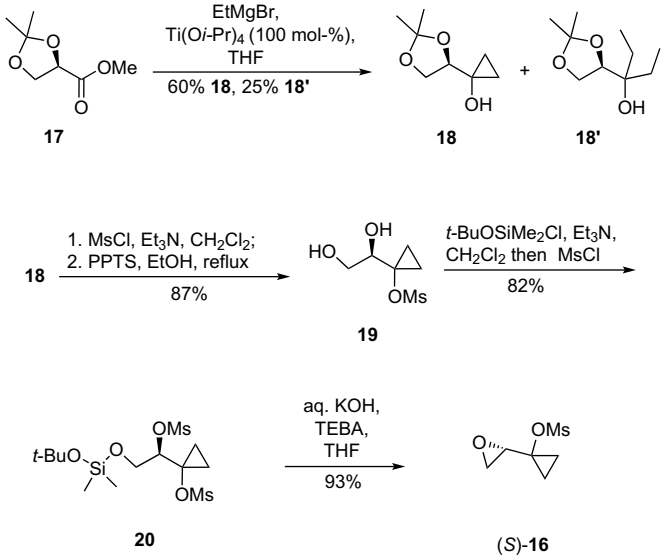
[a](*S*)-BINOL-titanium complex was used as the chiral catalyst.
[b]homoallylic alcohol derivative **13** (45%) along with starting compound **9** (55%) were detected in the reaction mixture after a month by 1H NMR.

Scheme 3.

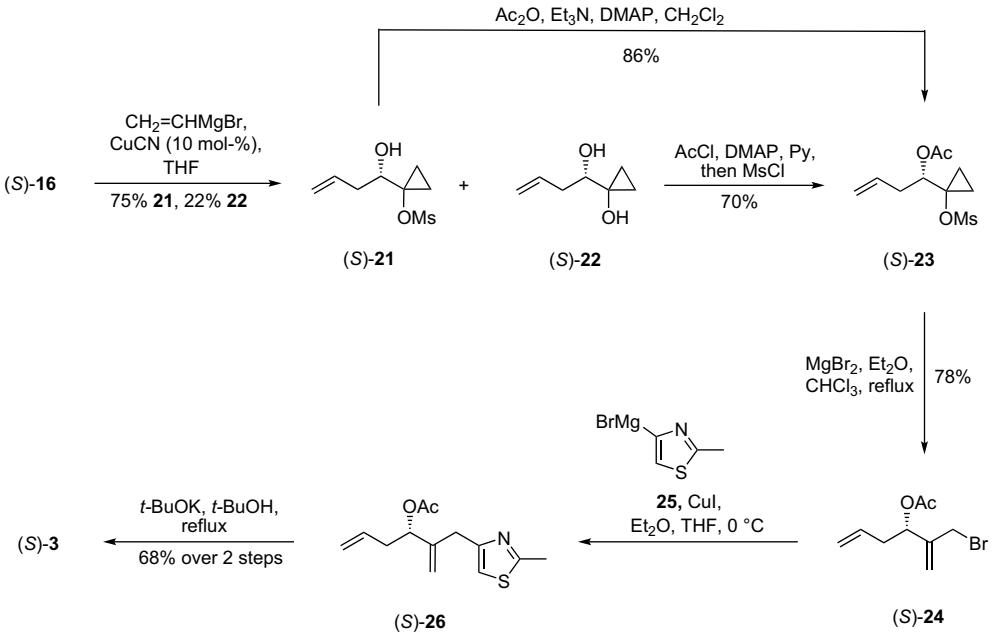
Because allylation of aldehyde **9** proceeded with disappointing enantioselectivity, we tried to prepare enantiomerically pure homoallylic alcohols (*S*)-**3** and (*R*)-**3** by the use of ring opening of the appropriate oxiranes (*S*)-**16** and (*R*)-**16** with vinylmagnesium bromide as the key step. Both oxiranes were synthesized by cyclopropanation of (*R*)-glycerate derivative **17**, which is easily available from relatively cheap D-mannitol,[13] and subsequent functional group manipulations. The cyclopropanation of ester **17** with ethylmagnesium bromide in the presence of equimolar amounts of titanium(IV) isopropoxide gave cyclopropanol **18** in 60% isolated yield (Scheme 4) along with the corresponding tertiary alcohol **18′** as the main side product.[14] Mesylation of **18**, followed by acetonide deprotection afforded cleanly the diol **19**, which was used as common intermediate for the preparation of oxiranes (*S*)-**16** and (*R*)-**16**.

To prepare oxirane (*S*)-**16** the primary hydroxyl group of diol **19** was protected as its *tert*-butoxydimethylsilyl ether[15] and subsequent mesylation of the secondary hydroxyl led to dimesylate **20**. Treatment of the latter with aqueous KOH in the presence of TEBA[16] caused desilylation and subsequent formation of oxirane (*S*)-**16**.

Treatment of oxirane (*S*)-**16** with vinylmagnesium bromide in the presence of CuI or CuCN furnished homoallylic alcohol (*S*)-**21** and its demesylation product (*S*)-**22** (Scheme 4). When the reaction was performed in the presence of equimolar amounts of CuI,[17] a 4:1 mixture of monomesylate (*S*)-**21** and diol (*S*)-**22** was obtained in 66% overall yield. The ring opening of (*S*)-**16** in the presence of catalytic amounts of CuCN[18] (10 mol %) gave the same mixture of products in excellent yield. Acetylation of mesylate (*S*)-**21**, as well as sequential acetylation of the less hindered secondary hydroxyl group of diol (*S*)-**22**, followed by mesylation of the tertiary hydroxyl unit, led to mesylate (*S*)-**23** in 82% combined yield.



Scheme 4.



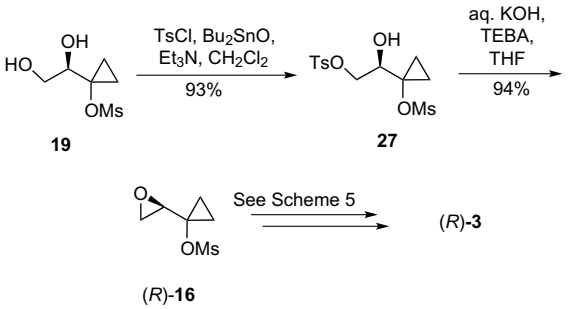
Scheme 5.

Cyclopropylsulfonate (*S*)-**23** was subjected to cationic cyclopropyl–allyl rearrangement by treatment with magnesium bromide in ether/chloroform mixture[19] to afford 2-substituted allyl bromide (*S*)-**24** in high yield.

The coupling of allyl bromide (*S*)-**24** with 2-methylthiazol-4-yl-magnesium bromide **25** in ether in the presence of CuI[6b] led to acetate (*S*)-**26** in low yield. The reaction proceeded more smoothly when ether/THF mixture (1:2) was used as solvent and allyl acetate (*S*)-**26** was obtained in this case in 85% yield. Base-catalyzed allylic shift of the disubstituted carbon–carbon double bond in compound (*S*)-**26** to the conjugated position[6b] proceeded simultaneously with acetate deprotection to give target homoallylic alcohol (*S*)-**3** with >99% ee.

Tosylation of the primary hydroxyl group of diol **19** in the presence of *n*-Bu_2SnO[20] furnished disulfonate **27** in excellent yield and regioselectivity, which under treatment with aqueous KOH in the presence of TEBA was smoothly converted to oxirane (*R*)-**16**. The transformation of the latter into homoallylic alcohol (*R*)-**3** was performed via the corresponding intermediates (*R*)-**21**–(*R*)-**26** (Scheme 6), in the same way as described for compound (*S*)-**3**, with >99% ee (Scheme 5).

The synthesis of homoallylic alcohols (*S*)-**3** and (*R*)-**3** described in this work required a longer reaction sequence than earlier published syntheses of (*S*)-**3** by asymmetric allylation of the corresponding aldehydes with an allylboron reagent[5a] or with allyltri-*n*-butylstannane in the presence of a chiral catalyst.[5b,c] Nevertheless, the cyclopropanol approach is based on simple reaction procedures and leads to the target products **3** with higher enantiomeric purity. In addition, a convenient way to both key oxiranes (*S*)-**16** and (*R*)-**16** described in this work has positive implications for these new bifunctional C-5 building blocks within other synthetically useful preparative approaches.



Scheme 6.

3. Conclusions

In conclusion, the reaction of 1-formylcyclopropyl pivalate **9** with chiral allylboron reagents gave the corresponding homoallylic alcohol **13** with moderate enantioselectivity, whereas asymmetric allylation of **9** under Keck conditions proceeded with lack of enantioselectivity. Homoallylic alcohol derivatives (*S*)-**23** and (*R*)-**23** in stereochemically pure form were effectively prepared starting from easily available (*R*)-methyl 2,3-*O*-isopropylideneglycerate **17** via the cyclopropanation of the ester group, followed by conversion of the cyclopropanol **18** into enantiomeric oxyranyl-substituted cyclopropylsulfonates (*S*)-**16** and (*R*)-**16** and copper-catalyzed epoxide ring opening with vinylmagnesium bromide. Compounds (*S*)-**23** and (*R*)-**23** were successfully converted into C13–C21 epothilone fragments (*S*)-**3** and (*R*)-**3** by use of earlier developed methods for stereoselective transformation of the cyclopropylsulfonate group into the alkenylthiazole fragment.

4. Experimental

4.1. General

Melting points were determined with a capillary apparatus. Optical rotations were measured at 20±2 °C with a CM-3 polarimeter (scale factor: 0.05°). Column chromatography was performed on Merck 60 silica gel (70–230 mesh). IR spectra were recorded with a Vertex 70 spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Bruker AC 400 instrument at 400 and 100 MHz, respectively, in $CDCl_3$ ($CHCl_3$ at δ=7.26 ppm for ^1H NMR and $CHCl_3$ at δ=77.0 ppm for ^{13}C NMR as internal standard).

4.2. 1-(2-Bromoethyl)cyclopropyl pivalate (12)

Pivaloyl chloride (9.5 mL, 67.6 mmol) was added to a solution of 1-(2-bromoethyl)cyclopropanol (7.67 g, 46.5 mmol), prepared in accordance with described procedure[9c] from ester **11** (10.0 g, 55.2 mmol) and ethylmagnesium bromide (120.8 mmol) in the presence of Ti(O*i*-Pr)$_4$ (1.64 mL, 5.5 mmol) in Et_2O, and pyridine (12.0 mL, 148 mmol) in CH_2Cl_2 (85 mL). The reaction mixture was left overnight at room temperature and quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give pivalate **12** (9.62 g, 83%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.73–0.76 (m, 2H, 2-H, 3-H), 0.82–0.85 (m, 2H, 2-H, 3-H), 1.19 (s, 9H, C(CH$_3$)$_3$), 2.30 (t, *J*=7.4 Hz, 2H, 1′-H), 3.44 (t, *J*=7.4 Hz, 2H, 2′-H). ^{13}C NMR ($CDCl_3$) δ 11.8 (×2), 26.9 (×3), 28.7, 38.1, 38.6, 58.2, 178.3. IR (CCl_4) ν_{max}: 1745 cm^{-1}. Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88. Found: C, 47.96; H, 6.95.

4.3. 1-Vinylcyclopropyl pivalate (10)

To a solution of *t*-BuOK prepared from potassium (1.46 g, 37.4 mmol) in *t*-BuOH (45 mL) was added pivalate **12** (6.21 g, 24.9 mmol). The mixture was refluxed for 45 min and concentrated in vacuo. The residue was quenched with aqueous NH_4Cl (50 mL) and extracted with ether (3×20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give **10** (2.51 g, 60%) as a colourless oil. bp 55–65 °C/10 Torr. ^{1}H NMR ($CDCl_3$) δ 0.95–1.00 (m, 2H, 2-H, 3-H), 1.03–1.08 (m, 2H, 2-H, 3-H), 1.19 (s, 9H, C(CH$_3$)$_3$), 4.96 (dd, *J*=17.2, 0.5 Hz, 1H, C*H*H=CH), 5.02 (dd, *J*=11.0, 0.5 Hz, 1H, CH*H*=CH), 5.67 (dd, *J*=17.2, 11.0 Hz, 1H, CH$_2$=C*H*). ^{13}C NMR ($CDCl_3$) δ 14.6 (×2), 27.0 (×3), 38.6, 58.4, 111.4, 137.6, 177.8. IR (CCl_4) ν_{max}: 1749 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.64.

4.4. 1-Formylcyclopropyl pivalate (9)

Ozone was bubbled at −78 °C through a solution of vinylcyclopropane derivative **10** (4.00 g, 23.8 mmol) in CH_2Cl_2 (120 mL) until a persistent blue solution was obtained. After elimination of excess ozone by oxygen bubbling, zinc dust (3.10 g, 47.6 mmol) and 50% acetic acid (64 mL) were added and the mixture was allowed to reach room temperature with vigorous stirring. The mixture was diluted with CH_2Cl_2 (100 mL), the organic layer was separated, washed with water, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a short column of silica gel (petroleum ether/ethyl acetate) to give aldehyde **9** (3.44 g, 85%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 9H, C(CH$_3$)$_3$), 1.26–1.30 (m, 2H, 2-H, 3-H), 1.51–1.55 (m, 2H, 2-H, 3-H), 9.21 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 15.4 (×2), 26.9 (×3), 38.5, 63.3, 178.4, 196.5. IR (CCl_4) ν_{max}: 1748, 1731 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C 63.29, H 8.38.

4.5. (*S*)-1-(1-Hydroxycyclopropyl)but-3-enyl pivalate (13)

4.5.1. Procedure A[10]

A mixture of (*S*)-BINOL (50 mg, 0.18 mmol), Ti(O*i*-Pr)$_4$ (1 M in CH_2Cl_2, 0.18 mL, 0.18 mmol) and oven-dried powdered 4 Å molecular sieves (0.70 g) in CH_2Cl_2 (1.8 mL) was heated under reflux for 1 h and cooled to ambient temperature. A solution of aldehyde **9** (0.30 g, 1.75 mmol) in CH_2Cl_2 (0.3 mL) was added and the reaction mixture was stirred for 10 min. The contents were cooled to −78 °C and allyltri-*n*-butylstannane (0.87 g, 2.6 mmol) was added dropwise. The reaction mixture was warmed to ambient temperature, stored for a month and quenched with aqueous $NaHCO_3$ (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Homoallylic alcohol **13** (45%) as well as starting aldehyde **9** (55%) was detected in the residue by ^{1}H NMR spectroscopy.

4.5.2. Procedure B[11]

A solution of aldehyde **9** (0.17 g, 1 mmol) in toluene (1 mL) was added dropwise at −78 °C to a stirred solution of (*R*,*R*)-diisopropyltartrate-modified allylboronate **14** (0.28 g, 1 mmol) in toluene (4 mL). The reaction mixture was stirred over 1 h, quenched with water (5 mL) and extracted with ether (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel (0.5 g) was added to a solution of the residue in petrol ether (3 mL) and the mixture was stirred overnight, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give homoallylic alcohol **13** (0.11 g, 51%) as a colourless oil.

4.5.3. Procedure C[12]

A solution of aldehyde **9** (0.11 g, 0.65 mmol) in ether (0.3 mL) was added dropwise at −78 °C to a stirred solution of (+)-diisopinocamphenyl-derived allylborane **15** (0.33 M in ether, 2 mL, 0.65 mmol). The reaction mixture was stirred for 1 h, warmed to ambient temperature, concentrated in vacuo and the residue was dissolved in THF (3 mL). Sodium perborate (0.30 g, 2 mmol) and water (2 mL) were added and the mixture was stirred overnight. The aqueous phase was separated and extracted with ether (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel (0.5 g) was added to a solution of residue in petrol ether (3 mL) and the mixture was stirred overnight, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give homoallylic alcohol **13** (72 mg, 52%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.56–0.66 (m, 2H, 2′-H, 3′-H), 0.74 (m, 1H, 2′-H), 0.83 (m, 1H, 3′-H), 1.19 (s, 9H, C(CH$_3$)$_3$), 2.48–2.61 (m, 2H, 2-H), 2.63 (br s, 1H, OH), 4.50 (dd, *J*=8.1, 5.8 Hz, 1H, 1-H), 5.03 (dd, *J*=10.2, 1.5 Hz, 1H, 4-H), 5.10 (dd, *J*=17.2, 1.5 Hz, 1H, 4-H), 5.77 (ddt, *J*=17.2, 10.2, 7.2 Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$) δ 12.3, 12.5, 27.2 (×3), 35.6, 38.9, 57.1, 77.7, 117.5, 133.9, 178.1. IR (CCl_4) ν_{max}: 3600, 3486, 1729 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.16; H, 9.39.

4.5.4. Determination of the enantiomeric purity of (*S*)-*13*

The ee value of (*S*)-1**3** was determined by Mosher's method[21] from the integral intensities of the signals of the protons at δ=4.81 and 4.87 ppm (C*H*OMTPA) in the ^{1}H NMR spectra of the (*S*)-MTPA esters. In this way the enantiomeric purity of compound (*S*)-**13** obtained in accordance with procedures A, B and C was determined to be 0%, 50% and 79%, ee, respectively.

4.6. (*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropanol (18) and (*R*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)pentan-3-ol (18′)

A solution of ethylmagnesium bromide prepared from magnesium (7.50 g, 313 mmol) and ethyl bromide (23.4 mL, 313 mmol) in a mixture of THF (210 mL) and benzene (20 mL) was added over 2 h to a stirred solution of ester **17** (10.00 g, 62.5 mmol) and Ti(O*i*-Pr)$_4$ (19.0 mL, 62.5 mmol) in THF (65 mL). The mixture was concentrated in vacuo, diluted with CH_2Cl_2 (150 mL), quenched with aqueous NH_4Cl (40 mL), filtered and the filter cake was washed thoroughly with CH_2Cl_2 (3×100 mL). The filtrate was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel

(petroleum ether/ethyl acetate) to give cyclopropanol derivative **18** (5.93 g, 60%) as a colourless oil and tertiary alcohol **18′** (2.90 g, 25%).

*4.6.1. Cyclopropanol **18***

$[\alpha]_D$ +12 (*c* 3.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.51 (m, 1H, 2-H), 0.64 (m, 1H, 3-H), 0.83–0.89 (m, 2H, 2-H, 3-H), 1.38 (s, 3H, 2′-Me), 1.47 (s, 3H, 2′-Me), 2.42 (br s, 1H, OH), 3.72 (t, *J*=6.9 Hz, 1H, 4′-H), 4.01 (dd, *J*=6.9, 0.8 Hz, 2H, 5′-H). ^{13}C NMR ($CDCl_3$) δ 9.5, 12.4, 25.3, 26.4, 53.8, 65.7, 80.9, 109.2. IR (CCl_4) ν_{max}: 3585, 3479 cm^{-1}. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H 8.92. Found: C, 60.61; H, 8.98.

*4.6.2. Tertiary alcohol **18′***

$[\alpha]_D$ +21 (*c* 5.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.87 (t, *J*=7.7 Hz, 3H, 1-H), 0.88 (t, *J*=7.7 Hz, 3H, 5-H), 1.28–1.48 (m, 2H, 2-H, 4-H), 1.36 (s, 3H, 2′-Me), 1.41 (s, 3H, 2′-Me), 1.55–1.66 (m, 2H, 1-H, 5-H), 1.86 (br s, 1H, OH), 3.87 (dd, *J*=8.2, 7.7 Hz, 1H, 4′-H), 3.93 (dd, *J*=7.7, 6.1 Hz, 1H, 4′-H), 4.04 (dd, *J*=8.2, 6.1 Hz, 1H, 4′-H). ^{13}C NMR ($CDCl_3$) δ 7.4, 7.7, 25.6, 26.1, 26.4, 28.7, 64.5, 73.3, 79.4, 108.7. IR (CCl_4) ν_{max}: 3580 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.91; H, 10.73.

4.7. (*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl methanesulfonate

Methanesulfonyl chloride (5.8 mL, 74.5 mmol) was added dropwise at 0 °C to a stirred solution of cyclopropanol derivative **18** (9.05 g, 57.3 mmol) and triethylamine (12.0 mL, 86.3 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred at room temperature for 30 min, quenched with aqueous $NaHCO_3$ (60 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl methanesulfonate (13.01 g, 96%), which was employed in the next step without further purification. $[\alpha]_D$ +4 (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 94 (m, 1H, 2-H), 1.01 (m, 1H, 3-H), 1.23–1.36 (m, 2H, 2-H, 3-H), 1.32 (s, 3H, 2′-Me), 1.39 (s, 3H, 2′-Me), 3.03 (s, 3H, Ms), 3.9 (dd, *J*=8.6, 6.0 Hz, 1H, 5′-H), 4.13 (dd, *J*=8.6, 6.6 Hz, 1H, 5′-H), 4.47 (t, *J*=6.4 Hz, 1H, 4′-H). ^{13}C NMR ($CDCl_3$): δ 8.5, 9.2, 25.0, 26.1, 39.6, 65.6, 66.8, 75.6, 109.7. IR (CCl_4) ν_{max}: 1355, 1168 cm^{-1}. Anal. Calcd for $C_9H_{16}O_5S$: C, 45.75; H, 6.83. Found: C, 45.98; H, 6.97.

4.8. (*R*)-1-(1,2-Dihydroxyethyl)cyclopropyl methanesulfonate (19)

A solution of unpurified (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl methanesulfonate (13.01 g, 55.1 mmol) and PPTS (1.4 g) in ethanol (120 mL) was heated under reflux for 2 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give mesylate **19** (9.88 g, 91%) as a viscous oil. $[\alpha]_D$ +10 (*c* 1.54, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.94 (m, 1H, 2-H), 1.05 (m, 1H, 3-H), 1.28 (m, 1H, 2-H), 1.48 (m, 1H, 3-H), 2.31 (br s, 1H, OH), 3.09 (s, 3H, Ms), 3.21 (br s, 1H, OH), 3.60 (m, 1H, 1′-H), 3.75 (dd, *J*=11.3, 6.9 Hz, 1H, 2′-H), 3.84 (dd, *J*=11.3, 4.1 Hz, 1H, 2′-H). ^{13}C NMR ($CDCl_3$) δ 9.9, 10.2, 39.6, 63.5, 66.8, 74.4. IR (film) ν_{max}: 3391, 1345, 1165 cm^{-1}. Anal. Calcd for $C_6H_{12}O_5S$: C, 36.73; H, 6.16. Found: C, 36.87; H, 6.22.

4.9. (*R*)-2-(*tert*-Butoxydimethylsiloxy)-1-(1-(methylsulfonyloxy)cyclopropyl)ethyl methanesulfonate (20)

tert-Butoxychlorodimethylsilane[15] (8.97 g, 54.0 mmol) was added dropwise at 0 °C to a stirred solution of diol **19** (9.60 g, 48.9 mmol) and triethylamine (20.5 mL, 147 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred for 10 min and methanesulfonyl chloride (5.7 mL, 74 mmol) was added dropwise at 0 °C. The mixture was allowed to reach room temperature, stirred for 30 min, quenched with aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give protected diol **20** (16.7 g, 82%) as a colourless oil. $[\alpha]_D$ +28 (*c* 6.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.14 (s, 6H, $SiMe_2$), 1.04 (m, 1H, 2′-H), 1.25 (m, 1H, 3′-H), 1.28 (s, 9H, $C(CH_3)_3$), 1.37 (m, 1H, 2′-H), 1.74 (dt, *J*=11.4, 7.3 Hz, 1H, 3′-H), 3.11 (s, 3H, Ms), 3.13 (s, 3H, Ms), 3.92 (dd, *J*=11.8, 7.8 Hz, 1H, 2-H), 4.03 (dd, *J*=11.8, 3.7 Hz, 1H, 2-H), 4.70 (dd, *J*=7.8, 3.7 Hz, 1H, 1-H). ^{13}C NMR ($CDCl_3$) δ −0.4 (×2), 11.2, 11.6, 31.9 (×3), 38.9, 39.5, 61.4, 64.6, 72.8, 85.4. IR (CCl_4) ν_{max}: 1366, 1178 cm^{-1}. Anal. Calcd for $C_{13}H_{28}O_8S_2Si$: C, 38.59; H, 6.98. Found: C, 38.26; H, 6.85.

4.10. (*S*)-1-(Oxiran-2-yl)cyclopropyl methanesulfonate ((*S*)-16)

TEBA (90 mg) and 25% aqueous KOH (6 mL) were added to a solution of protected diol **20** (0.92 g, 2.3 mmol) in THF (9 mL). The mixture was vigorously stirred for 1 h and diluted with ether (9 mL). The aqueous phase was separated and extracted with ether (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give oxirane (*S*)-**16** (0.38 g, 93%) as a colourless oil. CAUTION: neat oxiranes **16** were disposed to vigorous decomposition. A THF solution of the latter was stable upon storage in a fridge over a few months. $[\alpha]_D$ −11 (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.82–0.95 (m, 2H, 2-H, 3-H), 1.26–1.28 (m, 2H, 2-H, 3-H), 2.68 (dd, *J*=4.9, 2.4 Hz, 1H, 3′-H), 2.88 (dd, *J*=4.9, 3.8 Hz, 1H, 3′-H), 3.07 (s, 3H, Ms), 3.53 (dd, *J*=3.8, 2.4 Hz, 1H, 2′-H). ^{13}C NMR ($CDCl_3$) δ 8.6, 9.7, 39.5, 46.2, 51.1, 64.5. IR (CCl_4) ν_{max}: 1357, 1171 cm^{-1}. Anal. Calcd for $C_6H_{10}O_4S$: C, 40.44; H, 5.66. Found: C, 40.70; H, 5.77.

4.11. (*S*)-1-(1-Hydroxybut-3-enyl)cyclopropyl methanesulfonate ((*S*)-21) and (*S*)-1-(1-hydroxybut-3-enyl)cyclopropanol ((*S*)-22)

Vinylmagnesium bromide (1 M in THF, 58 mL, 58.0 mmol) was added dropwise at −15 °C under argon to a stirred suspension of CuCN (0.13 g, 1.4 mmol) in THF (70 mL). The mixture was stirred for 5 min and a solution of oxirane (*S*)-**16** (2.71 g, 14.5 mmol) in THF (10 mL) was added dropwise. After stirring for 45 min at −10 °C the reaction mixture was quenched with a mixture of saturated aqueous solutions of NH_4Cl (50 mL) and NH_4OH (50 mL), and extracted with diethyl ether (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give monomesylate (*S*)-**21** (2.36 g, 75%) as a colourless oil and diol (*S*)-**22** (0.41 g, 22%) as white crystals.

*4.11.1. Monomesylate (S)-**21***

$[\alpha]_D$ −21 (*c* 3.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.83 (m, 1H, 2-H), 1.03 (m, 1H, 3-H), 1.18 (m, 1H, 2-H), 1.52 (m, 1H, 3-H), 2.39 (m, 1H, 2′-H), 2.49 (m, 1H, 2′-H), 2.78 (m, 1H, OH), 3.11 (s, 3H, Ms), 3.44 (dt, *J*=8.4, 5.4 Hz, 1H, 1′-H), 5.13 (dd, *J*=10.2, 1.5 Hz, 1H, 4′-H), 5.17 (dd, *J*=17.2, 1.5 Hz, 1H, 4′-H), 5.88 (ddt, *J*=17.2, 10.2, 6.9 Hz, 1H, 3′-H). ^{13}C NMR ($CDCl_3$) δ 10.6, 10.8, 38.1, 39.5, 68.8, 74.5, 117.9, 134.0. IR (CCl_4) ν_{max}: 3537, 1351, 1169 cm^{-1}. Anal. Calcd for $C_8H_{14}O_4S$: C, 46.59; H, 6.84. Found: C, 46.54; H, 6.91.

*4.11.2. Diol (S)-**22***

Mp 58–59 °C. $[\alpha]_D$ +1 (*c* 2.7, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.53–0.63 (m, 2H, 2-H, 3-H), 0.79–0.90 (m, 2H, 2-H, 3-H), 1.97 (br s, 1H, OH), 0.40–2.52 (m, 3H, OH, 2′-H), 3.19 (dd, *J*=8.4, 4.6 Hz, 1H, 1′-H),

5.09 (d, J=9.9 Hz, 1H, 4′-H), 5.14 (d, J=17.2 Hz, 1H, 4′-H), 5.92 (ddt, J=17.2, 9.9, 7.2 Hz, 1H, 3′-H). ^{13}C NMR ($CDCl_3$) δ 11.1, 12.7, 37.9, 57.8, 76.2, 117.6, 135.0. IR (CCl_4) ν_{max}: 3587, 3481 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.93; H, 9.52.

4.12. (*S*)-1-(1-(Methylsulfonyloxy)cyclopropyl)but-3-enyl acetate ((*S*)-23)

4.12.1. Conversion of monomesylate (S)-*21* into homoallyl acetate (S)-*23*

Acetic anhydride (0.74 mL, 7.8 mmol) was added at 0 °C to a stirred solution of monomesylate (*S*)-**21** (1.40 g, 6.5 mmol), DMAP (0.16 g, 1.31 mmol) and triethylamine (1.8 mL, 13.0 mmol) in CH_2Cl_2 (35 mL). The reaction mixture was stirred for 1 h, warmed to ambient temperature and quenched with water (20 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give homoallyl acetate (*S*)-**23** (1.45 g, 86%) as a colourless oil. $[\alpha]_D$ −41 (*c* 2.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 1H, 2′-H), 1.12–1.20 (m, 2H, 2′-H, 3′-H), 1.54 (m, 1H, 3′-H), 2.09 (s, 3H, $COCH_3$), 2.42–2.58 (m, 2H, 2-H), 3.07 (s, 3H, Ms), 4.75 (dd, J=8.8, 5.3 Hz, 1H, 1-H), 5.07 (dd, J=10.2, 1.3 Hz, 1H, 4-H), 5.12 (dd, J=17.2, 1.3 Hz, 1H, 4-H), 5.74 (ddt, J=17.2, 10.2, 7.0 Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$) δ 10.5, 12.4, 20.9, 35.3, 39.7, 66.6, 75.2, 118.1, 132.8, 170.4. IR (CCl_4) ν_{max}: 1742, 1369, 1175 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50. Found: C, 48.38; H, 6.43.

4.12.2. Conversion of diol (S)-*22* into homoallyl acetate (S)-*23*

Acetyl chloride (0.21 mL, 2.9 mmol) was added at 0 °C to a solution of (*S*)-**22** (0.33 g, 2.6 mmol) and DMAP (63 mg, 0.52 mmol) in pyridine (5.2 mL). The reaction mixture was left in a fridge at 5 °C for 3 h. After that methanesulfonyl chloride (0.4 mL, 5.2 mmol) was added to the reaction mixture. The latter was left in a fridge at 5 °C overnight and quenched in the same manner as described above. Column chromatography on silica gel (petroleum ether/ethyl acetate) gave (*S*)-**23** (0.75 g, 70%) as a colourless oil.

4.13. (*S*)-2-(Bromomethyl)hexa-1,5-dien-3-yl acetate ((*S*)-24)

A solution of homoallyl acetate (*S*)-**23** (1.43 g, 3.8 mmol) in $CHCl_3$ (70 mL) was added to a solution of $MgBr_2$ prepared from magnesium (0.55 g, 23.1 mmol) and dibromoethane (2.2 mL, 25.4 mmol) in diethyl ether (20 mL). The mixture was heated under reflux for 5 h, quenched with water (50 mL) and extracted with $CHCl_3$ (2×20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give (*S*)-**24** (1.05 g, 78%) as a colourless oil. $[\alpha]_D$ −6 (*c* 4.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H, $COCH_3$), 2.44–2.58 (m, 2H, 4-H), 3.96 (d, J=10.8 Hz, 1H, 1′-H), 4.15 (d, J=10.8 Hz, 1H, 1′-H), 5.08 (d, J=6.9 Hz, 1H, 6-H), 5.11 (d, J=17.2 Hz, 1H, 6-H), 5.29 (s, 1H, 1-H), 5.38 (s, 1H, 1-H), 5.43 (dd, J=7.4, 5.6 Hz, 1H, 3-H), 5.73 (ddt, J=17.2, 10.2, 6.9 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$) δ 21.0, 32.1, 37.9, 73.3, 118.1 (×2), 133.0, 143.2, 170.0. IR (CCl_4) ν_{max}: 1744 cm^{-1}. Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.25; H, 5.79.

4.14. (*S*)-2-((2-Methylthiazol-4-yl)methyl)hexa-1,5-dien-3-yl acetate ((*S*)-26)

A solution of *n*-BuLi in hexane (1.6 M, 4.6 mL, 7.3 mmol) was added dropwise at −78 °C to a stirred solution of 4-bromo-2-methylthiazole **25**[22] (1.30 g, 7.3 mmol) in diethyl ether (4.6 mL). The reaction mixture was stirred for 3 h at the same temperature, warmed to −60 °C and a solution of $MgBr_2$ prepared from magnesium (0.23 g, 9.4 mmol) and dibromoethane (0.81 mL, 9.4 mmol) in diethyl ether (9 mL) was added. The contents were warmed to 0 °C and diluted with THF (35 mL) followed by the subsequent addition of CuI (93 mg, 0.49 mmol) and a solution of (*S*)-**24** (0.857 g, 3.68 mmol) in THF (5 mL). After stirring for 5 min the reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL). The aqueous phase was separated and extracted with ether (3×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give thiazole (*S*)-**26** (0.785 g, 85%) as a yellow oil. $[\alpha]_D$ −19 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, $COCH_3$), 2.40 (t, J=7.0 Hz, 2H, 4-H), 2.68 (s, 3H, 2″-Me), 3.48 (d, J=16.6 Hz, 1H, 1′-H), 3.53 (d, J=16.6 Hz, 1H, 1′-H), 4.94 (s, 1H, 1-H), 5.03 (dd, J=10.0, 1.5 Hz, 1H, 6-H), 5.06 (dd, J=17.3, 1.5 Hz, 1H, 6-H), 5.16 (s, 1H, 1-H), 5.30 (t, J=6.5 Hz, 1H, 3-H), 5.69 (ddt, J=17.3, 10.0, 7.0 Hz, 1H, 5-H), 6.81 (s, 1H, 5″-H). ^{13}C NMR ($CDCl_3$) δ 19.1, 21.0, 34.7, 37.6, 74.9, 114.2, 114.3, 117.6, 133.4, 144.4, 153.5, 165.5, 170.1. IR (CCl_4) ν_{max}: 1741 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82. Found: C, 61.77; H, 6.75.

4.14.1. Preparation of (S,E)-2-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-ol ((S)-*3*)

A solution of *t*-BuOK prepared from potassium (0.20 g, 5.0 mmol) and *t*-BuOH (20 mL) was added to (*S*)-**26** (0.519 mg, 2.07 mmol). The mixture was refluxed for 45 min and concentrated in vacuo. The residue was quenched with water (10 mL) and extracted with ether (3×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give (*S*)-**3** (344 mg, 80%) as a yellow oil. $[\alpha]_D$ −22 (*c* 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H, 2-Me), 2.29–2.46 (m, 3H, 4-H, OH), 2.69 (s, 3H, 2′-Me), 4.20 (t, J=6.3 Hz, 1H, 3-H), 5.11 (d, J=10.2 Hz, 1H, 6-H), 5.15 (dd, J=17.2, 1.3 Hz, 1H, 6-H), 5.81 (ddt, J=17.2, 10.2, 7.2 Hz, 1H, 5-H), 6.55 (s, 1H, 1-H), 6.92 (s, 1H, 5′-H). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.1, 40.0, 76.4, 115.5, 117.8, 119.0, 134.5, 141.4, 152.7, 164.6. IR (CCl_4) ν_{max}: 3615, 3311 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22. Found: C, 63.29; H, 7.10. The spectral data are in agreement with the literature data.[5a,b]

4.14.2. Determination of the enantiomeric purity of (S)-*3* and (R)-*3*

The ee values of (*S*)-**3** and (*R*)-**3** were determined by Mosher's method[21] from the integral intensities of the singlets of the protons at δ=6.57 and 6.45 ppm (1-H) in the ^{1}H NMR spectra of the (*R*)-MTPA esters. In this way the enantiomeric purity of compounds (*S*)-**3** and (*R*)-**3** was determined to be >99% ee.

4.15. (*R*)-2-Hydroxy-2-(1-(methylsulfonyloxy)cyclopropyl)-ethyl 4-methylbenzenesulfonate (27)

To a solution of diol **19** (3.00 g, 15.3 mmol) and triethylamine (2.34 mL, 16.8 mmol) in CH_2Cl_2 (50 mL) were added Bu_2SnO (76 mg, 0.31 mmol) and toluenesulfonyl chloride (3.06 g, 16.1 mmol). The reaction mixture was stirred for 5 h, filtered over silica gel, washed with water (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give tosylate **27** (5.00 g, 93%) as a viscous oil. $[\alpha]_D$ +10 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.93 (m, 1H, 2′-H), 1.03 (m, 1H, 3′-H), 1.24 (m, 1H, 2′-H), 1.52 (m, 1H, 3′-H), 2.45 (s, 3H, tosyl CH_3), 3.04 (s, 3H, Ms), 3.67 (t, J=5.8 Hz, 1H, 2-H), 4.14 (dd, J=10.5, 6.4 Hz, 1H, 1-H), 4.26 (dd, J=10.5, 5.4 Hz, 1H, 1-H), 7.36 (d, J=8.1 Hz, 2H, tosyl CH), 7.80 (d, J=8.1 Hz, 2H, tosyl CH). ^{13}C NMR ($CDCl_3$) δ 9.9, 10.5, 21.6, 39.3, 65.8, 70.0, 72.2, 128.0 (×2), 129.9 (×2), 132.5, 145.2. IR (film) ν_{max}: 3514,

1357, 1176 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_7S_2$: C, 44.56; H, 5.18. Found: C, 44.69; H, 5.23.

4.16. (*R*)-1-(Oxiran-2-yl)cyclopropyl methanesulfonate ((*R*)-16)

TEBA (0.47 g) and 25% aqueous KOH (24 mL) were added to a solution of tosylate **27** (4.70 g, 13.4 mmol) in THF (24 mL). The mixture was vigorously stirred over 1 h and diluted with ether (25 mL). The aqueous phase was separated and extracted with ether (3×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give (*R*)-**16** (2.40 g, 94%). This material was employed in the next step without further purification. CAUTION: neat oxiranes **16** were disposed to vigorous decomposition. $[\alpha]_D$ +10 (*c* 2.0, $CHCl_3$). IR and NMR data were identical with those of enantiomeric oxirane (*S*)-**16** (see above).

4.17. (*R*)-1-(1-Hydroxybut-3-enyl)cyclopropyl methanesulfonate ((*R*)-21) and (*R*)-1-(1-hydroxybut-3-enyl)cyclopropanol ((*R*)-22)

Compoumds (*R*)-**21** and (*R*)-**22** were obtained in the same manner as enantiomeric monomesilate (*S*)-**21** and diol (*S*)-**22** (see above).

*4.17.1. Monomesylate (R)-**21***

Yield: 75%. $[\alpha]_D$ +20 (*c* 2.5, $CHCl_3$). IR and NMR data were identical with those of enantiomeric sulfonate (*S*)-**21**.

*4.17.2. Diol (R)-**22***

Yield 22%. $[\alpha]_D$ −1 (*c* 4.1, $CHCl_3$). IR and NMR data were identical with those of enantiomeric diol (*S*)-**22**.

4.18. (*R*)-1-(1-(Methylsulfonyloxy)cyclopropyl)but-3-enyl acetate ((*R*)-23)

Acetate (*R*)-**23** was obtained from monomesylate (*R*)-**21** and diol (*R*)-**22** in the same manner as enantiomeric homoallyl acetate (*S*)-**23** in 85% combined yield (88% yield from monomesylate (*R*)-**21** and 73% yield from diol (*R*)-**22**). $[\alpha]_D$ +41 (*c* 2.2, $CHCl_3$). IR and NMR data were identical with those of enantiomeric acetate (*S*)-**23** (see above).

4.19. (*R*)-2-(Bromomethyl)hexa-1,5-dien-3-yl acetate ((*R*)-24)

Bromide (*R*)-**24** was obtained from sulfonate (*R*)-**23** in the same manner as enantiomeric bromide (*S*)-**24** (see above). Yield 76%. $[\alpha]_D$ +6 (*c* 4.3, $CHCl_3$). IR and NMR data were identical with those of enantiomeric bromide (*S*)-**24** (see above).

4.20. (*R,E*)-2-Methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-ol ((*R*)-3)

Homoallylic alcohol (*R*)-**3** was obtained from bromide (*R*)-**24** in the same manner as enantiomeric alcohol (*S*)-**3** (see above). Yield over two steps 70%. $[\alpha]_D$ +22 (*c* 1.4, $CHCl_3$). IR and NMR data were identical with those of enantiomeric homoallylic alcohol (*S*)-**3** (see above).

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