Tetrahedron Vol. 49, No. 5, pp 1025-1042, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Acyclic Diastereocontrol and Asymmetric Transmission via Anionic Oxy-Cope Rearrangement. Synthesis of Key Precursors of (+)-Faranal and (-)-Antirhine

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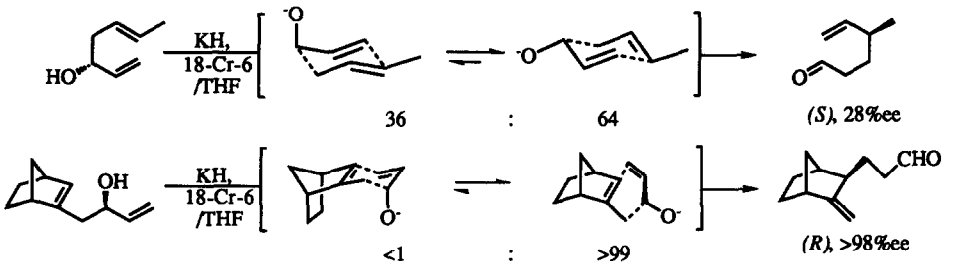
(*Received in Japan 22 October* 1992)

Key Words: oxy-Cope rearrangement; [2,3]Wittig rearrangement; diastereoselection; asymmetric transmission; (+)-faranal; (-)-antirhine

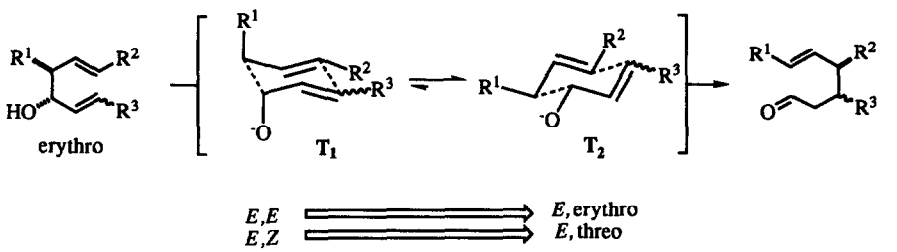
Abstract: *The anionic oxy-Cope rearrangements of acyclic 1,5-dien-3-ols, when their stereochemistries are properly designated, are shown to proceed with a high level of diastereoselection and asymmetric transmission. The utility of the acyclic oxy-Cope variants is demonstrated by the stereocontrolled synthesis of the key precursors of (+)-faranal (insect pheromone) and (-)-antirhine (Corynanthe-type indole alkaloid).*

The anionic oxy-Cope rearrangement has enjoyed wide applications as a versatile class of bond organization in synthesis.[1] In the context of acyclic stereocontrol, however, the *acyclic* oxy-Cope methodology still occupies a much lower position compared with the eminent position of the Claisen counterpart,[2] while several oxy-Cope examples of rigid, cyclic substrates have been reported to provide high levels of stereocontrol.[3] The key stereochemical issue inherent in the acyclic oxy-Cope process is associated with the oxyanion orientation (axial *vs.* equatorial) in the pericyclic transition states. Related studies[4] have shown that the oxyanion stereochemisty in acyclic systems cannot be effectively controlled unless other steric demand(s) such as favorable π-facial selectivity is imposed on the pericyclic array as exemplified by eq 1 *vs.* 2.[4a] We now disclose that the acyclic oxy-Cope rearrangement, when the substrate stereochemisty is properly designated, provides a synthetically useful level of diastereoselection and asymmetric transmission.[5]

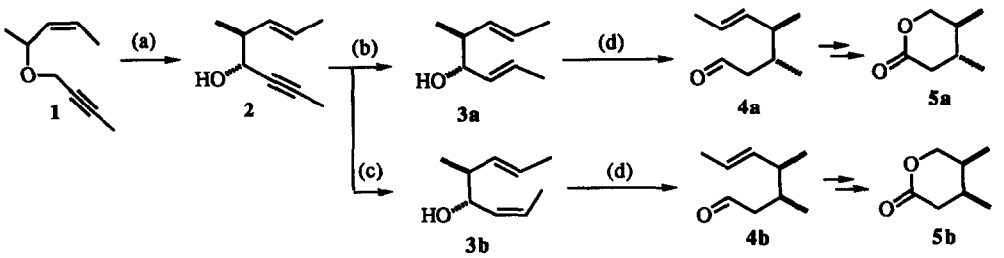


Diastereocontrol

At the outset, careful examination of our previously-reported transition state model[4c] led us to postulate that if an alkyl substituent (R^1) were added to the position adjacent to the hydroxy-bearing carbon *in the erythro configuration* (eq 3), the oxyanion substituent could be directed to the pseudoequatorial position as depicted by T_2 by virtue of the equatorial preference for the added R^1 group, thus affording the (*E*, erythro)- and (*E*, threo)-product from the (*E,E*)- and (*E,Z*)-substrate.



To test this hypothesis, we first examined the diastereoselection in the anionic oxy-Cope process of the two geometrically isomeric erythro substrates **3a** and **3b**, which were prepared via the [2,3]Wittig rearrangement of **1**[6] followed by trans and cis reduction of **2** (97% erythro, 99% *E*),[7] respectively (Scheme 1). We found that the standard anionic oxy-Cope rearrangement of **3a** (96% stereopurity)[7,8] and **3b** (92% stereopurity) afforded the erythro aldehyde **4a** with 94% de and 99% *E* and the threo aldehyde **4b** with 88% de and 97% *E*, respectively.[7] The % de's were determined by capillary GC analysis after conversions to the mixtures of the known cis- and trans-3,4-dimethyl-5-pentanolides **5**.[9,10] The high levels of stereocontrol thus observed indicate that, as predicted above, the [3,3]sigmatropy concerned proceeds almost exclusively through the chair-like transition state T_2 having both the oxyanion and the adjacent methyl in the equatorial positions.



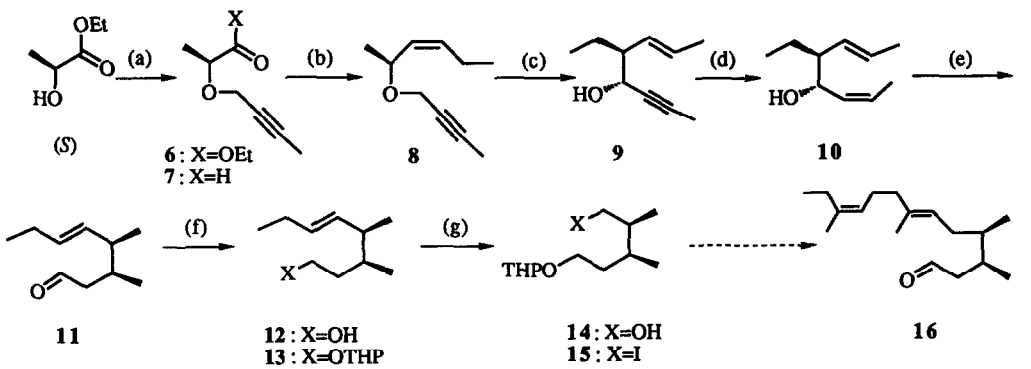
(a) *n*-BuLi, -78°C, 88%; (b) $LiAlH_4$, 91%; (c) H_2, P-2Ni, 82%; (d) KH, 18-crown-6 / THF, room temperature, 68-75%.

Scheme 1

Asymmetric Transmission

Asymmetric Synthesis of (+)-Faranal Precursor.

With the highly diastereoselective variants in hand, we examined the sense and degree of asymmetric transmission via the anionic oxy-Cope process within the context of the asymmetric synthesis of iodo ether **15**, a key precursor of (+)-faranal (**16**), a trail pheromone of the Pharaoh's ant[9b,11] (Scheme 2).



(a) (1) $CH_3C{\equiv}CCH_2OC(=NH)CCl_3$, H^+, 85%, (2) DIBAL, 82%; (b) *n*-$PrPPh_3Br$, *n*-BuLi, 98%; (c) *n*-BuLi, -78 °C, 75%; (d) H_2, P-2Ni, 95%; (e) KH, 18-crown-6, room temperature, 75%; (f) (1) DIBAL, 93%, (2) DHP, H^+, 95%; (g) (1) OsO_4, $NaIO_4$, then $NaBH_4$, 50%, (2) I_2, PPh_3, imidazole, 70%.

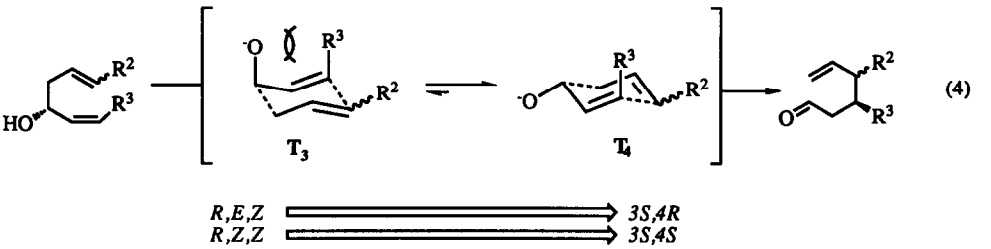
Scheme 2

Our synthesis of **15** began with the preparation of the optically pure [2,3]Wittig substrate **8**[7] from ethyl (*S*)-lactate. The [2,3]Wittig process of **8** followed by cis hydrogenation gave oxy-Cope substrate **10** in >96% ee (Mosher's assay) along with 100% *E*, 100% *Z* and >99% erythro.[7] The oxy-Cope process of **10** afforded the erythro aldehyde **11** essentially as a single product in 91% ee, which was then converted to **15**[10,11] as well as the known (*3S, 4S*)-3,4-dimethyl-5-pentanolide[9b,10] : $[\alpha]^{26}_D$ -45° (*c* 1.0, MeOH); lit. $[\alpha]^{22}_D$ -47°. The % ee of **11** was determined by HPLC analysis of the amide prepared via reaction of the pentanolide lactone and (*R*)-α-naphthylethylamine.[9b]

The most striking observation in the asymmetric oxy-Cope process is that both the absolute and relative stereochemistry of the substrate are specifically transmitted to the two new chiral centers in the product by virtue of complete transfer of the chiralities along the pericyclic array.

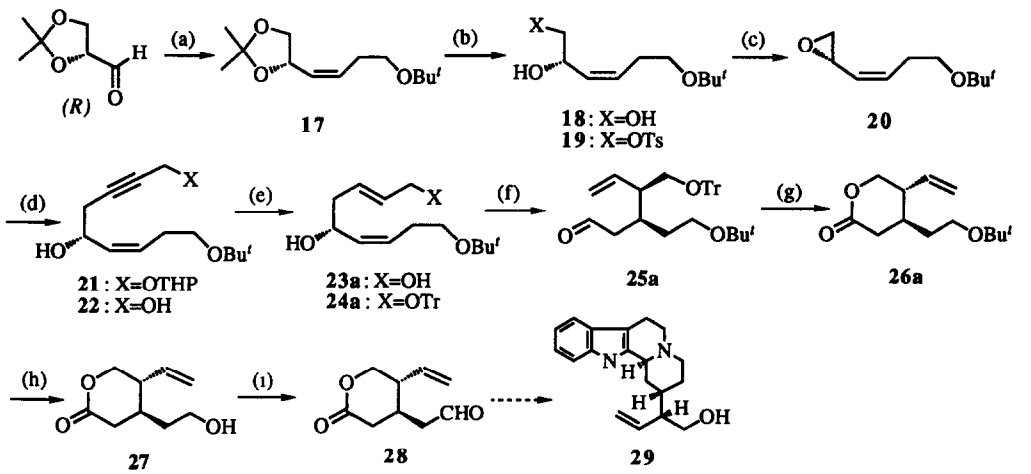
Asymmetric Synthesis of (+)-Antirhine Precursor.

Furthermore, our interest was directed to the asymmetric transmission problem in the different case where a stereo-directing erythro-alkyl group (R^1) is lacking but R^3 group is placed in *Z* geometry (eq 4). The question is whether the transition state with axial-oxyanion **T3** could be destabilized effectively *only* by the 1,3-diaxial interaction of $O^- \leftrightarrow R^3$, thus providing a similarly high level of asymmetric transmission.



(4)

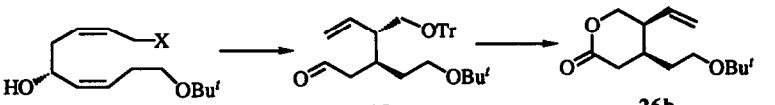
To answer this interesting question, we examined the asymmetric transmission via the oxy-Cope process of the optically active substrates of type **24** within the context of the asymmetric synthesis of δ-lactone **28**, a key synthetic intermediate for (-)-antirhine(**29**), a Corynanthe-type indole alkaloid[12] (Scheme 3).



(a) $PPh_3{=}CHCH_2CH_2OBu^t$, 95%; (b) (1) HCl / MeOH, 94%, (2) TsCl / pyr., 92%; (c) DBU, 91%; (d) (1) $LiC{\equiv}CCH_2OTHP$ / Et_2O-HMPA, 89%, (2) TsOH / MeOH, 85%; (e) (1) LAH, 90%, (2) TrCl / pyr., 92%; (f) method **A**: KH, 18-crown-6 / THF, 50 °C, 4h, 85-89%; method **B**: KH / DMSO, 50 °C, 3.5h, 80%; (g) TsOH / dioxane, then PCC, 72-75%; (h) CF_3CO_2H, 80%; (i) PDC, 75%.

Scheme 3

The geometrically isomeric substrates, **24a** and **24b**, were prepared as follows. The optically pure alcohol **21** (>99% *Z*)[7] was prepared from (*R*)-glyceraldehyde acetonide according to Corey's procedure.[13] After deprotection of the THP group, trans and cis reduction of diol **22** followed by selective tritylation gave **24a** with >99% *EZ*[7] and **24b** with 92% *ZZ*, respectively. We found that the anionic oxy-Cope process of **24a** and **24b** under the standard condition (KH, 18-crown-6, THF) afford the threo aldehyde **25a** with 80% de and 84% ee and the erythro aldehyde **25b** with 72% de and 82% ee, respectively (Scheme 3 and eq 5).



23b: X=OH
24b: X=OTr

25b **26b** (5)

These observed levels of diastereoselection and asymmetric transmission are a little lower than observed above for the rearrangement of **10**, suggesting that the 1,3-diaxial interaction concerned is large enough for effective stereocontrol but not good enough for complete stereocontrol.[14] Interestingly enough, however, we also found that the oxy-Cope process of **24a** with KH in DMSO *in the absence of 18-crown-6*,[15] provided an increased level of stereocontrol (94% de and 92% ee).[16] The relative stereochemistry of the oxy-Cope products was assigned by ^{1}H NMR analysis after conversions to δ-lactone **26**.[17] The % de's were determined by capillary GC analysis of **26**. The % ee's were determined by HPLC analysis of the diastereomeric amide prepared via reaction of lactone **26** and (*R*)- and (*S*)-α-naphthylethylamine. Finally, deprotection of **26a** (92% ee, 94% de) followed by PDC oxidation furnished the desired intermediate (+)-**28**[7,12b]: $[\alpha]^{27}_D$ +32.2° (*c* 0.35, $CHCl_3$).

In summary, this work has convincingly demonstrated that the acyclic anionic oxy-Cope rearrangement, when properly designed in terms of the substrate stereochemisty, gives a high level of diastereocontrol and asymmetric transmission, thus providing an efficient method for acyclic stereocontrol. Further application of the oxy-Cope rearrangement is in progress in our laboratory.

Acknowledgment

We are grateful to Professors Leo A. Paquette and Koichi Mikami for helpful discussions, and Sankyo Co., LTD. for the measurements of the mass spectra.

EXPERIMENTAL

Boiling points are uncorrected. IR spectra were recorded on JASCO FT/ IR-5000 spectrometers. ^1H NMR spectra were recorded on Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) spectrometers and ^{13}C NMR spectra were recorded on Varian Gemini-200 (200 MHz),Varian Gemini-300 spectrometer, and chemical shifts were reported in ppm using TMS or $CHCl_3$ as internal standard. High resolution mass spectra were performed on JEOL JMS-505H, AX-500 mass spectrometer. Optical rotations were measured with JASCO DIP-370. GC analyses were run on Shimazu GC-8A chromatography equipped with HR-20M (50 m) or OV-1 (30 m) by using N_2 as the carrier gas (1 kg cm^{-2}) at the indicated temperature. HPLC analyses were run on a Shimadzu LC-6A pump equipped with a 4.6 mm x 250 mm zorbax SIL column or 4.6 mm x 150 mm ODS-M column and Shimadzu SPD-6A as a UV detector (254 nm).

(3*Z*)-2-(2-Butynyloxy)-3-pentene (1).

Potassium hydride (1.2 g, 30 mmol, 35 wt% in mineral oil) was treated with hexane to remove oil and then suspended in THF. An *E/Z* mixture of 3-penten-2-ol (2.17 g, 24.7 mmol, 97%*Z*) was added to the suspension at -10 °C under argon atmosphere. After stirring for 30 min, a freshly prepared 2-butynyl methanesulfonate was added to this mixture. After stirring for another 30 min at -10 °C, the reaction mixture was quenched with water and then extracted with ether. The combined organic layers were washed with 1 N HCl and brine, dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by distillation to give **1** in 53% yield. bp 64-66 °C (15 mmHg); IR (neat) 2978, 2294, 1715, 1659, 1446, 1373, 1263, 1137, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, *J*=6.2 Hz, 3H), 1.70 (d, *J*=7.0 Hz, 3H), 1.85 (t, *J*=2.4 Hz, 3H), 3.90-4.22 (m, 2H), 4.40-4.55 (m, 1H), 5.19-5.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 3.70, 13.26, 21.30, 55.65, 69.33, 76.01, 81.89, 127.82, 132.51; HRMS found *m/z* 138.1061, calcd for $C_9H_{14}O$ 138.1045

(4*R,5*S**,6*E*)-5-Methyl-6-octen-2-yn-4-ol (2).**

To a solution of 1.4 g(10.1 mmol) of **1** in 15 mL of THF, a hexane solution of *n*-BuLi (1.6 M, 10.3 mL) was added over a period of 10 min at -78 °C under nitrogen atmosphere. After stirring for 2 h at -78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then extracted with ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Removal of the organic solvent in vacuo followed by silica gel chromatography to give **2** in 88% yield (1.23 g; 96% stereopurity by GC). IR (neat) 2978, 2294, 1715, 1659, 1446, 1373, 1263, 1137, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, *J*=7.0 Hz, 3H), 1.72 (d, *J*=5.6 Hz, 3H), 1.86 (d, *J*=2.2 Hz, 3H), 2.13 (brs, 1H), 2.18-2.51 (m, 1H), 4.10-4.30 (m, 1H), 5.47-5.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 3.63, 16.35, 18.25, 43.67, 66.63, 78.09, 82.03, 128.31, 132.04; MS (EI) *m/z* 123 (2, M^+-CH_3), 122 (10), 86 (20), 68 (100), 54 (30); HRMS found *m/z* 123.0844, calcd for $C_8H_{11}O$ 123.0810; GC (HR-20M, 80 °C) t_R=39.71 min for (*E*,erythro)-isomer, 96%; t_R=46.58 and 49.38 min for the other isomers, 4%.

(2*E*,4*S,5*S**,6*E*)-5-Methyl-2,6-octadien-4-ol (3a).**

To a stirred solution of 0.165 g (4.35 mmol) of $LiAlH_4$ in 20 mL of THF, 0.51 g (3.69 mmol) of **2** in 3 mL of THF was added at 0 °C. The reaction mixture was refluxed for 2 h, and then quenched by addition of 1 mL saturated aqueous Na_2SO_4 at 0 °C. After the filtration of aluminum salt, the solution was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **3a** in 91% yield (0.471 g; 96% stereopurity by GC). IR (neat) 3284, 1968, 1673, 1452, 1379, 1009, 967 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, *J*=6.8 Hz, 3H), 1.60-1.72 (m, 6H), 1.92 (brs, 1H), 2.10-2.40 (m, 1H), 3.75-3.95 (m, 1H), 5.25-5.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.71, 17.58, 18.19, 42.93, 76.41, 126.73, 127.83, 132.07, 133.13; HRMS found *m/z* 140.1121, calcd for $C_9H_{16}O$ 140.1201; GC (HR-20M, 60 °C) t_R=36.73 min for (*E,E*,erythro)-isomer, 96%; t_R=38.20, 39.33 and 42.24 min for the other isomers, 4%.

(2*Z*,4*S,5*S**,6*E*)-5-Methyl-2,6-octadien-4-ol (3b).**

To an ethanol solution of nickel acetate tetrahydrate (0.113 g, 0.45 mmol), $NaBH_4$ (1 M in ethanol, 0.45 mL) was added at room temperature under hydrogen atmosphere. The ethylene diamine (0.01 mL) was then added followed by **2** (0.5 g, 3.62 mmol). After stirring for 1 h, the catalyst was filtered through a celite pad. The filtrate was diluted with ether, washed with water and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **3b** in 82% yield (0.42 g; 92% stereopurity by GC). IR (neat) 3364, 2966, 1861, 1454, 1379, 996, 967, 920, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J*=6.8 Hz, 3H), 1.60-1.75 (m, 6H), 1.88 (brs, 1H), 2.25-2.41 (m, 1H), 4.25-4.37 (m, 1H), 5.30-5.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.51, 15.63, 18.21, 43.16, 70.80, 126.76, 127.20, 131.60, 132.86; HRMS found *m/z* 140.1176, calcd for $C_9H_{16}O$ 140.1201; GC (HR-20M, 60 °C) t_R=42.24 min for (*Z, E,* erythro)-isomer, 92%; t_R=36.73, 38.20 and 39.33 min for the other isomers, 8%.

General Procedure for the Oxy-Cope Rearrangement.

Potassium hydride (0.491 g, 4.28 mmol, 35 wt% in mineral oil) was treated with hexane to remove oil and then suspended in 20 mL of THF. A mixture of **3** (0.3 g 2.14 mmol) and 18-crown-6 ether (1.70 g, 6.42 mmol) in 10 mL of THF was added to the suspension and then the mixture was stirred for 6 h at room temperature. The resulting mixture was quenched by phosphate buffer solution (PH 7) and extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **4**. The *E/Z* ratios of **4** were determined by GC analysis [(HR-20M, 60 °C) t_R=12.61 min for *E*-isomers, t_R=13.28 min for Z-isomers; 99% *E* for **4a**, 97% *E* for **4b**]. The relative stereochemistry of **4** was assigned by ^1H NMR analysis after conversions to δ-lactone **5** as depicted below.

3,4-Dimethyl-5-heptenal (4).

(*E*,erythro)-4a: IR (neat) 2829, 1729, 1458, 1263, 1096, 1025, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, *J*=6.2 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 1.66 (d, *J*=5.8 Hz, 3H), 1.90-2.20 (m, 3H), 2.43-2.61 (m, 1H), 5.12-5.60 (m, 2H), 9.70-9.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.39, 17.44, 17.94, 33.31, 42.00, 48.79, 125.18, 134.98, 203.29; HRMS found *m/z* 140.1147, calcd for $C_9H_{16}O$ 140.1202.

(*E*,threo)-4b: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J*=6.6 Hz, 3H) 0.97 (d, *J*=6.8 Hz, 3H), 1.66 (d, *J*=5.0 Hz, 3H), 1.95-2.25 (m, 3H), 2.35-2.50 (m, 1H), 5.20-5.54 (m, 2H), 9.76(t, *J*=2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.41, 17.43, 18.02, 33.04, 41.11, 48.64, 125.37, 133.67, 203.25; HRMS found *m/z* 140.1204, calcd for $C_9H_{16}O$ 140.1201.

Determination of the Relative Stereochemistry of Oxy-Cope Product 4.

(a) General Procedure for PDC Oxidation and Esterification.

To a suspension of pyridinium dichromate (5 mmol) in 4 mL of DMF, the oxy-Cope product **4** (1 mmol) was added at room temperature. After stirring for over night, the reaction mixture was poured into a mixture of water and ethyl acetate. The mixture was washed with water and then with brine to remove DMF. The organic layer was dried over anhydrous $MgSO_4$, concentrated in vacuo. The residue was then treated with trimethylsilyldiazomethane (3 mmol, 10 wt% in hexane) in methanol at room temperature. After stirring for 1 h, the reaction mixture was diluted with ether and then washed with brine. The organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give the methyl ester.

Methyl 3,4-Dimethyl-5-heptenoate.

(*E*,erytheo)-isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, *J*=5.4 Hz, 3H), 0.94 (t, *J*=6.6 Hz, 3H), 1.64 (d, *J*=5.4 Hz, 3H), 1.75-2.12 (m, 3H), 2.35-2.52 (m, 1H), 3.65 (s, 3H), 5.18-5.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.09, 17.22, 18.01, 35.48, 39.39, 41.92, 51.55, 125.12, 135.52, 174.74.

(*E*,threo)-isomer: ^{1}H NMR ($CDCl_3$) δ 0.87 (d, *J*=6.4 Hz, 3H), 0.96 (t, *J*=6.8 Hz, 3H), 1.66 (d, *J*=5.6 Hz, 3H), 1.83-2.20 (m, 3H), 2.26-2.40 (m, 1H), 3.66 (s, 3H), 5.19-5.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.02, 17.69, 18.09, 35.38, 39.35, 41.13, 51.50, 125.50, 134.14, 174.62.

(b) General Procedure for Ozonization and Lactonization.

A stream of ozone was bubbled into a solution of the methyl 3,4-dimethyl-5-heptenoate (2 mmol) in methanol at -78 °C. After stirring for 10 min, the reaction mixture was warmed up to 0 °C, a methanol solution of $NaBH_4$ (1 M, 5 mL) was added to it at that temperature. After stirring for 2 h at room temperature, the methanol was removed with a rotary evaporator. The residue was diluted with water and then extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography gave the δ-lactone **5**. The spectra of the lactone **5a** are in good agreement with trans-isomer reported by Fleming,[9a] the lactone **5b** are in good agreement with cis-isomer reported by Mori,[9b] respectively. The % de's were determined by GC analysis [(OV-1, 150 °C) t_R=3.22 min for trans-isomer, t_R=4.05 min for cis-isomer; 94% de for **5a**, 88% de for **5b**].

3,4-Dimethyl-5-pentanolide (5).

Trans-5a: ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J*=6.1Hz, 3H), 1.02 (d, *J*=6.1Hz, 3H), 1.51-1.82 (m, 2H), 2.14 (dd, *J*=17.6, 9.8 Hz, 1H), 2.68 (dd, *J*=17.6, 5.5 Hz, 1H), 3.87 (dd, *J*=10.6, 10.5 Hz, 1H), 4.28 (dd, *J*=11.1, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.51, 19.57, 33.23, 35.01, 37.58, 74.18, 171.51.

Cis-5b: IR (neat) 2970, 2364, 1736, 1458, 1236, 1203, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, *J*=7.0 Hz, 3H), 0.97 (d, *J*=7.0 Hz, 3H), 2.03-2.20 (m, 2H), 2.59 (dd, *J*=18.0, 6.0 Hz, 1H), 2.83 (dd, *J*=18.2, 7.0 Hz, 1H), 4.11 (dd, *J*=11.0, 6.9 Hz, 1H), 4.28 (dd, *J*=11.3, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.33, 15.67, 29.94, 31.02, 36.25, 73.24, 170.70.

Asymmetric Synthesis of (+)-Faranal Precursor.

Ethyl (*S*)-2-(2-Butynyloxy)propionate (6).

To a mixture of 2-butyn-1-ol (4.66 mL, 62.3 mmol) and trichloroacetonitrile (6.6 mL, 65.8 mmol), a catalytic amount of sodium was added at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with 0.2 mL of acetic acid. The mixture was diluted with ether, washed with brine and then dried over anhydrous $MgSO_4$. The solvent was removed with a rotary evaporator and the residue was distilled (90 °C, 7 mmHg) to give (2-butynyloxy)trichloroacetimidate in 70% yield (9.35 g). The acetimidate was added to a solution of ethyl (*S*)-lactate (4.08 g, 34.5 mmol) in cyclohexane-CH_2Cl_2 (2 : 1, 120 mL). A catalytic amount of trifluoromethanesulfonic acid was then added to it at room temperature. After stirring for over night, the resulting mixture was filtered through a celite pad. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **6** in 85% yield (4.99 g). IR (neat) 2988, 2926, 1738, 1450, 1375, 1270, 1205, 1137, 1067, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 3H), 1.35 (d, *J*=6.6 Hz, 3H), 1.78 (t, *J*=2.0 Hz, 3H), 3.98-4.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 3.69, 14.31, 18.67, 57.86, 61.13, 73.19, 74.62, 83.39, 173.50; MS (EI) *m/z* 170 (0.4, M^+), 141 (2, M^+-C_2H_5), 101 (92, M^+-OC_4H_5), 96 (100), 73 (23), 68 (10); HRMS found *m/z* 171.1082, calcd for $C_9H_{15}O_3$ 171.1021.

(*S*)-2-(2-Butynyloxy)propanal (7).

To a solution of **6** (3.96 g, 23.3 mmol) in hexane (50 mL), DIBAL (1 M in hexane, 23 mL) was added at -78 °C under nitrogen atmosphere. After stirring for 30 min, the reaction mixture was quenched by addition of powdered Na_2SO_4•$10H_2O$ at -78 °C. The mixture was warmed to room temperature, and then 10 g of anhydrous Na_2SO_4 was added to it. After stirring for 1 h, the mixture was filtrated and then the filtrate was concentrated in vacuo. The residue was distilled to give **7** in 82% yield (2.41 g). bp 70 °C (13 mmHg); IR (neat) 2982, 2924, 1734, 1448, 1379, 1263, 1141, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, *J*=7.0 Hz, 3H), 1.78 (t, *J*=2.4 Hz, 3H), 3.96 (dq, *J*=1.8, 7.0 Hz, 1H), 4.10-4.29 (m, 2H), 9.62-9.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.66, 15.29, 58.12, 74.82, 79.24, 84.14, 204.11; MS (EI) *m/z* 126 (0.4, M^+), 97 (7, M^+-CHO), 95 (22), 68 (11), 52 (100).

(*S*,3*Z*)-2-(2-Butynyloxy)-3-hexene (8).

To a stirred and cooled suspension of *n*-propyl triphenylphosphonium bromide (11.0 g, 57.1 mmol) in THF-HMPA (10 : 1, 100 mL), *n*-BuLi (1.6 N in hexane, 16.7 mL) was added dropwise at 0 °C under nitrogen atmosphere. The stirring was continued for 1 h at 0 °C. The resulting red-colored solution was cooled to -78 °C and a freshly prepared **7** (2.25 g, 17.8 mmol) was added to it. The stirring was continued for 3 h at -78 °C, allowed to warm to -20 °C for another 2 h. The reaction mixture was diluted with pentane,

and then filtered through a celite pad. The filtrate was washed with water, dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **8** in 98% yield (2.66 g, >99% *Z* by ^{13}C NMR). IR (neat) 2974, 1446, 1373, 1137, 1083, 1056, 864, 750, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, *J*=7.6 Hz, 3H), 1.16 (d, *J*=6.2 Hz, 3H), 1.78 (t, *J*=2.4 Hz, 3H), 1.90-2.17 (m, 2H), 3.80-4.15 (m, 2H), 4.28-4.45 (m, 1H), 5.05-5.25 (m, 1H), 5.45-5.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.83, 14.58, 21.15, 21.75, 55.76, 69.70, 76.01, 82.06, 130.90, 135.54; HRMS found *m/z* 152.1080, calcd for $C_{10}H_{16}O$ 152.1201.

(4*R*,5*S*,6*E*)-5-Ethyl-6-octen-2-yn-4-ol (9).

The [2,3] Wittig rearrangement procedure was used similar to that used in the preparation of **2**. Starting with 2.0 g of **8**, 1.5 g of **9** was obtained (75% yield; 99.5% stereopurity by GC). The enantiomeric excess of **9** was determined to be 96% by GC analysis [(OV-1 30 m, 160 °C) t_R=31.94 and 34.37 min] of its (*R*)-MTPA ester. IR (neat) 3330, 2968, 2220, 1717, 1676, 1454, 1381, 1025, 971 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J*=7.4 Hz, 3H), 1.74 (d, *J*=6.2 Hz, 3H), 1.85 (t, *J*=2.2 Hz, 3H), 1.90-2.29 (m, 3H), 3.40-3.55 (m, 1H), 4.20-4.35 (m, 1H), 5.25-5.45 (m, 1H), 5.52-5.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.60, 11.81, 18.17, 24.10, 51.41, 64.96, 78.29, 81.68, 129.65, 129.92; MS (EI) *m/z* 151 (3, M^+-1), 150 (5, M^+-2), 137 (5, M^+-CH_3), 136 (40), 122 (100), 106 (43), 92 (30); HRMS found *m/z* 137.0936, calcd for $C_9H_{13}O$ 137.0967; GC (HR-20M, 80 °C) t_R=32.00 min for (*E*,erythro)-isomer, 99.5%; t_R=35.44 min for the other isomers, 0.5%.

(2*Z*,4*S*,5*S*,6*E*)-5-Ethyl-2,6-octadien-4-ol (10).

The cis reduction procedure was used similar to that used in the preparation of **3b**. Starting with 1.09 g of **9**, 1.05 g of **10** was obtained (95% yield; 99.5% stereopurity by GC). IR (neat) 3372, 2966, 1661, 1454, 1379, 1019, 967, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.3 Hz, 3H), 1.59-1.72 (m, 6H), 1.08-1.75 (m, 2H), 1.94-2.22 (m, 2H), 4.28-4.39 (m, 1H), 5.09-5.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.02, 13.54, 18.23, 23.58, 51.72, 69.64, 126.94, 128.74, 131.04, 131.67; MS (EI) *m/z* 137 (0.7, M^+-OH), 136 (4, M^+-H_2O), 92 (6), 90 (10), 82 (100), 78 (13); HRMS found *m/z* 137.1329, calcd for $C_{10}H_{17}$ 137.1330; GC (OV-1, 80 °C) t_R=19.03 min for (*Z*,*E*,erythro)-isomer, 99.5%; t_R=20.29 min for the other isomers, 0.5%.

(3*S*,4*S*,5*E*)-3,4-Dimethyl-5-octenal (11).

Prepared from **10** according to general procedure (KH, 18-crown-6 / THF, yield: 75%; >99% stereopurity by ^{13}C NMR and GC). IR (neat) 2968, 1727, 1458, 973 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, *J*=6.4 Hz, 3H), 0.97 (t, *J*=7.5 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H), 1.80-2.30 (m, 5H), 2.30-2.60 (m, 1H), 5.15-5.55 (m, 2H), 9.70-9.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.03, 16.42, 17.48, 25.69, 33.05, 41.02, 48.65, 131.39, 132.66, 203.26; HRMS found *m/z* 154.1243, calcd for $C_{10}H_{18}O$ 154.1358; GC (OV-1, 60 °C) t_R=25.00 min. The stereochemistry of **11** was determined after conversions to the δ-lactone **5b** (>99% de by GC) by the same manner as described above (**4** → **5**). The optical rotation of this δ-lactone **5b** : $[\alpha]_D^{26}$ -45° (*c* 1.00, MeOH) is in agreement with (*3S,4S*)-isomer reported by Mori.[9b] The % ee of (-)-**5b** was determined as depicted below.

Determination of Enantiomeric Excess of 11.

A mixture of (-)-**5b** or (±)-**5b** and (*R*)-α-naphthylethylamine was stirred and heated at 100 °C for 1.5 h. After cooling, the mixture was diluted with $CHCl_3$, washed with aqueous 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was analyzed by HPLC [(Zorbax SIL, EtOAc / MeOH=10 / 1, Flow rate 1.0 mL/min) t_R=5.91 and 6.61 min] showed the enantiomeric excess of the δ-lactone which prepared from **11** to be 91%ee.

(3*S*,4*S*,5*E*)-3,4-Dimethyl-5-octen-1-ol (12).

To a hexane solution of **11** (0.20 g, 1.3 mmol), DIBAL (1 M in hexane, 2 mL) was added at -78 °C under nitrogen atmosphere. After stirring for 30 min, the reaction mixture was quenched by addition of powdered $Na_2SO_4 \cdot 10H_2O$ at -78 °C. The mixture was warmed to room temperature, and then 5 g of anhydrous Na_2SO_4 was added to it. After stirring for 1 h, the mixture was filtrated and then concentrated in vacuo. The residue was purified by silica gel chromatography to give **12** in 93% yield (0.19 g). IR (neat) 3282, 2964, 1458, 1379, 1056, 971 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81-1.05 (m, 9H), 1.10-1.75 (m, 5H), 1.90-2.15 (m, 2H), 3.55-3.80 (m, 2H), 5.20-5.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.14, 15.82, 17.86, 25.74, 34.60, 37.29, 41.13, 61.40, 131.75, 132.12; MS (EI) *m/z* 156 (0.6, M^+), 154 (3), 128 (18), 111 (100, M^+-C_2H_6O), 108 (16), 94 (21), 84 (30).

(3*S*,4*S*,5*E*)-3,4-Dimethyl-1-(tetrahydropyran-2-yloxy)-5-octene (13).

To a solution of **12** (0.03 g, 0.19 mmol) and dihydropyran (0.026 mL, 0.28 mmol) in CH_2Cl_2, a catalytic amount of *p*-toluenesulphonic acid was added at 0 °C. After stirring for 3 h, the reaction mixture was diluted with ether, washed with water and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **13** in 95% yield (0.044 g). IR (neat) 2944, 1456, 1352, 1201, 1123, 1077, 1025, 971, 909, 870, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.9 Hz, 3H), 0.96 (t, *J*=7.5 Hz, 3H), 1.18-2.12 (m, 12H), 3.30-3.71 (m, 2H), 3.68-3.92 (m, 2H), 4.58 (m,1H), 5.18-5.48 (m,2H); MS (EI) *m/z* 154 (1, M^+-$C_5H_{10}O$), 124 (1, M^+-$C_6H_{12}O_2$), 111 (25), 82 (64), 68 (16), 54 (100).

(2*S*,3*S*)-2,3-Dimethyl-5-(tetrahydropyran-2-yloxy)-1-pentanol (14).

To a solution of **13** (47 mg, 0.21 mmol) in EtOH-H_2O (1 : 1, 2 mL), osmium tetraoxide (0.2 mL, 2.5 wt% in *tert*-butanol) and sodium periodate (0.1 g) was added at room temperature. After stirring for 10 h, the reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was treated with a methanol solution of $NaBH_4$ (1 M, 0.2 mL), and then stirred for 2 h at room temperature. After the methanol was removed with a rotary evaporator, the residue was diluted with water, and extracted with CH_2Cl_2. The extract was dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **14** in 50% yield (20 mg). IR (neat) 3398, 2942, 2876, 1715, 1456, 1354, 1203, 1120, 1077, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72-1.08 (m, 6H), 1.10-1.92 (m, 11H), 3.20-3.92 (m, 6H), 4.57 (m, 1H);

MS (EI) *m/z* 216 (0.3, M^+), 130 (15, M^+-$C_5H_{10}O$), 115(8, M^+-$C_5H_9O_2$), 114 (76), 100 (42), 96 (100), 85 (24); HRMS found *m/z* 115.1100 calcd for $C_7H_{15}O$ 115.1123.

(2*S*,3*S*)-1-Iodo-2,3-dimethyl-5-tetrahydropyranyloxypentane (15).

To a mixture of imidazole (14 mg, 0.2 mmol), triphenylphosphine (54 mg, 0.2 mmol) and iodine (40 mg, 0.16 mmol) in 1 mL of benzene, 18 mg (0.09 mmol) of **14** was added at room temperature. After stirring for 30 min, the reaction mixture was quenched with saturated aqueous Na_2SO_3, extracted with ether. The combined organic extracts were washed with brine, and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **15** in 70% yield (19 mg). The spectra of **15** are in agreement with the literature values.[11] IR (neat) 2936, 2876, 1729, 1456, 1381, 1276, 1201, 1183, 1122, 1077 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, *J*=7.2 Hz, 3H), 1.01 (d, *J*=6.7 Hz, 3H), 1.45-1.95 (m, 10H), 3.08-3.60 (m, 4H), 3.67-3.92 (m, 2H), 4.59 (m,1H); MS (EI) *m/z* 325 (3, M^+-H), 225 (15), 199 (14, M^+-I), 85 (100), 55 (100).

Asymmetric Synthesis of (-)-Antirhine Precursor.

(2*Z*,4*S*)-2,2-Dimethyl-4-[4-(*tert*-butyloxy)-2-butenyl]-1,3-dioxolane (17).

To a stirred and cooled suspension of 3-(*tert*-butyloxy)propyl triphenylphosphonium bromide (8.21 g, 17.95 mmol) in THF-HMPA (10 : 1, 80 mL), *n*-BuLi (1.6 N in hexane, 12 mL) was added dropwise at 0 °C under nitrogen atmosphere. The stirring was continued for 1 h at 0 °C. The resulting red-colored solution was cooled to -78 °C and a freshly prepared (*R*)-glyceraldehyde acetonide (2.34 g, 18.0 mmol) was added to it. The stirring was continued for 6 h at -78 °C, and allowed to warm to -20 °C for another 2 h. The reaction mixture was diluted with pentane, and then filtered through a celite pad. The filtrate was washed with water, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **17** in 92% yield (3.78 g, >99% *Z* by ^{13}C NMR) IR (neat) 2978, 1365, 1199, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 9H), 1.39 (s, 3H), 1.42 (s, 3H), 2.22-2.45 (m, 2H), 3.20-3.50 (m, 2H), 3.51 (t, *J*=8.0 Hz, 1H), 4.08 (t, *J*=6.9 Hz, 1H), 4.80-4.95 (m, 1H), 5.45-5.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.00, 26.75, 27.54, 29.38, 60.93, 69.50, 72.10, 72.73, 109.04, 128.88, 131.23; HRMS found *m/z* 228.1726 calcd for $C_{13}H_{24}O_3$ 228.1727.

(2*S*,3*Z*)-6-(*tert*-Butyloxy)-3-hexen-1,2-diol (18).

To a methanol solution of **17** (3 g, 13.16 mmol), 1 ml of 1N HCl was added at room temperature. After stirring for 4 h at that temperature, the solvent was removed with a rotary evaporator. The residue was diluted with AcOEt, then washed with aqueous $NaHCO_3$, and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **18** in 89% yield (2.2 g). IR (neat) 3330, 2976, 1365, 1197, 1079, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 2.18-2.56 (m, 2H), 3.25-3.80 (m, 5H), 4.00-4.30 (m, 1H), 4.38-4.58 (m, 1H), 5.45-5.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.46, 29.27, 60.42, 66.24, 67.93, 73.65, 131.06, 131.51; MS (EI) *m/z* 189 (3.5, M^+H), 171 (0.5, M^+-OH), 157 (6), 140 (3), 133 (5), 115 (16), 101 (28), 83 (57), 57 (100).

(2*S*, 3*Z*)-6-(*tert*-Butyloxy)-1,2-epoxy-3-hexene (20).

To a pyridine solution of **18** (6.28 g, 33.4 mmol), 6.37 g of tosyl chloride was added at 0 °C. After stirring for over night at 0 °C, the pyridine was removed in vacuo. The residue was diluted with AcOEt, washed with aqueous $CuSO_4$, $NaHCO_3$, and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo afforded **19** (8.59 g), which was used for next reaction without further purification. ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 2.44 (s, 3H), 2.15-2.52 (m, 3H), 3.22-3.55 (m, 2H), 3.95-4.12 (m, 2H), 4.52-4.70 (m, 1H), 5.48-5.72 (m, 2H), 7.34 (d, *J*=8.2 Hz, 2H), 7.81 (d, *J*=8.2 Hz, 2H).

To a solution of **19** (8.0 g, 24.42 mmol) in THF, 5.48 ml (36.6 mmol) of 1,8-diazabicyclo [5,4,0] undec-7-ene was added at room temperature under nitrogen atmosphere. After stirring for one day at room temperature, the reaction mixture was quenched by addition of aqueous NH_4Cl, and then extracted with ether. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by distillation to give **20** in 91% yield (3.78 g). bp: 85 °C (7 mmHg); IR (neat) 2976, 1365, 1199, 1085, 924, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 2.32-2.60 (m, 2H), 2.64 (dd, *J*=5.2, 2.6 Hz, 1H), 2.98 (dd, *J*=5.2, 4.2 Hz, 1H), 3.40 (dt, *J*=1.6, 6.6 Hz, 2H), 3.60-3.70 (m, 1H), 5.08 (dd, *J*= 11.0, 9.2 Hz, 1H), 5.77 (dt, *J*=11.0, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.39, 29.14, 47.97, 48.44, 60.83, 72.62, 128.65, 133.05; MS (EI) *m/z* 155 (0.5, M^+-Me), 140 (1), 122 (1.5), 115 (3), 97 (4), 83 (15), 67 (15), 57 (100); HRMS found *m/z* 155.1087, calcd for $C_9H_{15}O_2$ 155.1072.

(5*R*,6*Z*)-9-(*tert*-Butyloxy)-1-(tetrahydropyran-2-yloxy)-nona-6-en-2-yne-5-ol (21).

To a solution of 3-(tetrahydropyran-2-yloxy)-1-propyne (3.3 g, 23.6 mmol) in Et_2O-HMPA (10:1, 100 ml), *n*-BuLi (1.6 N in hexane, 14 ml) was added dropwise at -78 °C. The stirring was continued for 1 h at -78 °C and **20** (0.8 g, 4.7 mmol) was added to it. The reaction mixture was then warmed to room temperature. After stirring for over night, the mixture was quenched by addition of aqueous NH_4Cl and then extracted with AcOEt. The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **21** in 89% yield (1.31 g). IR (neat) 3400, 2946, 1365, 1201, 1079, 1025, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.30-1.85 (m, 6H), 2.04-2.24 (m, 1H), 2.24-2.52 (m, 3H), 3.15-3.35 (m, 1H), 3.30-3.52 (m, 2H), 3.57 (brs, 1H), 3.67-3.82 (m, 1H), 4.01-4.25 (m, 2H), 4.42 (q, *J*=6.9 Hz, 1H), 4.72 (s, 1H), 5.40-5.71 (m, 2H).

(5*R*,6*Z*)-9-(*tert*-Butyloxy)-nona-6-en-2-yne-1,5-diol (22).

To a methanol solution of **21** (1.5 g, 4.84 mmol), a catalytic amount of *p*-toluenesulphonic acid was added at room temperature. After stirring for 30 min , the solvent was removed with a rotary evaporator. The residue was diluted with AcOEt, then washed with aqueous $NaHCO_3$, and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **22** in 95% yield (1.04 g). IR (neat) 3320, 2976, 1365, 1197, 1021, 752 cm^{-1}; ^1H NMR (D_2O) δ .1.19 (s, 9H), 2.15-2.79 (m, 2H), 2.46 (d, *J*=6.6 Hz, 2H), 3.20-3.54 (m, 2H), 4.21 (s, 2H), 4.54 (q, *J*=6.6 Hz, 1H), 5.48-5.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.92, 27.28, 28.99, 50.89, 59.99, 65.08, 73.55, 80.30, 82.41, 130.30, 133.66; MS (EI) *m/z* 227 (3.5, M^+H), 211 (0.5, M^+-Me), 171 (5), 157 (9), 153 (9), 122 (14), 101 (43), 83 (79), 57 (100).

(2*E*,5*R*,6*Z*)-9-(*tert*-Butyloxy)-2,6-nonadien-1,5-diol (23a).

The trans reduction procedure was used similar to that used in the preparation of **3a**. Starting with 0.23 g of **22**, 0.21 g of **23a** was obtained (90% yield). IR (neat) 3320, 2976, 1365, 1197, 1081, 973, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.95-2.65 (m, 4H), 2.76 (brs, 2H), 3.18-3.60 (m, 2H), 4.09 (d, *J*=3.8 Hz, 2H), 4.42 (q, *J*=6.9 Hz, 1H), 5.30-5.95 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 27.40, 29.04, 39.48, 59.94, 63.50, 65.87, 73.50, 128.52, 129.70, 131.69, 134.76; MS (EI) *m/z* 229 (1, M^+H), 211 (0.5, M^+-OH), 172 (1, M^+-*tert*-Bu), 157 (12), 101 (47), 83 (88), 70 (22), 57 (100); HRMS found *m/z* 229.1807, calcd for $C_{13}H_{25}O_3$ 229.1804.

(2*Z*,5*R*,6*Z*)-9-(*tert*-Butyloxy)-2,6-nonadien-1,5-diol (23b).

The cis reduction procedure was used similar to that used in the preparation of **3b**. Starting with 0.28 g of **22**, 0.24 g of **23b** was obtained (85% yield). IR (neat) 3308, 3020, 1365, 1197, 1079, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 2.12-2.42 (m, 2H), 2.35-2.64 (m, 2H), 2.92 (brs, 2H), 3.27-3.64 (m, 2H), 3.98-4.32 (m, 2H), 4.38 (q, *J*=5.3 Hz, 1H), 5.45-5.73 (m, 3H), 5.80-6.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.34, 28.99, 34.23, 57.40, 59.69, 64.61, 73.72, 129.13, 130.20, 131.34, 134.67; MS (EI) *m/z* 229 (2, M^+H), 211 (2, M^+-OH), 175 (1), 157 (13), 155 (13), 106 (19), 101(48), 57 (100).

(2*E*,5*R*,6*Z*)-9-(*tert*-Butyloxy)-1-triphenylmethyloxy-2,6-nonadien-5-ol (24a).

To a pyridine solution of **23a** (1.06 g, 4.65 mmol), 1.43 g of trityl chloride was added at 0 °C. After stirring for over night at room temperature, the pyridine was removed in vacuo. The residue was diluted with AcOEt, washed with aqueous $CuSO_4$, $NaHCO_3$, and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **24a** in 92% yield (2.02 g; >99% *EZ* by HPLC). IR (neat) 3410, 2976, 1450, 1365, 1197, 1033, 971, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 2.10-2.58 (m, 5H), 3.20-3.50 (m, 2H), 3.57 (d, *J*=3.6 Hz, 2H), 4.41 (q, *J*=6.9 Hz, 1H), 5.45-5.82 (m, 4H), 7.10-7.62 (m, 15H) ; ^{13}C NMR ($CDCl_3$) δ 27.34, 29.04, 39.77, 59.97, 64.91, 65.74, 73.39, 86.76, 126.85, 127.72, 128.24, 128.62, 129.54, 129.69, 135.07, 144.23; HPLC (ODS-M, MeOH / H_2O=4 / 1, Flow rate 1.0 mL/min) t_R=39.4 min for *ZZ*-isomer, <1%; t_R=41.7 min for *EZ*-isomer, >99%.

(2*Z*,5*R*,6*Z*)-9-(*tert*-Butyloxy)-1-triphenylmethyloxy-2,6-nonadien-5-ol (24b).

The tritylation procedure was used similar to that used in the preparation of **24a**. Starting with 0.85 g of **23b**, 1.30 g of **24b** was obtained (74% yield; 92% *ZZ* by HPLC). IR (neat) 3374, 2976, 1450, 1365, 1197, 1060, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 9H), 1.95-2.60 (m, 5H), 3.15-3.60 (m, 2H), 3.68 (d, *J*=6.3 Hz, 2H), 4.32 (q, *J*=6.6 Hz, 1H), 5.35-5.70 (m, 3H), 5.65-5.90 (m, 1H), 7.08-7.63 (m, 15H) ; ^{13}C NMR ($CDCl_3$) δ 27.29, 28.94, 34.84, 59.88, 60.43, 65.63, 73.35, 86.76, 126.83, 127.60, 127.71, 128.59, 128.77, 129.87, 134.95, 144.13; HPLC (ODS-M, MeOH / H_2O=4 / 1, Flow rate 1.0 mL/min) t_R=39.4 min for *ZZ*-isomer, 92%; t_R=41.7 min for *EZ*-isomer, 8%.

Rearrangement of 24 by Method A or B.

Method A: The oxy-Cope procedures of **24** were used similar to that used in the rearrangement of **3** at 50 °C. Starting with 0.17 g of **24a**, 0.15 g of **25a** was obtained (89% yield), and starting with 0.22 g of **24b**, 0.187 g of **25b** was obtained (85% yield).

Method B: Potassium hydride (60 mg, 1.5 mmol, 35 wt% in mineral oil) was treated with hexane to remove oil and then 5 ml of DMSO was added at room temperature under argon atmosphere. To this solution was added a solution of 0.23 g (0.49 mmol) of **24a** in 3 ml of DMSO at room temperature. After stirring for 3.5 h at 50 °C, the resulting mixture was quenched by phosphate buffer solution (PH 7) and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo followed by silica gel chromatography to give **25a** in 80% yield (0.184 g).

3-[2-(*tert*-Butyloxy)-ethyl]-4-triphenylmethyloxymethyl-5-hexenal (25).

(3*S*,4*R*)-25a: IR (neat) 2976, 1725, 1450, 1197, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.50-1.65 (m, 1H), 2.15-2.60 (m, 5H), 3.11 (d, *J*=6.5 Hz, 2H), 3.27 (t, *J*=6.6 Hz, 2H), 4.98-5.20 (m, 2H), 5.54-5.74 (m, 1H), 7.10-7.60 (m, 15H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.45, 31.02, 31.14, 46.62, 47.87, 59.76, 64.23, 72.56, 86.47, 117.80, 126.87, 127.69, 128.65, 136.86, 144.06, 202.89.

(3*S*,4*S*)-25b: IR (neat) 2976, 1723, 1450, 1199, 1077 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.30-1.65 (m, 1H), 2.0-2.65 (m, 5H), 2.95-3.22 (m, 2H), 3.31 (t, *J*=6.6 Hz, 2H), 4.98-5.20 (m, 2H), 5.48-5.75 (m, 1H), 7.10-7.60 (m, 15H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.50, 30.53, 33.30, 45.16, 47.08, 59.22, 64.13, 72.59, 86.47, 117.83, 126.92, 127.87, 128.63, 136.73, 144.04, 203.07.

(3*S*,4*R*)-3-[2-(*tert*-Butyloxy)-ethyl]-4-vinyl-5-pentanolide (26a).

To a dioxane solution of **25a** (0.3 g, 0.64 mmol), a catalytic amount of *p*-toluenesulphonic acid was added at room temperature. After stirring for over night, the solvent was removed with a rotary evaporator. The residue was diluted with AcOEt, then washed with water, and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo give the crude lactol. To a CH_2Cl_2 (3 mL) solution of this lactol, 0.5 g of PCC was added at room temperature. After stirring for over night, the resulting mixture was diluted with ether and then filtered through a celite pad. Removal of the solvent in vacuo followed by silica gel chromatography to give **26a** in 75% yield (0.108 g; 80-94% de by GC). An analytical sample (94% de) was prepared via oxy-Cope method B. $[\alpha]_D^{29}$ +20.5 ° (*c* 1.35, $CHCl_3$); IR (neat) 2976, 1744, 1365, 1199, 1081, 924 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.68-2.45 (m, 4H), 2.27 (dd, *J*=17.4, 9.5 Hz, 1H), 2.80 (dd, *J*=17.4, 6.3 Hz, 1H), 3.28-3.45 (m, 2H), 4.06 (dd, *J*=11.4, 9.9 Hz, 1H), 4.28 (dd, *J*=11.4, 5.0 Hz, 1H), 5.15-5.32 (m, 2H), 5.52-5.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.46, 33.35, 34.75, 34.87, 43.96, 58.14, 71.47, 72.72, 118.85, 135.48, 171.25; GC (OV-1, 150 °C) t_R=11.61 min for trans-isomer and t_R=13.00 min for the cis-isomer; MS (EI) *m/z* 227 (3.5, M^+H), 211 (55, M^+-Me), 171 (50), 153 (43), 140 (13), 126 (13), 107 (27), 93 (35), 81 (33), 57 (71), 41 (35); HRMS found *m/z* 227.1634, calcd for $C_{13}H_{23}O_3$ 227.1648.

(3*S*,4*S*)-3-[2-(*tert*-Butyloxy)-ethyl]-4-vinyl-5-pentanolide (26b).

Prepared from **25b** according to the same procedure with **26a** (yield: 72%; 72% de by GC). ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 2.20-2.75 (m, 6H), 3.25-3.50 (m, 2H), 4.41 (d, *J*=3.6 Hz, 2H), 5.16-5.35 (m, 2H), 5.78-5.92 (m, 1H); MS (EI) *m/z* 227 (1, M^+H), 211 (38, M^+-Me), 170 (23), 153 (51), 140 (13), 136 (16), 107 (28), 93 (53), 81 (50), 57 (100).

Determination of enantiomeric excess of 26a, 26b.

A mixture of **26** and (*R*) or (*S*)-α-naphthylethylamine was stirred and heated at 100 °C for 1.5 h. After cooling, the mixture was diluted with $CHCl_3$, washed with aqueous 1 N HCl and water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was analyzed by HPLC [(Zorbax SIL, EtOAc / hexane / MeOH=20 / 20 / 1, Flow rate 1.0 mL/min) t_R=7.91, 8.31, 8.88 and 9.03 min] which showed the enantiomeric excess of **26a** to be 84 % ee (via oxy-Cope method A) and 92 % ee (via oxy-Cope method B) and **26b** to be 82% ee (via oxy-Cope method A).

(3*S*,4*R*)-3-(2-Hydroxyethyl)-4-vinyl-5-pentanolide (27).

To 10 mg (0.044 mmol) of **26a** (94% de, 92% ee), 0.5 ml of anhydrous CF_3CO_2H was added at room temperature. After stirring for 3 h, the reaction mixture was quenched with aqueous $NaHCO_3$ and then extracted with AcOEt. The combined organic extracts were washed with brine, and then dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo afforded **27** (6 mg, 80% yield), which was used for next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 1.40-2.20 (m, 5H), 2.21 (dd, *J*=17.2, 9.3 Hz, 1H), 2.76 (dd, *J*=17.2, 6.3 Hz, 1H), 3.45-3.72 (m, 2H), 4.00 (dd, *J*=11.4, 10.2 Hz, 1H), 4.22 (dd, *J*=11.4, 5.0 Hz, 1H), 5.00-5.30 (m, 2H), 5.42-5.67 (m, 1H).

(3*S*,4*R*)-3-(2-Hydroxyethyl)-4-vinyl-5-pentanolide (28).

To a CH_2Cl_2 (2 mL) solution of **27** (6 mg), 0.2 g of PDC was added at room temperature. After stirring for over night, the resulting mixture was diluted with ether and then filtered through a celite pad. Removal of the solvent in vacuo followed by silica gel chromatography to give **28** in 75% yield (4.4 mg). The (3*S*,4*R*) configuration of the lactone **28** was determined by optical rotation in comparison with that reported by Takano.[11b] $[\alpha]_D^{27}$ +32.2° (*c* 0.35, $CHCl_3$); IR (neat) 2910, 1715, 1222, 932 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.20-2.58 (m, 3H), 2.27 (dd, *J*=17.3, 9.5 Hz, 1H), 2.62-2.80 (m, 1H), 2.89 (dd, *J*=17.3, 5.6 Hz, 1H), 4.09 (dd, *J*=11.5, 10.2 Hz, 1H), 4.31 (dd, *J*=11.5, 4.8 Hz, 1H), 5.20-5.35 (m, 2H), 5.42-5.60 (m, 1H), 9.76 (s, 1H); HRMS found *m/z* 168.0780 calcd for $C_9H_{12}O_3$ 168.0786.

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7. Determined by capillary GC, HPLC and ^{13}C NMR analysis. The spectral data are in accord with the assigned structures (see Experimental).
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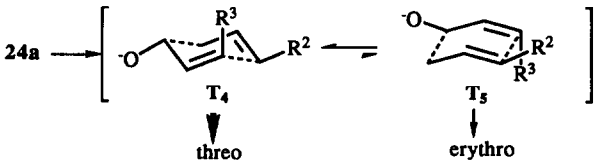
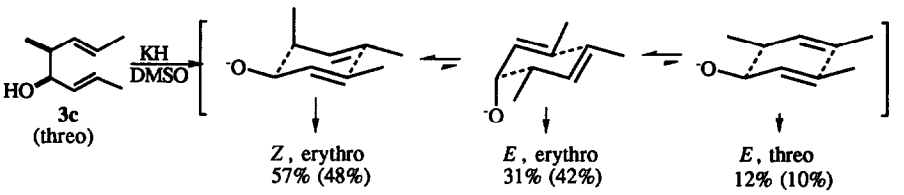
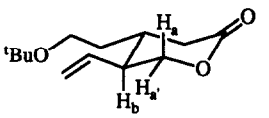
14. The significant decrease of %de in particular suggests that the rearrangement proceeds through the boat-like transition state **T5** to some extant (*ca.* 10%) as depicted below.



15. For the DMSO-facilitated anionic oxy-Cope process, see: (a) Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1025. (b) Gajewski, J. J.; Gee, K. R.; *Ibid.* **1991**, *113*, 967.
16. This increase of stereoselectivity is explicable in terms of an increased equatorial preference for the oxyanion which arises from tightening of the ion pair $O^{-}\cdots K^{+}$ in DMSO. A similar increase in equatorial preference for the oxyanion was also observed in the rearrangement of **3c** in DMSO as shown below, where the values in parentheses refer to the selectivities observed with KH in THF in the presence of 18-crown-6.



17. The δ-lactone **26** was assigned by the magnitudes of the vicinal coupling constants (J_{ab} and $J_{a'b}$) : 9.9 and 5.5 Hz for the trans-isomer and 3.6 and 3.6 Hz for the cis-isomer. For the stereochemical assignments of β,γ-disubstituted δ-valerolactone, see: Ronchetti, F.; Toma, L. *Tetrahedron* **1986**, *42*, 6535.



26a