Synthesis of Enantiomerically Enriched 2,5-Dihydrofuran Derivatives from Easily Available Enantiomerically Enriched 2-Butyne-1,4-diols by Stereospecific Transformation

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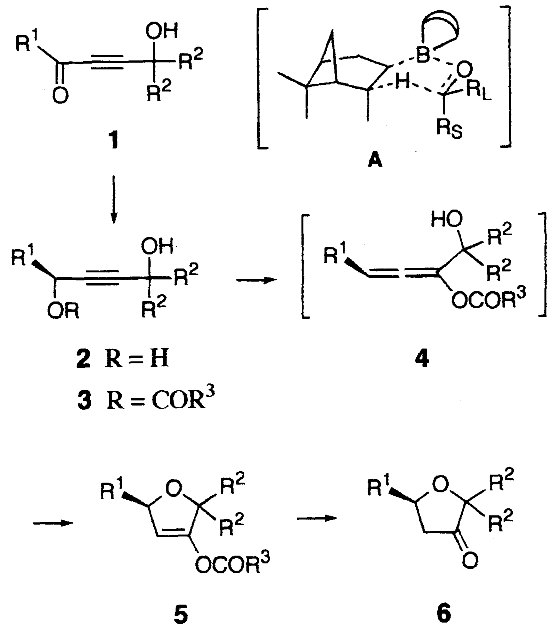
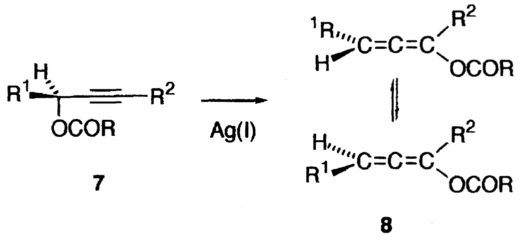
The transformation of enantiomerically enriched 1,1,4-trisubstituted 4-acyloxy-2-butyn-1-ols **3** into 2,2,5-trisubstituted 3-acyloxy-2,5-dihydrofurans **5** with complete stereospecificity was achieved by an Ag(I)-mediated rearrangement of the monoesters **3** to allenic intermediates **4**, followed by Ag(I)-assisted cyclization. A stereochemical analysis revealed that the newly formed carbon–oxygen bond in **5** was formed from the back side of the cleaved carbon–oxygen bond in **3**. The propargyl esters **3** were prepared by an enantioselective reduction of the corresponding alkynyl ketones **1**, followed by acylation. Since 3-acyloxy-2,5-dihydrofurans **5** were easily converted to the corresponding 4,5-dihydro-3(2*H*)-furanones **6**, this sequence was successfully applied to the synthesis of a differentiation-inducing antibiotic, (*S*)-(−)-ascofuranone.

The preparation of optically active substituted di- and tetrahydrofuran-3-ones has gained increasing attention as biologically important synthetic targets and useful building blocks.[1] Among the various methods reported, the Ag(I)-promoted transformation of propargyl esters **3** to chiral dihydrofurans **5** appears to be the most convenient synthetic route (Scheme 1),[2] because there are many methods for the enantioselective preparation of substituted propargylic alcohols,[3,4] which are then converted to the propargyl esters **3**. Although an Ag(I)-catalyzed rearrangement of propargyl esters **7** has been extensively applied to obtain allenyl esters **8**, as shown in Scheme 2,[5] this process has not been applied to the synthesis of optically active allenes, due to racemization during the transformation.[6] If chiral propargyl esters, such as **3**, which possess a strategically located hydroxy group, are employed as a starting material instead of **7**, the proposed allenic intermediate **4** would be stereospecifically trapped by an intramolecular alcohol oxygen to give chiral 3-acyloxy-2,5-dihydrofurans **5**.[7] Herein we report on the first quantitative transfer of stereogenicity from enantiomerically enriched propargyl esters **3** into **4** and then into **5**.[8] The enantiomerically enriched substrates **3** were easily prepared from the corresponding aldehydes (or ketones) and propargylic alcohols via alkynones **1**[9] and 2-butyne-1,4-diols **2**. The enol ester moiety of dihydrofurans **5** was hydrolyzed to leave a carbonyl group. Therefore, this sequence provides a practical method for the synthesis of optically active 4,5-dihydro-3(2*H*)-furanones **6**, as exemplified by the synthesis of (*S*)-(−)-ascofuranone (**9**),[10,11] which is one of the phenolic natural products that possess hypolipidemic and differentiation-inducing activity.[12]



Scheme 1.



Scheme 2.

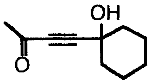
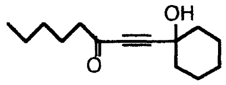
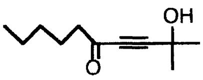
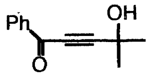
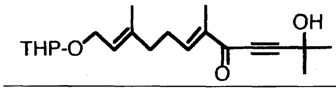
Preparation of Enantiomerically Enriched Propargyl

Esters 3. Alkynones **1b**, **1c**, and **1e** (Table 1) were prepared by an addition reaction of the corresponding propargyl alcohol (2-propyn-1-ol) derivatives to hexanal or (*E*,*E*)-2,6-dimethyl-8-(tetrahydropyran-2-yloxy)-2,6-octadienal[11] followed by oxidation, as reported for the synthesis of **1a** and **1d**.[9,13] As shown in Table 1, the enantioselective reduction of keto alcohols **1** to diols **2** was accomplished using (+)- or (−)-*B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (**10**)[3b] without protection of the hydroxy group in **1**. Monoesters **3a**—**d** were obtained by the acetylation of the less-hindered hydroxy group in diols **2**. As we reported on the synthesis of *dl*-ascofranone from the pivaloyl ester *dl*-**3e**,[14] **2e** was subjected to pivaloylation. The enantiomeric excess values (76—91%ee) of **2a**—**d** were determined by examining ^{1}H NMR signals corresponding to the acetyl group of **3a**—**d** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) ($Eu(hfc)_3$). In the case of (*E*,*E*)-2,6,10-trimethyl-12-(tetrahydropyran-2-yloxy)dodeca-6,10-dien-3-yne-2,5-diol (**2e**), ^{1}H NMR analyses of both the pivaloyl derivative **3e** and the monoacetate of **2e** failed to estimate the enantiomeric purity at the C-5 position. Therefore, **2e** was transformed into the chloroacetate **11** (74% yield) by chloroacetylation followed by removal of the tetrahydropyran-2-yl (THP) protecting group, as shown in Scheme 3, and the ratio of (5*S*)- to (5*R*)-**2e** (vide infra) was determined to be 92 : 8 based on an examination of the chloroacetyl signals of each enantiomer in the $Eu(hfc)_3$-shifted ^{1}H NMR spectra of **11**.

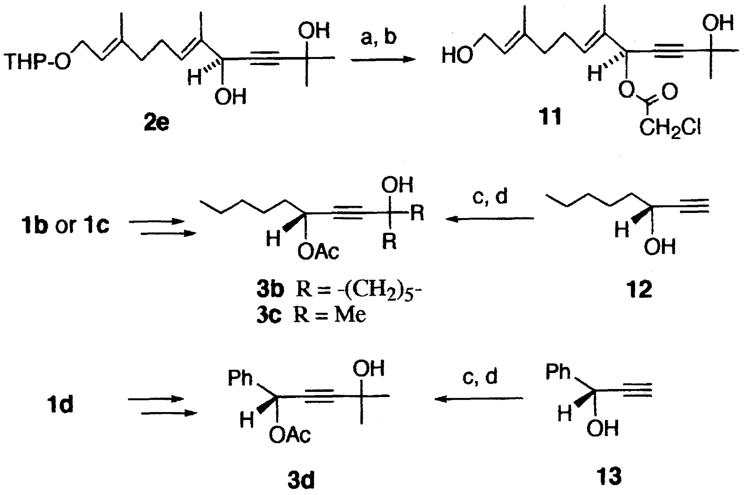
In the reduction of prochiral α,β-ynones with **10**, the acetylenic group generally functions as a smaller carbonyl substituent (R_S), rather than an alkyl or aryl group (the larger substituent: R_L) in the transition state **A**[3b,15] in Scheme 1. However, a recent report suggested that the alkynyl group that possesses the bulky tertiary alcohol unit of **1** may function as an R_L.[3e] In order to estimate the absolute configuration of **2**, the $Eu(hfc)_3$-shifted ^{1}H NMR spectra of monoacetates **3b**—**d** derived from **1b**—**d** were compared with those of (*R*)-**3b**—**d** prepared from known (*R*)-1-octyn-3-ol (**12**)[3b] or (*S*)-1-phenyl-2-propyn-1-ol (**13**)[4a] in relatively low yields in Scheme 3. In every case examined, the reduction of **1b**—**d** with (+)-**10** was found to form (*R*)-**2b**—**d** enantioselectively. These results suggest that the acetylenic group in prochiral α,β-ynones **1** functions as an independent smaller carbonyl substituent (R_S) on the bulky tertiary alcohol unit. By analogy, the absolute configuration of the newly formed secondary alcohol in **2a** should be *R* and that in **2e** should be *S*.

Transformation of Propargylic Esters 3 into 2,5-Dihydrofurans 5 and 4,5-Dihydro-3(2*H*)-furanones 6. As shown in Table 1, the treatment of **3** with $AgBF_4$ in benzene at 80 °C in the dark gave 2,5-dihydrofurans **5** in good yields. The enantiomeric excess values of acetates **5a**—**d** were determined by an examination of the acetyl signals in the $Eu(hfc)_3$-shifted ^{1}H NMR spectra. In the case of **5e**, according to the ^{1}H NMR study on **11** mentioned above, the primary alcohol **14** in Scheme 4 was initially chloroacetylated. However, a ^{1}H NMR study of the chloroacetate of **14** in the presence of $Eu(hfc)_3$ was not successful. Ultimately, a quantitative transfer of stereogenicity from **3e** to **5e** was estimated by a HPLC analysis of the furanone **15** ($[\alpha]^{25}_{D}$ −38.7° (c = 4.66, $ClCH_2CH_2Cl$)), which was obtained from **5e** (overall 68% yield) by removal of the THP protecting group with pyridinium *p*-toluenesulfonate (PPTS), solvolysis of the ester group, and acetylation of the regenerated primary

Table 1. Transformation of Acetylenic Keto Alcohols Keto Alcohols **1** to Dihydrofurans **5**

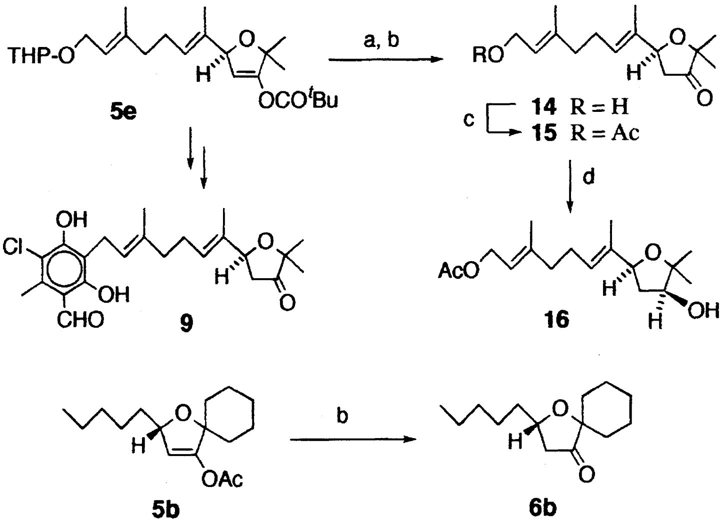
Keto alcohol		Reducing agent	Diol $2^{a)}$				Acyl ester $3^{b)}$			Dihydrofuran $5^{c)}$		
				Yield/%	ee/%	Configuration		R^3	Yield/%		Yield/%	ee/%
	**1a**	(−)-**10**	**2a**	—	76	*R*	**3a**	Me	88[d]	**5a**	61	76
	**1b**	(−)-**10**	**2b**	96	88	*R*	**3b**	Me	87	**5b**	61	88
	**1c**	(−)-**10**	**2c**	90	89	*R*	**3c**	Me	88	**5c**	82	89
	**1d**	(−)-**10**	**2d**	84	91	*R*	**3d**	Me	89	**5d**	67	91[e]
	**1e**	(+)-**10**	**2e**	81	84[f]	*S*	**3e**	*t*-Bu	87[g]	**5e**	65	84[f]

a) Molar ratio, **1** : **10** = 1 : 3—3.5 (neat); room temperature. b) Molar ratio, **2** : Ac_2O : pyridine = 1 : 2.3—5.0 : 0.5—3.0; CH_2Cl_2; room temperature. c) $AgBF_4$ (8—15 mol%), benzene, 80 °C, in the dark. d) Yield from **1a**. e) Reaction temperature, 40 °C. f) Enantiomeric purity at C-5 position. g) Molar ratio, **2e** : *t*-BuCOCl : pyridine : DMAP = 1 : 1.8 : 3 : 0.2; ether; 0 °C.



a: $(ClCH_2CO)_2O$, pyridine; b: PPTS, EtOH; c: BuLi, $R_2C{=}O$;
d: Ac_2O, pyridine.

Scheme 3.



a: PPTS, EtOH; b: MeONa, MeOH; c: Ac_2O, DMAP, pyridine;
d: $NaBH_4$, MeOH.

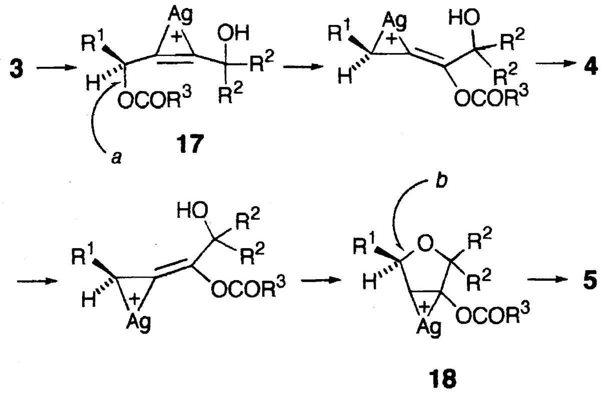
Scheme 4.

alcohol, as shown in Scheme 4.

Although the stereogenicity of monoacetates **3a**—**c** and **3e** was quantitatively transferred, 6% of the enantiomeric purity was lost during the transformation held at 80 °C in the case of **3d**, which possesses an aromatic substituent at the chiral center. Therefore, the transformation of **3d** to **5d** was carried out at 40 °C to prevent the loss of enantiomeric purity. These results given in Table 1 mean that the combination of the rearrangement of propargylic esters **3** with subsequent cyclization of the allenic intermediate **4** has established a means to capture the stereogenicity transferred from an enantiomerically enriched **3** to a racemization-prone allenic intermediate **4**, by providing an intramolecular nucleophile trap.

The synthesis of 4,5-dihydro-3(2*H*)-furanones **6** from **5** was exemplified by the conversion of **5e** to **14**, mentioned above, and the solvolysis of **5b** with MeONa/MeOH to produce **6b** (76% yield) in Scheme 4.

Because a determination of the absolute configuration of dihydrofurans **5** is necessary to better understand the reaction mechanism, the furanone **15** was reduced with $NaBH_4$ to give a known *cis*-alcohol,[11b)] (3*R**,5*R**)-5-[(*E*,*E*)-7-acetoxy-1,5-dimethylhepta-1,5-dienyl]tetrahydro-2,2-dimethylfuran-3-ol (**16**) (92% yield). A comparison of the optical rotation of **16** ($[\alpha]_D^{21}$ +12.2° (c = 3.69, $CHCl_3$)) with that of the reported alcohol (3*S*,5*S*)-**16**[11b)] revealed the absolute configuration



Scheme 5.

at the C-5 position of synthetic **16** to be *S*. Thus, (5*S*)-**5e** is obtained from (5*S*)-**3e**. A possible mechanism for the silver(I)-catalyzed rearrangement and cyclization is shown in Scheme 5, in which the carbon–oxygen bond *b* in **18** is formed from the back side of the carbon–oxygen bond *a* in **17**. As we have already reported on the synthesis of *dl*-ascofuranone (**9**) from *dl*-**5e**,[14] a formal synthesis of enantiomerically enriched (−)-(*S*)-**9** is achieved by the described procedure.

Experimental

All of the reactions were carried out under an argon atmosphere. All bps were uncorrected. A microscale distillation was performed with Kugelrohr (Büchi). The ^{1}H NMR spectra (270 MHz) in $CDCl_3$ were recorded on a JEOL JNM-GX270 spectrometer, and the IR spectra (neat liquid film samples unless otherwise noted) on a Shimadzu FT-IR-4200 spectrometer. Electron-impact mass spectra (70 eV) were obtained on a JEOL JMS-DX303 instrument. Column chromatography was performed using Wakogel C-200 and C-300 (Woko Pure Chemical Industries, Ltd.). Preparative TLC plates were prepared using Kieselgel 60 PF_{254} (Merck). A HPLC analysis was performed using Chiralcel OJ (4.6 mm×25 cm, Daicel Chem. Ind., Ltd.; hexane : 2-propanol = 19 : 1 (v/v), 1 ml min^{-1}; 40 °C; detected at 220 nm).

Preparation of Keto Alcohols 1 from Racemic Diols *dl*-2. Keto alcohols **1** were produced by CrO_3 or MnO_2 oxidation of the corresponding racemic diols *dl*-**2**, which were prepared from the corresponding carbonyl compounds and propargyl alcohol derivatives by a previously reported modification.[2,9,13c] The starting carbonyl compounds, racemic diols (yield/%), and keto alcohols (yield/%) were as follows: cyclohexanone, *dl*-**2a** (90),[2] **1a** (90);[13a] cyclohexanone, *dl*-**2b** (90),[16] **1b** (85); hexanal, *dl*-**2c** (87), **1c** (86); benzaldehyde, *dl*-**2d** (98),[2] **1d** (75).[13b] Physical and spectral data of **1a**, **1b**, *dl* -**2c**, **1c**, and **1d** are summarized below.

1-(3-Oxo-1-butynyl)cyclohexanol (1a).[13a] Bp 77—80 °C (bath temp)/13.3 Pa; IR 3410, 2220, 1676, 1218 cm^{-1}; ^{1}H NMR δ = 1.2—2.1 (10H, m), 2.45 (3H, s), 2.93 (1H, s).

1-(3-Oxo-1-octynyl)cyclohexanol (1b). Bp 132—138 °C (bath temp)/36.0 Pa; IR 3400, 2950, 2200, 1680 cm^{-1}; ^{1}H NMR δ = 0.90 (3H, t, *J* = 6.8 Hz), 1.2— 2.1 (16H, m), 2.27 (1H, br s), 2.56 (2H, t, *J* = 7.6 Hz); MS *m*/*z* (%) 222 (M^+; 4), 81 (100), 53 (78). Found: C, 75.35; H, 9.97%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

***dl*-2-Methyl-3-decyne-2,5-diol *dl*-(2c) and 2-Hydroxy-2-methyl-3-decyn-5-one (1c).** ***dl*-2c:** IR 3350, 2940, 1160 cm^{-1}; ^{1}H NMR δ = 0.90 (3H, t, *J* = 6.8 Hz), 1.28—1.73 (14H, m+s (δ = 1.51)), 2.48 (1H, br s), 2.61 (1H, br s), 4.37 (1H, t, *J* = 6.6 Hz); MS *m*/*z* (%) 169 ($M^+ - Me$; 4), 95 (100).

1c: IR 3400, 2950, 2210, 1670, 1170 cm^{-1}; ^{1}H NMR δ = 0.90 (3H, t, *J* = 6.8 Hz), 1.3—1.8 (12H, m+s (δ = 1.51)), 2.39 (1H, br s), 2.55 (2H, t, *J* = 6.8 Hz); MS *m*/*z* (%) 183 ($M^+ + 1$; 10), 69 (52), 53 (100). Found: C, 72.41; H, 9.93%. Calcd for $C_{14}H_{22}O_2$: C, 72.49; H, 9.95%.

4-Hydroxy-4-methyl-1-phenyl-2-pentyn-1-one (1d).[13b] IR 3410, 2240, 1643, 1262, 700 cm^{-1}; ^{1}H NMR δ = 1.67 (6H, s), 2.67 (1H, br s), 7.27—8.13 (5H, m).

(*E*,*E*)-2-Hydroxy-2,6,10-trimethyl-12-(tetrahydropyran-2-yloxy)dodeca-6,10-dien-3-yn-5-one (1e). Treatment of *dl*-**2e**[14] (1.21 g, 3.60 mmol) with pyridinium dichromate (2.05 g, 5.45 mmol) in CH_2Cl_2 at −20—−30 °C for 162 h gave crude products (1.11 g), which were purified by flash chromatography (hexane : ethyl acetate = 3 : 1) to afford (*E*,*E*)-2-hydroxy-2,6,10-trimethyl-12-(tetrahydropyran-2-yloxy)dodeca-6,10-dien-3-yn-5-one (**1e**) (921 mg, 77% yield): bp 211—214 °C (bath temp)/62.7 Pa; IR 3400, 2930, 2210, 1630, 1270 cm^{-1}; ^{1}H NMR δ = 1.44—1.88 (18H, m+s (δ = 1.58)+s (δ = 1.70)+s (δ = 1.79)), 2.18—2.28 (2H, m), 2.38—2.50 (2H, m), 3.26 (1H, br s), 3.46—3.59 (1H, m), 3.80—3.93 (1H, m), 4.07 (1H, dd, *J* = 7.6, 12.1 Hz), 4.25 (1H, dd, *J* = 5.9, 12.1 Hz), 4.6—4.7 (1H, m), 5.37—5.48 (1H, m), 7.11 (1H, t, *J* = 6.8 Hz); MS *m*/*z* (%) 232 ($M^+ - DHP - H_2O$; 11), 93 (100). Found: C, 71.60; H, 9.07%. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04%.

Transformation of Keto Alcohols 1 into Enantiomerically Enriched Diols 2. Preparation of (*E*,*E*)-2,6,10-Trimethyl-12-(tetrahydropyran-2-yloxy)-dodeca-6,10-dien-3-yne-2,5-diol (2e). According to the reported method,[3b] a THF (60 ml) solution of (+)-**10** (30 mmol)((*S*)-Alpine-Borane®) was concentrated under reduced pressure to clear syrup, to which **1e** (2.82 g, 8.73 mmol) was added dropwise at 0 °C. The reaction mixture was gradually warmed to 25 °C with stirring for 158 h. After the addition of propionaldehyde (1.31 g, 22.5 mmol), the reaction mixture was stirred for 1.5 h at 25 °C, and then concentrated in vacuo at 40—50 °C. The residue was treated with NaOH (3 mol dm^{-3}, 11 ml), THF (15 ml), and 30% aqueous H_2O_2 at 40—50 °C for 3 h. Ethereal extracts were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and concentrated to give crude products, which were purified by column chromatography (hexane : ethyl acetate = 1 : 1) to afford **2e** (2.30 g, 81% yield).

This procedure applies to the enantioselective synthesis of **2a**—**2d** from **1a**—**1d**. Spectral properties of **2a**—**2e** were identical with those of the corresponding *dl*-compounds.[2,14,16]

Transformation of Diols 2 into 2,5-Dihydrofurans 5 via Esters 3. Preparation of 3-(2,2-Dimethylpropanoyloxy)-5-[(*E*,*E*)-1,5-dimethyl-7-(tetrahydropyran-2-yloxy)hepta-1,5-dienyl]-2,2-dimethyl-2,5-dihydrofuran (5e). (A Typical Procedure). 2,2-Dimethylpropanoyl chloride (1.28 g, 10.6 mmol) was added dropwise at 0 °C to a mixture of **2e** (1.97 g, 5.85 mmol), 4-dimethylaminopyridine (DMAP) (148 mg, 1.21 mmol), and pyridine (1.39 g, 17.6 mmol) in ether (1.66 ml). After stirring at 0 °C for 80 min, an extractive workup followed by column chromatography (hexane : ethyl acetate = 3 : 1) gave **3e**[14] (5.10 g, 87% yield).

The ester **3e** (1.10 g, 2.61 mmol) was treated with $AgBF_4$ (33 mg, 0.17 mmol) in refluxing benzene (26 ml) for 2.5 h in the dark. The reaction mixture was diluted with dichloromethane (50 ml) and washed with 10% aq ammonia (30 ml) and saturated aq NaCl (30 ml). The organic phase was dried over Na_2SO_4 and concentrated. Purification by flash chromatography (hexane : ethyl acetate = 10 : 1) gave **5e**[14] (0.71 g, 65%).

Similarly, enantiomerically enriched diols **2** were transformed into esters **3** and then into dihydrofurans **5** according to the reported procedure.[2,14] The spectral properties of **3a**, **3b**, **3d**, **3e**, **5a**, **5b**, **5d**, and **5e** were identical with those of the corresponding *dl*-compounds.[2,14,16]

In the Eu(hfc)$_3$-shifted ^{1}H NMR analysis, low-field shifts of ^{1}H NMR signals of enantiomerically enriched samples were examined based on those of racemic samples. The concentration of **3** (or **5**) (mol dm^{-3}), the concentration of Eu(hfc)$_3$ (mol dm^{-3}), and the chemical shifts of the acetyl signals of (*R*)- and (*S*)-isomers were as follows: **3a** 0.086, 0.032, δ = 3.28 and 3.37; **3b** 0.075, 0.013, δ = 2.78 and 2.83; **3d** 0.061, 0.021, δ = 3.43 and 3.52; **5a** 0.095, 0.089, δ = 4.86 and 5.04; **5b** 0.075, 0.023, δ = 2.69 and 2.73; **5d** 0.082, 0.045, δ = 3.43 and 3.38.

5-Acetoxy-2-methyl-3-decyn-2-ol (3c) and 3-Acetoxy-2,5-dihydro-2,2-dimethyl-5-pentylfuran (5c). **3c**: IR 3400, 2930, 1730, 1220 cm^{-1}; ^{1}H NMR δ = 0.89 (3H, t, *J* = 6.8 Hz), 1.24—1.54 (12H, m+s (δ = 1.50)), 1.67—1.79 (2H, m), 2.07 (3H, s, Ac), 2.77 (1H, br s), 5.36 (1H, t, *J* = 6.8 Hz); MS *m*/*z* (%) 211 (M$^+$−Me; 63), 169 (93), 99 (100). In the presence of Eu(hfc)$_3$ (0.027 mol dm^{-3}), ^{1}H NMR signals of the acetyl group in **3c** (0.088 mol dm^{-3}) were observed at δ = 3.32 ((*R*)-isomer) and 3.39 ((*S*)-isomer).

5c: IR 2900, 1790, 1770, 1670, 1470, 1200, 1180, 1160 cm^{-1}; ^{1}H NMR δ = 0.88 (3H, t, *J* = 6.8 Hz), 1.22—1.67 (14H, m+s (δ = 1.30)+s (δ = 1.36)), 2.20 (3H, s, Ac), 4.80 (1H, dt, *J* = 1.8, 5.9 Hz), 5.71 (1H, d, *J* = 1.8 Hz). Found: C, 68.71; H, 10.07%. Calcd for $C_{20}H_{30}O_4$: C, 68.99; H, 9.80%. In the presence of Eu(hfc)$_3$ (0.077 mol dm^{-3}), ^{1}H NMR signals of the acetyl group in **5c** (0.080 mol dm^{-3}) were observed at δ = 2.93 ((*R*)-isomer) and 2.97 ((*S*)-isomer).

Alternative Synthesis of Monoacetates 3 from Known (*R*)-1-Octyn-3-ol and (*S*)-1-Phenyl-2-propyn-1-ol. Preparation of (*R*)-1-(3-Acetoxy-1-octynyl)cyclohexanol ((*R*)-3b). A hexane solution of butyllithium (1.6 mol dm^{-3}, 20.6 mmol) was added dropwise in 15 min at −78 °C to a THF (104 ml) solution of (*R*)-1-octyn-3-ol (**12**)[3b] (1.30 g, 10.3 mmol, $[\alpha]_D^{25}$ +16.79° (c = 1.79, Et$_2$O), 88%ee based on the Eu(hfc)$_3$-shifted ^{1}H NMR analysis of (*R*)-1-ethynylhexyl acetate). After stirring for 2 h, cyclohexanone (1.52 g, 15.5 mmol) in THF (6.4 ml) was added to the reaction mixture for 10 min at −50 °C. This mixture was stirred for 16 h and warmed up to 25 °C. An extractive workup gave crude diol (2.48 g). A part of the crude product (531 mg) was treated with acetic anhydride (1.09 g, 10.7 mmol) and pyridine (98 mg, 1.24 mmol) in dichloromethane (0.5 ml) at 25 °C for 1.5 h. Concentration of the reaction mixture, followed by purification by column chromatography (hexane : ethyl acetate = 3 : 1), gave (*R*)-**3b** (308 mg, 53% yield from (*R*)-1-octyn-3-ol, 88%ee).

Similarly, (*R*)-**3c** (32% yield, 88%ee) and (*R*)-**3d** (11% yield, 89%ee, $[\alpha]_D^{25}$ +25.5° (c = 0.22, CH$_2$Cl$_2$)) were prepared from (*R*)-1-octyn-3-ol and (*S*)-1-phenyl-2-propyn-1-ol (**13**)[4a] ($[\alpha]_D^{25}$ +27.3° (c = 3.38, CHCl$_3$)), respectively. The spectral properties, including Eu(hfc)$_3$-shifted ^{1}H NMR data, were identical with those of the corresponding monoacetates **3** prepared from keto alcohols **1**.

Synthesis of 2-Pentyl-1-oxaspiro[4.5]decan-4-one (6b). Dihydrofuran **5b** (99 mg, 0.42 mmol) was treated with MeONa/MeOH (0.1 mol dm^{-3}, 1.5 ml) at 25 °C for 80 min. An extractive workup followed by preparative TLC (benzene : ethyl acetate = 15 : 1) gave **6b** (colorless oil, 64 mg, 76% yield). IR 2930, 2855, 1755, 1450, 1055 cm^{-1}; ^{1}H NMR δ = 0.91 (3H, t, *J* = 6.8 Hz), 1.3—1.8 (18H, m), 2.20 (1H, dd, *J* = 10.2, 18.0 Hz), 2.50 (1H, dd, *J* = 4.4, 18.0 Hz), 4.10 (1H, ddt, *J* = 4.4, 10.2, 5.9 Hz); ^{13}C NMR δ = 14.0, 21.2, 21.6, 22.6, 25.2, 29.5, 31.8, 33.2, 36.2, 42.5, 72.8, 82.0, 218.2; MS *m*/*z* (%) 224 (M$^+$; 5), 196 (98), 109 (98), 79 (100). Found: C, 74.72; H, 10.55%. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%.

Preparation of (*E*,*E*)-8-Chloroacetoxy-3,7,11-trimethyldodeca-2,6-dien-9-yne-1,11-diol (11). A mixture of diol **2e** (83 mg, 0.24 mmol), chloroacetic anhydride (89 mg, 0.52 mmol), and pyridine (20 mg, 0.25 mmol) in dichloromethane (0.4 ml) was stirred at 0 °C for 15 min. An extractive workup, followed by concentration under reduced pressure, gave crude chloroacetate (181 mg), which was treated with PPTS (112 mg, 0.45 mmol) in ethanol (2.0 ml) at 55 °C for 6 h. An extractive workup and purification by preparative TLC (benzene : ethyl acetate = 1 : 2) afforded **11** (60 mg, 74% yield, 84%ee based on the Eu(hfc)$_3$-shifted ^{1}H NMR study and HPLC analysis). Bp 189—191 °C (bath temp)/49.3 Pa; IR 3380, 1742, 1671, 1169, 955 cm^{-1}; ^{1}H NMR δ = 1.55 (6H, s), 1.65—2.21 (12H, m+s (δ = 1.67)+s (δ = 1.87)), 4.05 (2H, s, ClCH$_2$C=O), 4.15 (2H, d, *J* = 6.7 Hz), 5.22 (1H, t, *J* = 6.7 Hz), 5.39 (1H, t, *J* = 5.9 Hz), 5.56 (1H, s); MS *m*/*z* (%) 328 (M$^+$; trace), 216 (M$^+$−H$_2$O−ClCH$_2$CO$_2$H; 55), 183 (M$^+$−2H$_2$O−ClCH$_2$CO$_2$H−Me; 100); $[\alpha]_D^{25}$ −27.3° (c = 0.43, ClCH$_2$CH$_2$Cl). Found: C, 61.85; H, 7.60%. Calcd for $C_{17}H_{25}ClO_4$: C, 62.09; H, 7.66%.

In the presence of Eu(hfc)$_3$ (0.035 mol dm^{-3}), ^{1}H NMR signals of the chloroacetyl group of **11** (0.12 mol dm^{-3}) were observed at δ = 4.40 (d, *J* = 15 Hz) and 4.47 (d, *J* = 15 Hz) for the (*R*)-isomer and at δ = 4.39 (s) for the (*S*)-isomer. The enantiomeric excess value was also confirmed by a HPLC analysis under the prescribed conditions (hexane : 2-propanol = 9 : 1; (*R*)-isomer: Rt 20.3 min; (*S*)-isomer: Rt 17.6 min).

Conversion of Dihydrofuran 5e to Known Tetrahydrofuran 16. The treatment of **5e** (668 mg, 1.59 mmol) with PPTS (162 mg, 0.64 mmol) in ethanol (13 ml) at 55 °C for 2 h, followed by an extractive workup, gave crude alcohol (580 mg), which was purified by preparative TLC (hexane : ethyl acetate = 3 : 1) to afford 3-(2,2-dimethylpropanoyloxy)-2,5-dihydro-5-[(*E*,*E*)-7-hydroxy-1,5-dimethylhepta-1,5-dienyl]-2,2-dimethylfuran[14] (445 mg, 83% yield, $[\alpha]_D^{25}$ −37.4° (c = 3.57, ClCH$_2$CH$_2$Cl)). The alcohol (199 mg, 0.59 mmol) was treated with MeONa/MeOH (0.01 mol dm^{-3}, 5.0 ml) at 25 °C for 45 min. An extractive workup, followed by preparative TLC (hexane : ethyl acetate = 1 : 1), gave 5-[(*E*,*E*)-7-hydroxy-1,5-dimethylhepta-1,5-dienyl]-2,2-dimethyl-4,5-dihydro-3(2*H*)-furanone (**14**)[11a] (colorless oil, 137 mg, 91% yield). IR 3400, 1750, 1662, 1370, 1170, 1110, 995 cm^{-1}; ^{1}H NMR δ = 1.18 (3H, s), 1.25 (3H, s), 1.61 (3H, s), 1.63 (3H, s), 1.80—2.25 (4H, m), 2.39 (1H, dd, *J* = 9.8, 18.1 Hz), 2.48 (1H, dd, *J* = 6.4, 18.1 Hz), 4.09 (2H, d, *J* = 6.8 Hz), 4.52 (1H, dd, *J* = 6.4, 9.8 Hz), 5.35 (1H, t, *J* = 6.8 Hz), 5.51 (1H, t, *J* = 6.4 Hz); MS *m*/*z* (%) 252 (M$^+$; 5), 234 (M$^+$−H$_2$O; 38), 135 (96), 42 (100); $[\alpha]_D^{25}$ −38.5° (c = 6.64, ClCH$_2$CH$_2$Cl).

A mixture of **14** (103 mg, 0.41 mmol), acetic anhydride (216 mg, 2.1 mmol), pyridine (98 mg, 1.2 mmol), DMAP (25 mg, 0.21 mmol) in dichloromethane (0.6 ml) was stirred at 25 °C for 30 min and then concentrated. Purification by preparative TLC (hexane : ethyl acetate = 3 : 1) gave 5-[(*E*,*E*)-7-acetoxy-1,5-dimethylhepta-1,5-dienyl]-2,2-dimethyl-4,5-dihydro-3(2*H*)-furanone (**15**)[11] (slightly yellowish oil, 108 mg, 90% yield). ^{1}H NMR δ = 1.24 (3H, s), 1.31 (3H, s), 1.67 (3H, s), 1.71 (3H, s), 1.9—2.3 (7H, m+s (δ = 2.04)), 2.43 (1H, dd, *J* = 9.8, 18.1 Hz), 2.53 (1H, dd, *J* = 6.4, 18.1 Hz), 4.4—4.7 (3H, m+d (δ = 4.59, *J* = 7.0 Hz)), 5.35 (1H, t, *J* = 7.0 Hz), 5.56 (1H, t, *J* = 6.3 Hz); $[\alpha]_D^{25}$ −38.7° (c = 4.66, ClCH$_2$CH$_2$Cl). The enantiomeric excess (84%ee) was estimated by the HPLC analysis ((*S*)-isomer: Rt 11.3 min; (*R*)-isomer: Rt 14.2 min).

To a methanol (0.82 ml) solution of **15** (78 mg, 0.26 mmol) was added $NaBH_4$ (8 mg, 0.20 mmol) at −78 °C. After stirring for 80 min, acetic acid (230 mg, 3.8 mmol) in methanol (0.5 ml) was added. The mixture was stirred for 10 min at −78 °C and then gradually warmed to 25 °C. An extractive workup gave crude products (124 mg), which were purified by column chromatography (chloroform : ether = 7 : 1) to give ($3R^*,5R^*$)-5-[(*E*,*E*)-7-acetoxy-1,5-dimethylhepta-1,5-dienyl]tetrahydro-2,2-dimethylfuran-3-ol (**16**) (colorless syrup, 72 mg, 92% yield) along with a small amount of ($3R^*,5S^*$)-isomer.[11b)]

($3R^*,5R^*$)-**16**: ^{1}HNMR δ = 1.21 (3H, s), 1.28 (3H, s), 1.62 (3H, s), 1.70 (3H, s), 1.78 (1H, ddd, J = 4.4, 6.8, 12.7 Hz) 1.99—2.22 (7H, m+s (δ = 2.05)), 2.42 (1H, ddd, J = 6.4, 7.8, 12.7 Hz), 3.96 (1H, t, J = 5.4 Hz), 4.31 (1H, t, J = 7.3 Hz), 4.58 (2H, d, J = 7.1 Hz), 5.33 (1H, t, J = 7.1 Hz), 5.50 (1H, t, J = 6.1 Hz); ^{1}HNMR (CCl_4) δ = 1.14 (3H, s), 1.18 (3H, s), 1.44—1.78 (7H, m+s (δ = 1.58)+s (δ = 1.71)), 1.92—2.22 (8H, m + s (δ = 1.98)), 2.27—2.40 (1H, m), 3.75—3.83 (1H, m), 4.17 (1H, t, J = 7.4 Hz), 4.48 (2H, d, J = 6.4 Hz), 5.22—5.32 (1H, m), 5.33—5.44 (1H, m); $[\alpha]_D^{21}$ +12.2° (c = 3.69, $CHCl_3$).

(($3S,5S$)-**16**:[11b)] $[\alpha]_D^{21}$ +15.4° (c = 1.07, $CHCl_3$)). ($3R^*,5S^*$)-Isomer was distinguished by the signal at δ = 4.52 (dd, J = 6.8, 8.8 Hz). The absolute configuration at the C-5 position of ($3R^*,5R^*$)-**16** was determined to be S by a comparison of its optical rotation $[\alpha]_D^{21}$ +12.2° (c = 3.69, $CHCl_3$) with that of known ($3S,5S$)-**16**.[11b)]

References

1) a) For example: a) G. Adam, R. Zibuck, and D. Seebach, *J. Am. Chem. Soc.*, **109**, 6176 (1987); b) H. Suh and C. S. Wilcox, *J. Am. Chem. Soc.*, **110**, 470 (1988); c) S. Hormuth and H.-U. Reissig, *Synlett*, **1991**, 179; d) A. B. Smith, III, M. Fukui, H. A. Vaccaro, and J. R. Empfield, *J. Am. Chem. Soc.*, **113**, 2071 (1991); e) M. C. Pirrung, W. L. Brown, S. Rege, and P. Laughton, *J. Am. Chem. Soc.*, **113**, 8561 (1991); f) R. K. Boeckman, Jr., S. K. Yoon, and D. K. Heckendorn, *J. Am. Chem. Soc.*, **113**, 9682 (1991); g) P. A. Evans and J. D. Roseman, *Tetrahedron Lett.*, **36**, 31 (1995); h) J. D. White, G. L. Bolton, A. P. Dantanarayana, C. M. J. Fox, R. N. Hiner, R. W. Jackson, K. Sakuma, and U. S. Warrier, *J. Am. Chem. Soc.*, **117**, 1908 (1995); i) J. S. Clark, A. G. Dossetter, and W. G. Whittingham, *Tetrahedron Lett.*, **37**, 5605 (1996); j) J. S. Clark, M. Fretwell, G. A. Whitlock, C. J. Burns, and D. N. A. Fox, *Tetrahedron Lett.*, **39**, 97 (1998).

2) a) H. Saimoto, T. Hiyama, and H. Nozaki, *J. Am. Chem. Soc.*, **103**, 4975 (1981); b) H. Saimoto, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **56**, 3078 (1983).

3) Leading references of the enantioselective reduction of acetylenic ketones: a) R. S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.*, **99**, 8339 (1977); b) M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai, and D. B. Cardin, *Tetrahedron*, **40**, 1371 (1984); c) R. Noyori, I. Tomino, M. Yamada, and M. Nishizawa, *J. Am. Chem. Soc.*, **106**, 6717 (1984); d) K. A. Parker and M. W. Ledeboer, *J. Org. Chem.*, **61**, 3214 (1996); e) C. J. Helal, P. A. Magriotis, and E. J. Corey, *J. Am. Chem. Soc.*, **118**, 10938 (1996).

4) Other methods for the enantioselective synthesis of propargylic alcohols: a) A. Viola, G. F. Dudding, and R. J. Proverb, *J. Am. Chem. Soc.*, **99**, 7390 (1977); b) T. Mukaiyama, K. Suzuki, K. Soai, and T. Sato, *Chem. Lett.*, **1979**, 447; c) K. Ishihara, A. Mori, I. Arai, and H. Yamamoto, *Tetrahedron Lett.*, **26**, 983 (1986); d) J. A. Marshall and J. Lebreton, *J. Am. Chem. Soc.*, **110**, 2925 (1988); e) T. Ito, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **30**, 7083 (1989); f) S. Kusuda, K. Kawamura, Y. Ueno, and T. Toru, *Tetrahedron Lett.*, **34**, 6587 (1993); g) E. J. Corey and K. A. Cimprich, *J. Am. Chem. Soc.*, **116**, 3151 (1994), and references cited therein.

5) a) R. C. Cookson, M. C. Cramp, and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, **1980**, 197; b) D. G. Oelberg and M. D. Schiavelli, *J. Org. Chem.*, **42**, 1804 (1977); c) A. C. Day and M. C. Whiting, *J. Chem. Soc. C*, **1966**, 464; d) G. Saucy, R. Marbet, H. Lindlar, and O. Isler, *Helv. Chim. Acta*, **42**, 1945 (1959); e) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, **1956**, 1015.

6) a) H. Schlossarczyk, W. Sieber, M. Hesse, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 875 (1973); b) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968).

7) Electrophile-induced addition of oxygen nucleophiles to allenes with high stereospecificity: a) J. A. Marshall and X.-j. Wang, *J. Org. Chem.*, **56**, 960 (1991); b) R. D. Walkup and G. Park, *J. Am. Chem. Soc.*, **112**, 1597 (1990); c) M. Mualla and R. S. Macomber, *Synth. Commun.*, **19**, 1997 (1989); d) S. S. Nikam, K.-H. Chu, and K. K. Wang, *J. Org. Chem.*, **51**, 745 (1986); e) T. Gallagher, *J. Chem. Soc., Chem. Commun.*, **1984**, 1554; f) P. L. Beaulieu, V. M. Morisset, and D. G. Garratt, *Tetrahedron Lett.*, **21**, 129 (1980); g) T. L. Jacobs, R. Macomber, and D. Zunker, *J. Am. Chem. Soc.*, **89**, 7001 (1967); h) H. F. Schuster and G. M. Coppola, "Allenes in Organic Synthesis," John Wiley and Sons, New York (1984), Chaps. 3 and 5, and references cited therein.

8) Y. Shigemasa, M. Yasui, S. Ohrai, M. Sasaki, H. Sashiwa, and H. Saimoto, *J. Org. Chem.*, **56**, 910 (1991).

9) H. Saimoto, M. Shinoda, S. Matsubara, K. Oshima, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **56**, 3088 (1983).

10) a) H. Sasaki, T. Okutomi, T. Hosokawa, Y. Nawata, and K. Ando, *Tetrahedron Lett.*, **1972**, 2541; b) H. Sasaki, T. Hosokawa, M. Sawada, and K. Ando, *J. Antibiot.*, **26**, 676 (1973).

11) First synthesis of *dl*-form: a) K. Mori and T. Fujioka, *Tetrahedron Lett.*, **24**, 1547 (1983). (*S*)-Form: b) K. Mori and S. Takechi, *Tetrahedron*, **41**, 3049 (1985).

12) a) M. Sawada, T. Hosokawa, T. Okutomi, and K. Ando, *J. Antibiot.*, **26**, 681 (1973); b) T. Hosokawa, K. Suzuki, T. Okutomi, M. Sawada, and K. Ando, *Jpn. J. Pharmacol.*, **25**, 35 (1975); c) J. Magae, K. Nagai, K. Ando, and G. Tamura, *Agric. Biol. Chem.*, **52**, 3143 (1988); d) N. Minagawa, Y. Yabu, K. Kita, K. Nagai, N. Ohta, K. Meguro, S. Sakajo, and A. Yoshimoto, *Mol. Biochem. Parasitol.*, **81**, 127 (1996).

13) a) M. F. Shostakovskii, T. A. Favorskaya, A. S. Medvedeva, L. P. Safronova, and V. K. Voronov, *Zh. Org. Khim.*, **6**, 2377 (1970); *J. Org. Chem. USSR*, **6**, 2390 (1970); b) L. I. Vereshchagin, S. R. Gainulina, and L. P. Kirillova, *Biol. Aktiv. Soedin.*, **1968**, 154; *Chem. Abstr.*, **71**, 123446y (1969); c) W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.*, **1958**, 3871.

14) a) H. Saimoto, Y. Kusano, and T. Hiyama, *Tetrahedron Lett.*, **27**, 1607 (1986); b) H. Saimoto, S. Ohrai, H. Sashiwa, Y. Shigemasa, and T. Hiyama, *Bull. Chem. Soc. Jpn.*, **68**, 2727 (1995).

15) H. C. Brown and G. G. Pai, *J. Org. Chem.*, **50**, 1384 (1985).

16) Y. Shigemasa, H. Oikawa, S. Ohrai, H. Sashiwa, and H. Saimoto, *Bull. Chem. Soc. Jpn.*, **65**, 2594 (1992).