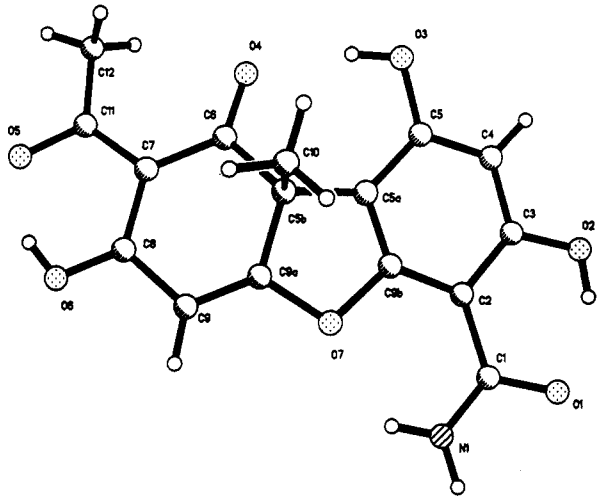

Figure 1. A computer-generated perspective drawing of the final X-ray model of cercosporamide (1). The absolute configuration shown is arbitrary.

protons were shifted downfield to δ 10.50 and 13.28 due to hydrogen bonding with adjacent carbonyl groups. Slowly exchangeable amide protons between δ 6.54 and 7.12 were clearly observed in 2D NOESY.[5]

The lowest shifted signal at δ 18.80 suggested the presence of a keto-enol tautomer. This was verified by ^{13}C NMR (125 MHz) signals at δ 200.76, 104.60, and 190.89, appropriate for a tautomeric system. These spectral data and the approximately equal bond lengths (~1.45 Å) determined by X-ray analysis for C7–C8, C8–C9, and C8–C11 indicate that cercosporamide exists, both in solution and in the solid state, as a tautomeric mixture. Further assignments of the ^{13}C NMR spectrum were performed with 2D long-range ^{1}H–^{13}C COSY (see the supplementary material). An aromatic proton at δ 6.10 on C4 has cross peaks in 2D ^{1}H–^{13}C COSY with C5 at 156.5 and C3 at 164.7 by a two-bond coupling, and C2 at δ 93.0 by a three-bond coupling. Similarly, an olefinic proton at δ 6.00 on C9 has cross peaks with C9a at δ 177.7 by a two-bond coupling and C5b at 57.9 and C7 at 104.5 by a three-bond coupling.

Cercosporamide is related to the well-known fungal metabolite usnic acid, and they presumably share an oxidative coupling biosynthesis.[7] But while usnic acid and known related metabolites arise from the coupling of two identical units, cercosporamide unites two different units. The biological activity of cercosporamide is also noteworthy. In leaf puncture wound tests[8] (2 μL of a 0.1 mg/mL solution) cercosporamide produces lesions on cassava, corn (*Zea mays*), and purslane (*Portulaca oleracea*). Since cercosporamide has no effect on dandelion (*Taraxacum offinale*), tomato (*Lycopersicon esculentum*), and cucumber (*Cucumis sativus*), it is a host-selective toxin. In a cassava protoplast assay cercosporamide exhibited an LD_{50} of 20 μM at 2 h in a flow cytometry assay system.[9] Cercosporamide was also tested against various human pathogenic yeasts, dermatophytes, and opportunistic fungi employing an in vitro minimum concentration test[10] that gave values as low as 1 μg/mL. Inhibition of serine/threonine kinases, including protein kinase C (IC_{50} 1.6 μM) and myosin light chain kinase (IC_{50} 13 μM) was also observed.

Acknowledgment. J.C. and G.S. thank the NSF (DMB86-07347) for financial support. Appreciation is expressed to J. Sears, Montana State University, for gathering MS data, to G. Gray of the Beckman Instrument Company for doing COSY and NOESY experiments, to J. Uzawa for collecting ^{1}H NMR data, to David Loebenberg for antifungal assays, and to Robert Bishop for PKC/MLCK assays. The culture of *C. henningsii* used in this work was obtained from the Commonwealth Mycological Institute, London, England.

Supplementary Material Available: Experimental procedures, spectral assignments, tables of fractional coordinates, thermal parameters, and interatomic distances and angles for 1 and spectral data for 1 and 2 (9 pages). Ordering information is given on any current masthead page.

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(8) Sugawara, F.; Strobel, G. A.; Fisher, L. E.; VanDuyne, G. D.; Clardy, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *197*, 8291-8294.
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Enantioselective Transformation of Propargyl Esters to Dihydrofurans

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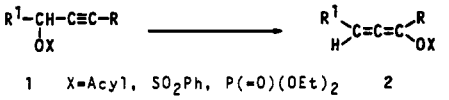
Summary: Transformation of enantiomerically enriched propargyl esters **5** into dihydrofurans **6** with complete enantiospecificity is achieved by Ag(I)-catalyzed rearrangement and cyclization, and the sequence is successfully applied to the enantioselective synthesis of an antitumor protective and hypolipidemic antibiotic, (*S*)-(−)-ascofuranone.

Silver(I)-mediated rearrangement of propargyl esters **1** has been known to give allenic products **2** as shown in Scheme I.[1] Racemization, however, took place during the transformation of enantiomerically enriched esters **1** into **2**.[2] Previously, we proposed allenic species **2** (R = C(OH)R^2_2) as reaction intermediates of silver(I)-mediated conversion of the 2-butyne-1,4-diol derivatives **5** into dihydrofurans **6**.[3] If cyclization of **2** (R = C(OH)R^2_2) into **6** was much faster than the racemization, chiral products might be produced with stereospecificity.[4] Herein we

Scheme I



1 X=Acyl, SO_2Ph, P(=O)(OEt)$_2$ 2

(1) (a) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804. (b) Pelletier, S. W.; Mody, N. V. *Ibid.* **1976**, *41*, 1069. (c) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hanson, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875. (d) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Ibid.* **1959**, *42*, 1945. (e) F. Hoffman-Laroche & Co., A.-G. Belg. Patent 617,174 (1962); *Chem. Abstr.* **1963**, *59*, 1540f.

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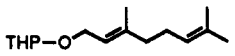
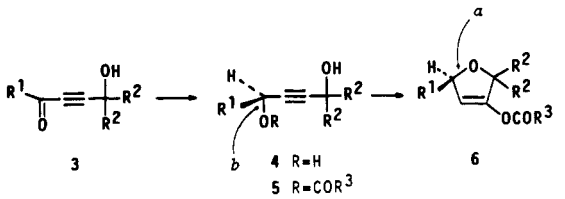
Table I. Transformation of 2-Butyne-1,4-diol Derivatives[a]

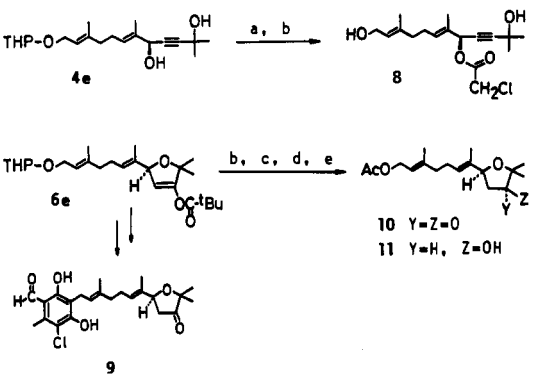
diol					acyl ester			dihydrofuran		
R^1	R^2		ee, %	config	R^3		yield, %		yield, %	ee, %
Me	$-(CH_2)_5-$	**4a**	76	*R*	Me	**5a**	88[b]	**6a**	61	76
n-C_5H_{11}	$-(CH_2)_5-$	**4b**	88	*R*	Me	**5b**	87	**6b**	61	88
n-C_5H_{11}	Me	**4c**	89	*R*	Me	**5c**	88	**6c**	82	89
Ph	Me	**4d**	91	*R*	Me	**5d**	89	**6d**[c]	67	91
	Me	**4e**	84[d]	*S*	*t*-Bu	**5e**[e]	87	**6e**	59	84[d]

[a] Preparation of **5**: molar ratio, **4a–d**: Ac_2O:C_5H_5N = 1:2.3–5.0:0.5–3.0; CH_2Cl_2; room temperature. Synthesis of **6**: $AgBF_4$ (8–15 mol %), benzene, 80 °C, in the dark. Enantiomeric excess was determined by Eu(hfc)$_3$-shifted ^1H NMR analysis. [b] Yield from the corresponding keto alcohol **3a**. [c] 40 °C. [d] Diastereomeric excess, %. [e] Molar ratio, **4e**:*t*-BuCOCl:C_5H_5N:4-$(Me_2N)C_5H_4N$ = 1:1.8:3.0:0.2; ether; 0 °C.

Scheme II

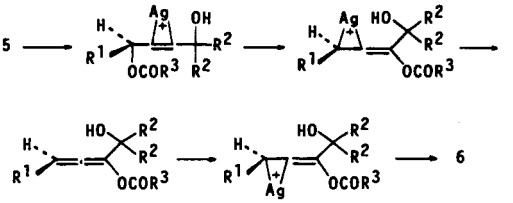


Scheme III[a]



[a] (a) $(ClCH_2CO)_2O$, C_5H_5N; (b) $C_5H_5N^+H$ OTs^-, EtOH; (c) MeONa, MeOH; (d) Ac_2O, C_5H_5N, 4-$(Me_2N)C_5H_4N$; (e) $NaBH_4$, MeOH.

Scheme IV



report the first quantitative transfer of stereogenicity from **5** into **2** (R = $C(OH)R^2_2$) and then into **6**.

The enantiomerically enriched esters **5** were obtained by monoacylation of 2-butyne-1,4-diols **4**, which were prepared by the reduction of the corresponding 3-hydroxy-1-alkynyl ketones **3** with (+)- or (−)-*B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (**7**)[5] without protection of the hydroxyl group of **3**[6] (Scheme II). Table I shows complete stereospecificity in the transformation of **5** into **6**.

A typical procedure is as follows. Treatment of **3e** (2.82 g, 8.73 mmol) with (+)-**7** (30 mmol, neat) at room temperature for 158 h followed by oxidative workup[5] gave (*E*,*E*)-2,6,10-trimethyl-12-(tetrahydropyran-2-yloxy)dodeca-6,10-dien-3-yne-2,5-diol (**4e**) (2.30 g, 81% yield, 84% de[7]). The diol **4e** (1.97 g, 5.9 mmol) was allowed to react with pivaloyl chloride (11 mmol), pyridine (18 mmol), and 4-(dimethylamino)pyridine (1.2 mmol) in ether at 0 °C for 80 min to give **5e** (2.1 g, 87% yield). Then the transformation of **5** into **6** was applied to the enantioselective preparation of the synthetic intermediate **6e**[8] of an antitumor protective and hypolipidemic antibiotic, (−)-ascofuranone (**9**).[9] The pivalate **5e** (0.65 g, 1.54 mmol) was treated with $AgBF_4$ (10 mol %) in benzene (16 ml) at 80 °C for 75 min in the dark. Purification of the crude product by column chromatography (hexane–ethyl acetate 10:1) gave 5-[(*E*,*E*)-1,5-dimethyl-7-(tetrahydropyran-2-yloxy)hepta-1,5-dienyl]-2,2-dimethyl-3-(pivaloyloxy)-2,5-dihydrofuran (**6e**) (0.38 g, 59% yield, 84% de[10]).

The dihydrofuran **6e** was converted into **10** by removal of THP protecting group (73% yield), hydrolysis of the ester group (91% yield), and acetylation of the regenerated primary alcohol (90% yield). Reduction of **10** gave (3*S**,5*S**)-5-[(*E*,*E*)-7-acetoxy-1,5-dimethylhepta-1,5-dienyl]-2,2-dimethyltetrahydrofuran-3-ol (**11**) (92% yield), whose absolute configuration at C-5 position was determined to be *S* by comparison of its optical rotation with that of the reported alcohol (3*S*,5*S*)-**11**.[11] The result means (5*S*)-**5e** has been transformed into (5*S*)-**6e**. Therefore, the carbon–oxygen bond a in the formula **6** (Scheme II) is formed from the back side of the carbon–oxygen bond b in the formula **5** (Scheme II). As we have already reported synthesis of *dl*-**9** from *dl*-**6e**,[8] formal enantioselective synthesis of (−)-(*S*)-**9** is achieved by the described procedure.

Finally, a possible mechanism for the transfer of stereogenicity is shown in Scheme IV. In the case of a propargylic ester **5d** having an aromatic substituent, 6% of

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(7) The ratio of (5*S*)- to (5*R*)-**4e** (92:8) was estimated by the examination of Eu(hfc)$_3$ shifted ^1H NMR spectra of the chloroacetate **8**, which was obtained by chloroacetylation of **4e** followed by deprotection of the primary alcohol (74% yield).

(8) Saimoto, H.; Kusano, Y.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 1607.

(9) (a) Sasaki, H.; Okutomi, T.; Hosokawa, T.; Nawata, Y.; Ando, K. *Tetrahedron Lett.* **1972**, 2541. (b) Ando, K.; Sasaki, H.; Hosokawa, T.; Nawata, Y.; Iitaka, Y. *Ibid.* **1975**, 887. (c) Magae, J.; Nagai, K.; Ando, K.; Tamura, G. *Agric. Biol. Chem.* **1988**, *52*, 3143. (d) Magae, J.; Hosokawa, T.; Ando, K.; Nagai, K.; Tamura, G. *J. Antibiot.* **1982**, *35*, 1547. (e) Sawada, M.; Hosokawa, T.; Okutomi, T.; Ando, K. *Ibid.* **1973**, *26*, 681.

(10) The ratio of (5*S*)-**6e** to (5*R*)-**6e** (92:8) was estimated by the HPLC analysis of **10** (Chiralcel OJ, hexane–2-propanol, 19:1).

(11) Synthesis of (−)-ascofuranone was achieved via optical resolution: Mori, K.; Takechi, S. *Tetrahedron* **1985**, *41*, 3049.

enantiomeric purity was lost during the transformation held at 80 °C. In order to prevent loss of enantiomeric purity, transformation of **5d** into **6d** was carried out at 40 °C (Table I).

In summary, quantitative transfer of stereogenicity from 4-(acyloxy)-2-butyn-1-ol derivatives **5** into dihydrofurans **6** is achieved by silver(I)-catalyzed rearrangement and cyclization, and the sequence is successfully applied to the synthesis of (−)-ascofuranone.

Acknowledgment. We are indebted to the analytical laboratory of Sagami Chemical Research Center for microanalysis and Dr. Koji Kimura, Department of Biochemistry, Tottori University School of Medicine, for recording mass spectra. We are also grateful for partial financial support by a Takeda Chemical Industries, Ltd. Award in Synthetic Organic Chemistry, Japan, and a Grant-in-Aid for Scientific Research (No. 62750801) from the Ministry of Education, Science, and Culture of Japan.

Supplementary Material Available: Detailed information on the obtainment of starting materials and physical and spectral data for compounds **3–6**, **8**, **10**, and **11** (7 pages). Ordering information is given on any current masthead page.

Enantioselective Total Synthesis of (−)-9-Epi-Ambrox, a Potent Ambergris-Type Olfactory Agent

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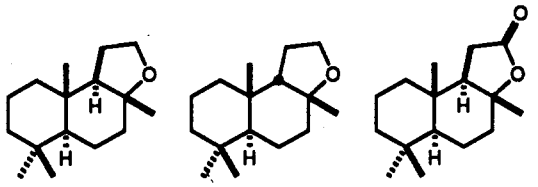
Summary: Addition of the cerium reagent derived from 5-lithio-2,3-dihydrofuran and anhydrous $CeCl_3$ to bicyclic enone **5** (92% ee by lipase hydrolysis of its chloroacetate precursor) affords **6** selectively. Anionic oxy-Cope rearrangement of **6** in refluxing THF induces [3,3] sigmatropy and subsequent enolate ion equilibration. This tandem sequence of reactions allows for an efficient pathway to (−)-**2**.

Ambergris is produced as a metabolite of the blue sperm whale (*Physeter macrocephalus* L.) and occurs as concretions in the gut.[1] During several years of aging, the original major constituent (+)-ambrein[2] undergoes light- and air-induced oxidation to give odoriferous degradation products that combine a most fragrant woody scent with unique fixative properties. Release of the ambergris fragrance is related principally to the presence of Ambrox (**1**). The growing demand for ambergris-type odorants, coupled with an almost complete worldwide ban on whaling, has stimulated an intense search for substitutes. Indeed, several syntheses of **1** have recently been reported.[3] In addition, Ohloff,[4] Näf,[5] and Winter[6] and their co-workers have undertaken a detailed examination of structure–activity relationships within these tricyclic labdane ethers and related molecules. Of the distinct odors of varying quality and strength uncovered to the present, (−)-9-epi-Ambrox (**2**) has been found to possess the strongest scent and lowest threshold concentration (0.15 ppb) of all. The ability of **1** and **2** to trigger a strong sensory response and achieve good receptor affinity has been attributed to the presence of three axial methyl groups (the so-called "triaxial rule"[1,4,7]).



1 **2** **3**

The only documented synthesis of **2** has been realized by chemical transformations of (+)-sclareolide (**3**), a labdane diterpene derivative in its own right.[4c] We wish to delineate here a very different approach to this class of compounds, and particularly (−)-**2**, that extends the remarkable utility of the anionic oxy-Cope rearrangement[8] in accessing polycyclic compounds.

In our approach the bicyclo[2.2.2]octenone **5**, holding functionality so positioned as to allow for the realization of high levels of π-facial selectivity during nucleophilic attack at its carbonyl group, was first elaborated (Scheme I). The known racemic alcohol **4**[9] was converted to its chloroacetate (96%) and subjected to hydrolysis with lipase P-30.[10] By carrying out the enzymatic reaction to 60% completion and saponifying the unreacted ester, we were able to obtain (−)-**4** of high optical purity (92% ee)[11] at an

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(11) 80 MHz ^1H NMR spectra were recorded on 20 mg samples of (+)-enriched alcohol in 1 mL of $CDCl_3$ at 25 °C to which 25 mol % $Eu(dcm)_3$ [McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038] had been added. The carbinol proton for the (+)- (δ 10.53; $\Delta\delta$ 6.65) and (−)-enantiomers (δ 9.90 ppm; $\Delta\delta$ 6.10) exhibited a sufficient "sense of nonequivalence" [Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150] such that integration of the signals allowed for % ee determination. By examining four samples of varying optical purity, it was possible to construct a plot of % ee vs $[\alpha]^{25}_D$ whose slope was 1.12 (r = 0.99). Later % ee determinations were made by extrapolation or interpretation.

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