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A Novel and Efficient Route to Chiral A-Ring Aromatic Trichothecanes—The First Enantiocontrolled Total Synthesis of (-)-Debromofiliformin and (-)-Filiformin

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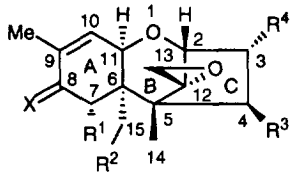
Abstract: The first examples of asymmetric dihydroxylation (AD) of the cyclopropylidene derivatives **12a~e** followed by enantiospecific 1,2-rearrangement of the resulted diols **13a~e** to give the optically active cyclobutanones **15a~d** and **11**, and also the first enantiocontrolled total synthesis of (-)-debromofiliformin (**7a**) and (-)-filiformin (**7b**) starting from **11** *via* the regiocontrolled cyclization of the phenolic allyl alcohol **25** to the A-ring aromatic trichothecane **26**, were reported.

Introduction

The trichothecanes are a group of structurally related sesquiterpenes isolated from various species of fungi.[1] The general structure **1** of this family that consists of the A/B/C ring system including an exo-epoxide, is depicted in Figure 1.

Figure 1

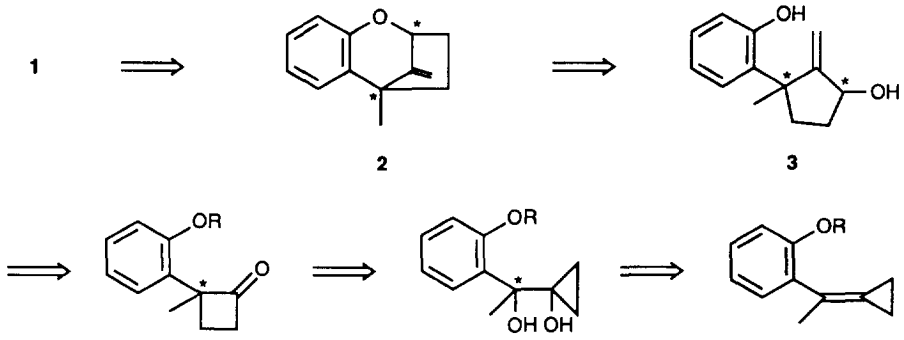


1a : X = H_2; R^1 = R^2 = R^3 = R^4 = H
1b : X = H_2; R^1 = R^2 = R^4 = H ; R^3 = OC(O)CH = CHMe
1c : X = H_2; R^1 = R^4 = H; R^2 = R^3 =OH
1d : X = H_2; R^1 = R^3 = H; R^2 = R^4 =OAc
1e : X = H_2; R^1 = H; R^2 = R^3 = OAc; R^4 =OH
1f : X = O; R^1 = R^2 = R^3 = R^4 =OH

The representatives of trichothecanes shown in Figure 1 mainly differ from the oxidation states of one of the bridgehead substituents (R^2) and of the substituents in A (X and/or R^1) and C (R^3 and/or R^4) rings ranging in complexity from scirpene (**1a**), trichothecin (**1b**), verrucarol (**1c**), calonectrin (**1d**), and anguidine (**1e**) to more heavily oxidized compounds such as nivalenol (**1f**). Members of this class exhibit significant biological activities such as antifungal, antibacterial, antiviral, and insecticidal properties[2] and also some of this family

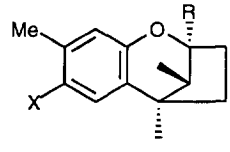
inhibit the growth of tumor cells.[3] Because of these biological activities and unique structural feature, a number of their synthesis have been published[4] so far including the total synthesis of **1c**,[5] **1d**,[6] and **1e**.[7] But, all of the syntheses afford the final product in low overall yield and cannot be regarded as generally applicable for the synthesis of a wide variety of compounds for thorough biological studies. These facts stimulated us to develop an enantioselective approach to this type of compounds which would be efficient and versatile. In our basic analysis for the synthesis of trichothecanes **1**, A-ring aromatic trichothecanes **2** emerged as the cornerstone, since the A-ring aromatic trichothecane analogue itself has been shown to possess significant *in vivo* antileukemic activity[8] and also could be transformed into **1** through the standard manipulation on the aromatic ring and olefin. We chose to develop the tricyclic structure by a cyclization of the phenolic allyl alcohol **3** which in turn could be prepared by ring expansion[9] of the cyclobutanone **4**. The chiral center of **4** could be introduced by enantiospecific 1,2-rearrangement of the chiral diol **5** which would be obtained by asymmetric dihydroxylation of the cyclopropylidene derivative **6** (Scheme 1).

Scheme 1



In this context, we set (-)-filiformin (**7b**)[10] and its debromo analogue **7a**[11] as initial target molecules which have been known to be marine sesquiterpenes together with **7c**~**7e**[12] having additional bromines on the bridgehead substituent (R) depicted in Figure 2.

Figure 2



7

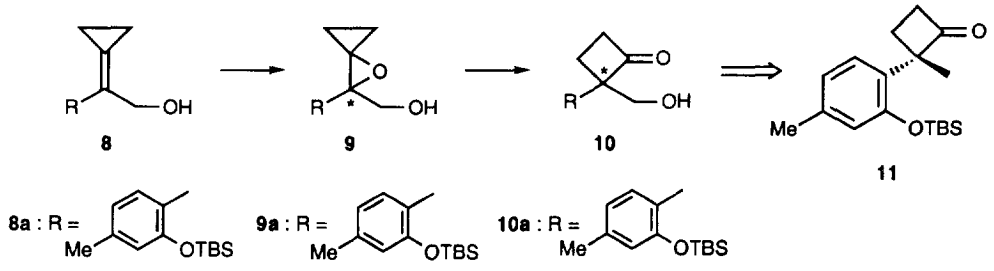
7a : X = H ; R = Me
7b : X = Br; R = Me
7c : X = H ; R = CH_2Br
7d : X = Br; R = CH_2Br
7e : X = H ; R = $CHBr_2$

Although this family of sesquiterpenes has opposite absolute configuration at C_2 and C_5 (trichothecane numbering) and additional one carbon at C_2 and lacks substituent at C_6 in comparing with trichothecanes, both of these families of sesquiterpenes have the same basic ring framework and could be classified as the same type of compound at least in the synthetic point of view (not in the sense of biogenesis). In contrast to great synthetic interest for trichothecanes described above, the few efforts have been made at the synthetic development of **7**.[13] We describe herein the first enantiocontrolled total synthesis of (-)-debromofiliformin (**7a**) and (-)-filiformin (**7b**) with full experimental details which consists of a novel synthesis of chiral cyclobutanones and a regiocontrolled cyclization of phenolic allyl alcohols.

Results and Discussion

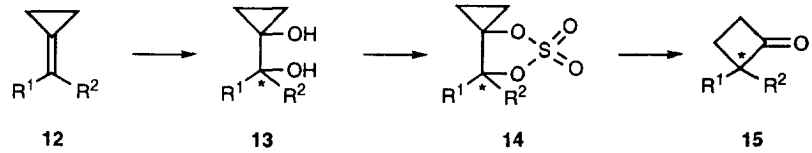
Synthesis of Chiral Cyclobutanones via Asymmetric Dihydroxylation of Cyclopropylidenes. Recently, we have introduced the chiral bicyclooxapentanes **9** as a new class of precursors of the optically active cyclobutanones **10** and demonstrated the synthetic usefulness of **10** for various types of biologically important compounds.[9,14] In these studies,[9] we have succeeded to prepare the chiral cyclobutanone **10a** starting from **8a** *via* **9a** in high enantiomeric excess. However, substrates used in these studies are limited only to the cyclopropylideneethanol **8** since the generation of **9** relies on Sharpless asymmetric epoxidation (Scheme 2).

Scheme 2



With respect to the scope of this new strategy, it would be very important to develop a new condition which is applicable to unfunctionalized olefins providing directly the cyclobutanones such as **11** to make this approach more effective. Thus, Sharpless asymmetric dihydroxylation (AD)[15] emerged as one of the most promising candidates, because the AD is now established as an effective method for the enantioselective oxidation of almost all classes of prochiral olefins except for our cyclopropylidene cases and the cyclic sulfates of the resulted diols are found to behave like epoxides.[16] So, the chiral diols **13** derived by the AD of the cyclopropylidene derivatives **12** might be rearranged in enantiospecific manner to the optically active cyclobutanones **15** *via* the cyclic sulfates **14** (Scheme 3).

Scheme 3



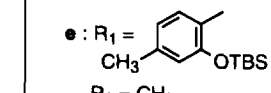
Here, we describe the first trial of the AD of cyclopropylidene derivatives and subsequent rearrangement to optically active cyclobutanones.

Thus, the AD reaction of the cyclopropylidene derivatives **12a~e**[17] was examined by following Sharpless procedure[15] using AD-mix-β and the resulted chiral diols **13** were then treated with thionyl chloride in the presence of triethylamine expecting to give the cyclic sulfites **18**.[20] However, it was found that the 1,2-rearrangement of the 1,2-diols **13** proceeded under these conditions possibly *via* the cyclic sulfites **18** as intermediates to furnish the cyclobutanones **15** directly[21] (Table 1).

Table 1

Asymmetric Dihydroxylation[a] and 1,2-Rearrangement[b]

12 $\xrightarrow{\text{AD mix-}\beta}$ **13** $\xrightarrow[Et_3N]{SOCl_2}$ **15**

entry	12	13 (%)[c]	15 and 11 [c]	
			yield (%) (from 13)	Opt. yield (% ee)[d]
1	**a** : $R_1 = CH_3(CH_2)_6$, $R_2 = H$	85	91	5 (R)
2	**b** : $R_1 = CH_3(CH_2)_7$, $R_2 = H$	78	100	3 (R)
3	**c** : $R_1 = Ph$, $R_2 = H$	67	94.3	29 (s)
4	**d** : $R_1 = Ph$, $R_2 = CH_3$	57	85	44 (S)
5	**e** : R_1 =  $R_2 = CH_3$	52	96 (11)	55 (S)

[a] The AD was run as described in ref. 15a with 0.1 - 1.0 mol% of OsO_4.

[b] 1,2-Rearrangement reaction was carried out at 0 °C for 12 h in CH_2Cl_2.

[c] All yields are isolated one.

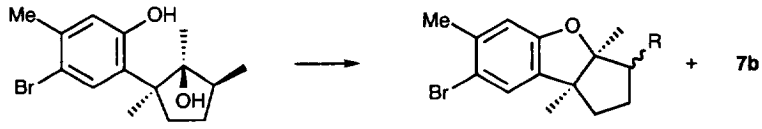
[d] All of the absolute configurations, except that of entry 5, where the direct comparison of rotation {$[\alpha]_D^{25}$ -40.2 ° ($CHCl_3$) for **11**} with that of an authentic sample[9] {$[\alpha]_D^{25}$ -105.0 ° ($CHCl_3$) was achieved, are tentatively assigned by using the mnemonic device described in ref. 15a. Enantiomeric excess was determined by ^1H NMR analysis of the MTPA esters derived from the corresponding cyclobutanols **21a~e**.[22]

From the results described in Table 1, it could be clear that the cyclopropylidene derivatives could be substrates for these enantioselective reactions (AD) as well and the disubstituted cyclopropylidene derivatives (entries 4,5) are much better substrates than the monosubstituted cyclopropylidene derivatives (entries 1~3). Of these disubstituted cyclopropylidene derivatives, **12e** having bulky substituent on aromatic ring, showed moderate enantioselectivity to give the optically active cyclobutanone **11** in high yield. Thus, we could disclose the first example of AD reaction of cyclopropylidene derivatives exemplifying a short synthesis of the chiral

cyclobutanone **11**, which is a key intermediate for the synthesis of (-)-debromofiliformin (**7a**) and (-)-filiformin (**7b**), although the enantioselectivity is not sufficiently high for practical use at the moment.

Total Synthesis of (-)-Debromofiliformin (7a) and (-)-Filiformin (7b). In the recent approach[13b] to (±)-filiformin (**7b**), the lack of regioselectivity for the cyclization of the phenolic alcohol **22** *via* carbocation intermediate has been encountered to give the mixture of aplysin (**23**), epi-aplysin (**24**), and **7b** (Scheme 4).

Scheme 4

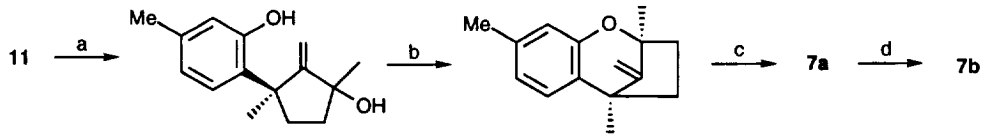


22

23 : R = —Me
24 : R = ····Me

So, we examined the regiocontrolled cyclization to build up this particular benzooxabicyclo[3.2.1]octane ring system. Thus, the optically active cyclobutanone **11**[23] was converted into the phenolic allyl alcohol **25** according to the previous procedure.[9] Then, **25** was treated with pyridinium *p*-toluenesulfonate (PPTs) in refluxing benzene for 3 h to give the benzooxabicyclo[3.2.1]octane **26** the only isolated compound in 95% yield which on hydrogenation in the presence of palladium carbon as a catalyst afforded (-)-debromofiliformin (**7a**) {$[\alpha]_D^{25}$ -11.6 ° ($CHCl_3$)} stereoselectively in 100% yield which was identical with the reported[11] spectroscopic data.[24] This stereochemical outcome could be due to the effective size of the π system making the aromatic region of **26** to be the more encumbered one.[13a] The *syn* relationship of the apical methyl group and the aromatic ring was evidenced at this stage by the high field signal (0.77 ppm) of this methyl group in the ^{1}H-nmr spectrum of **7a**. Finally, bromination of **7a** with bromine in the presence of sodium bicarbonate in $CHCl_3$ furnished (-)-filiformin (**7b**) {$[\alpha]_D^{20}$ -16.4 ° ($CHCl_3$), lit.,[10] $[\alpha]_D^{20}$ -20.0 ° ($CHCl_3$)} in 80% yield. The sample thus obtained was identical with the authentic compound[10] in its ^{1}H-nmr (300 MHz, $CDCl_3$) spectral comparison. Thus, we could develop a novel method for the synthesis of chiral cylcobutanones and a facile construction of benzooxabicyclo[3.2.1]octane system leading to the first enantiocontrolled total synthesis of (-)-debromofiliformin (**7a**) and (-)-filiformin (**7b**) (Scheme 5).

Scheme 5



25 **26**

Reagents and conditions: a ref.9 ; b PPTs, benzene, reflux 3 h; c H_2, 10% Pd-C, AcOEt, room temp., 5 h; d Br_2, $NaHCO_3$, $CHCl_3$, room temp.

Experimental Section

General: All reactions were carried out under a positive atmosphere of dry N_2 unless indicated otherwise. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone, and DMSO, DMF, CH_2Cl_2, and Et_3N were distilled from CaH_2 and kept over 4 Å molecular sieves. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Silica gel column chromatography was carried out with Wako gel C-200, while Merck Kieselgel 60 Art. 9385 was used for flash chromatography.

Methyl 2-*t*-butyldimethylsiloxy-4-methylphenyl ketone (16e). To a stirred solution of the phenol **17** (4 g, 26.6 mmol), imidazole (8.15 g, 106.4 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) in DMF (40 mL) was added TBSCl (12.04 g, 79.08 mmol) at 0 °C, and stirring was continued for 10 h at the same temperature. The reaction mixture was treated with 10% HCl solution and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (9 : 1 v/v) as eluant to give the silyl ether **16e** (13.8 g, 100%) as a colorless oil: IR (neat) 1670 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.26 (6H, s), 0.99 (9H, s), 2.30 (3H, s), 2.60 (3H, s), 6.72 (1H, d, J = 9 Hz), 7.20 (1H, s), 7.52 (1H, d, J = 9 Hz); MS *m/z* 207 (M^+ -57); HRMS calcd for $C_{11}H_{15}O_2Si$ 207.0841 (M^+ -57), found 207.0814.

General Procedure for the Preparation of Cyclopropylidene Derivatives. Preparation of 1-(2-*t*-Butyldimethylsiloxy-4-methylphenyl)-1-cyclopropylideneethane (12e). To a stirred suspension of NaH (666 mg, of 60% oil suspension, 16.6 mmol) in THF (20 mL) was added cyclopropyltriphenylphosphonium bromide (6.4 g, 16.6 mmol) at room temperature. After the mixture had been stirred for 10 h at 62 °C, a solution of the ketone **16e** (2 g, 7.6 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (4.85 mL, 15.1 mmol) in THF (10 mL) was added in 30 min, and stirring was continued for 2 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (49 : 1 v/v) as eluant to give the cyclopropylidene derivative **12e** (884.3 mg, 40.1%) as a colorless oil: IR (neat) 1600 (C=C) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.91 (9H, s), 0.80 - 1.11 (4H, m), 2.15 (3H, s), 2.30 (3H, s), 6.63 (1H, d, J = 9 Hz), 6.82 (1H, s) 7.05 (1H, d, J = 7 Hz); MS m/z 231 (M^+ -57). Anal. Calcd for $C_{17}H_{28}OSi$: C, 74.94; H, 9.78. Found: C, 74.93; H, 9.85.

Cyclopropylideneoctane (12a): yield 88%; colorless oil; IR (neat) 1605 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.6 Hz), 0.97 - 1.05 (4H, m), 1.20 - 1.50 (10H, m), 2.12 - 2.22 (2H, m), 5.71 - 5.80 (1H, m); MS m/z 152 (M^+); HRMS Calcd for $C_{11}H_{20}$ 152.1565, found 152.1541.

Cyclopropylidenenonane (12b): yield 89%; colorless oil; IR (neat) 1605 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.6 Hz), 0.93 - 1.08 (4H, m), 1.20 - 1.49 (12H, m), 2.10 - 2.21 (2H, m), 5.70 - 5.81 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.94, 2.25, 14.2, 22.9, 29.5, 32.1, 118.6, 120.8; MS *m/z* 166 (M^+); HRMS calcd for $C_{12}H_{22}$ 166.1730 (M^+), found 166.1720.

1-Cyclopropylidene-1-phenylethane (12d): yield 73%; colorless oil: This was used directly for the next reaction without further characterization because of instability.

General Procedure for Asymmetric Dihydroxylation of Cyclopropylidene Derivatives. Preparation of (S)-1-(2-*t*-Butyldimethylsiloxy-4-methylphenyl)-1-(1-hydroxycyclopropyl)-ethanol (13e). To a stirred solution of AD-mix-β (2.42 g) and methanesulfonamide (660 mg, 6.92 mmol) in *t*-butyl alcohol (8.7 mL) and water (8.7 mL) was added the cyclopropylidene derivatives **12e** (500 mg, 1.73 mmol) at 0 °C and stirring was continued for 1 week at the same temperature. The reaction mixture was treated with sodium sulfite (2.6 g), stirred for 1 h at room temperature and extracted with CH_2Cl_2. The combined extracts were washed with 2N NaOH and saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (41 : 9 v/v) as eluant to give the diol **13e** (292.3 mg, 52.4%) as a colorless oil: $[\alpha]_D^{25}$ +12.40 ° (c 0.51, $CHCl_3$); IR (neat) 3420 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (6H, s), 0.52 - 0.97 (4H, m), 1.05 (9H, s), 1.59 (3H, s), 2.28 (3H, s), 2.99 (1H, s), 5.80 (1H, s), 6.63 (1H, d, *J* = 2.0 Hz), 6.75 (1H, dd, *J* = 2.0 and 7.5 Hz), 7.25 (1H, d, *J* = 7.5 Hz); MS *m/z* 304 (M^+ -18); HRMS calcd for $C_{18}H_{28}O_2Si$ 304.1858 (M^+ -18), found 304.1818.

(S)-(+)-1-(1-Hydroxycyclopropyl)octanol (13a): yield 85%; colorless plates, mp 84.2 - 84.3 °C (Et_2O-hexane); $[\alpha]_D^{19}$ +15.6 ° (c 0.90, $CHCl_3$); IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.51 - 0.62 (2H, m), 0.75 - 0.93 (5H, m), 1.23 - 1.55 (10H, m), 1.55 - 1.70 (2H, m), 1.74 (1H, d, *J* = 4.5 Hz), 2.35 (1H, s), 3.10 - 3.18 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 12.6, 14.2, 22.7, 26.2, 29.4, 29.8, 31.9, 33.3, 58.3, 77.3; MS m/z 186 (M^+); HRMS calcd for $C_{11}H_{22}O_2$ 186.1619 (M^+), found 186.1649.

(S)-(+)-1-(1-Hydroxycyclopropyl)nonanol (13b): yield 78%; colorless plates, mp 78.0 - 78.1 °C (Et_2O-hexane); $[\alpha]_D^{22}$ +14.89 ° (c 0.79, $CHCl_3$); IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.51 - 0.62 (2H, m), 0.74 - 0.93 (5H, m), 1.21 - 1.53 (12H, m), 1.55 - 1.70 (3H, m), 2.32 (1H, br s), 3.12 - 3.18 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 12.5, 13.9, 22.6, 26.1, 29.3, 29.7, 29.9, 31.8, 33.1, 58.0, 77.2; MS *m/z* 200 (M^+); HRMS calcd for $C_{12}H_{24}O_2$ 200.1775 (M^+), found 200.1787.

(S)-(+)-1-(1-Hydroxycyclopropyl)benzyl alcohol (13c): yield 67%; colorless needles, mp 69 - 70 °C (Et_2O-hexane): $[\alpha]_D^{19}$ +1.80 ° (c 1.39, $CHCl_3$); IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.65 - 0.95 (4H, m), 2.24 (1H, s), 2.34 (1H, d, *J* = 4.4 Hz), 4.49 (1H, d, *J* = 4.4 Hz) 7.30 - 7.49 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 12.2, 59.3, 78.1, 126.7, 127.9, 128.4, 140.8; MS *m/z* 164 (M^+); HRMS calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0836.

(S)-(+)-1-(1-Hydroxycylopropyl)-1-phenylethanol (13d): yield 57%: colorless oil; $[\alpha]_D^{25}$ +3.92 ° (c 0.46, $CHCl_3$); IR (neat) 3430 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 - 0.76 (2H, m), 0.77 - 0.93 (5H, m), 2.31 (1H, br s), 2.65 (1H, br s), 7.23 - 7.38 (3H, m), 7.52 - 7.59 (2H, m); MS m/z 160 (M^+ -18); HRMS calcd for $C_{11}H_{14}O_2$ 160.0888, found 160.0897.

General Procedure for 1,2-Rearrangement of 1,2-Diols. Preparation of (S)-(-)-2-(2-*t*-Butyldimethylsiloxy-4-methylphenyl)-2-methylcyclobutanone (11). To a stirred solution of the diol

13e (15 mg, 0.047 mmol) and triethylamine (Et_3N) (0.016 mL, 0.11 mmol) in CH_2Cl_2 (0.3 mL) was added a solution of $SOCl_2$ (0.004 mL, 0.061 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C and stirring was continued for 5 min at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (9 : 1 v/v) as eluant to give the cyclobutanone **11** (13.7 mg, 96%) as a colorless oil $[\alpha]_D^{25}$ -40.2 ° (c 1.15, $CHCl_3$); IR (neat) 1775 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.31, 0.34 (6H, each s), 1.03 (9H, s), 1.52 (3H, s), 1.97 - 2.62 (2H, m), 2.27 (3H, s), 2.97 - 3.17 (2H, m), 6.66 (1H, d, *J* = 1.5 Hz), 6.68 (1H, dd, *J* = 1.5 and 8.1 Hz), 7.25 (1H, d, *J* = 8.1 Hz); MS *m/z* 304 (M^+); HRMS calcd for $C_{18}H_{28}O_2Si$ 304.1857, found 304.1853.

(R)-(-)-2-Heptylcyclobutanone (15a): yield 84%; colorless oil; $[\alpha]_D^{26}$ -7.97 ° (c 0.30, $CHCl_3$); IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.12 - 1.82 (13H, m) 2.08 - 2.29 (1H, m), 2.80 - 3.11 (2H, m), 3.19 - 3.35 (1H, m); MS *m/z* 168 (M^+); HRMS calcd for $C_{11}H_{20}O$ 168.1514 (M^+), found 168.1541.

(R)-(-)-2-Octylcyclobutanone (15b): yield 100%; colorless oil; $[\alpha]_D^{23}$ -8.71 ° (c 0.94, $CHCl_3$); IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.18 - 1.55 (13H, m), 1.55 - 1.75 (2H, m), 2.10 - 2.24 (1H, m), 2.84 - 3.08 (2H, m), 3.20 - 3.35 (1H, m); MS *m/z* 182 (M^+); HRMS calcd for $C_{12}H_{22}O$ 182.1669 (M^+), found 182.1676.

(S)-(-)-2-Phenylcyclobutanone (15c): yield 81%; colorless oil; $[\alpha]_D^{23}$ +74.95 ° (c 0.66, $CHCl_3$); IR (neat) 1785 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 - 2.31 (1H, m), 2.46 - 2.62 (1H, m), 2.96 - 3.11 (1H, m), 3.15 - 3.30 (1H, m), 4.48 - 4.60 (1H, m), 7.20 - 7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 44.9, 64.6, 127.0, 128.6, 136.5, 207.7; MS *m/z* 146 (M^+); HRMS calcd for $C_{10}H_{10}O$ 146.0732 (M^+), found 146.0713.

(S)-(-)-2-Methyl-2-phenylcyclobutanone (15d): yield 85%; colorless oil; $[\alpha]_D^{27}$ -24.37 ° (c 0.75, $CHCl_3$); IR (neat) 1775 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (3H, s), 2.09 - 2.22 (1H, m), 2.46 - 2.59 (1H, m), 2.97 - 3.24 (2H, m), 7.19 - 7.38 (5H, m); MS *m/z* 160 (M^+); HRMS calcd for $C_{11}H_{12}O$ 160.0887 (M^+), 160.0909.

General Procedure for Reduction of Cyclobutanones. Reduction of 15a. To a stirred solution of the cyclobutanone **15a** (30.8 mg, 0.183 mmol) in CH_2Cl_2 (1 mL) and MeOH (0.5 mL) was added $NaBH_4$ (20.2 mg, 0.534 mmol) at 0 °C and stirring was continued for 10 min at the same temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (41 : 1 v/v) as eluant to give the alcohol **20a** (7.1 mg, 23%) and then **21a** (21.2 mg, 68%) as colorless oils.

(1R,2R)-(-)-2-Heptylcyclobutanol (20a): $[\alpha]_D^{29}$ -8.39 ° (c 0.77, $CHCl_3$); IR (neat) 3400 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.30 - 1.78 (15H, m), 1.85 - 1.99 (1H, m), 2.21 - 2.32 (1H, m), 2.32 - 2.43 (1H, m), 4.28 - 4.42 (1H, m); MS *m/z* 170 (M^+); HRMS calcd for $C_{11}H_{22}O$ 170.1669, found 170.1693.

(1S,2R)-(-)-2-Heptylcyclobutanol (21a): $[\alpha]_D^{30}$ -8.09 ° (c 0.865, $CHCl_3$); IR (neat) 3380 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.3 Hz), 0.91 - 1.10 (1H, m), 1.18 - 1.40 (11H, m), 1.40 - 1.57 (1H, m), 1.57 - 1.75 (2H, m), 1.73 - 1.85 (1H, m), 1.97 - 2.20 (1H, m), 2.13 - 2.24 (1H, m), 3.71 - 3.82 (1H, m); MS *m/z* 170 (M^+); HRMS calcd for $C_{11}H_{22}O$ 170.1669, found 170.1565.

Reduction of 15b

(1R,2R)-(-)-2-Octylcyclobutanol (20b): yield 28%; colorless oil; $[\alpha]_D^{27}$ -5.66 ° (c 1.59, $CHCl_3$); IR (neat) 3390 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 1.15 - 1.53 (15H, m), 1.53 - 1.78 (2H, m), 1.85 - 1.98 (1H, m), 2.20 - 2.33 (1H, m), 2.33 - 2.44 (1H, m), 4.28 - 4.39 (1H, m); MS *m/z* 184 (M^+); HRMS calcd for $C_{12}H_{24}O$ 184.1826 (M^+), found 184.1833.

(1S,2R)-(-)-2-Octylcyclobutanol (21b): yield 72%; colorless oil; $[\alpha]_D^{29}$ -7.28 ° (c 1.02, $CHCl_3$); IR (neat) 3320 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.6 Hz), 0.96 - 1.09 (1H, m), 1.20 - 1.40 (13H, m), 1.40 - 1.57 (1H, m), 1.57 - 1.86 (3H, m), 1.96 - 2.12 (1H, m), 2.12 - 2.24 (1H, m), 3.72 - 3.83 (1H, m); MS *m/z* 184 (M^+); HRMS calcd for $C_{12}H_{24}O$ 184.1826, found 184.1850.

Reduction of 15c

(1R,2S)-(+)-2-Phenylcyclobutanol (20c): yield 20%; colorless oil; $[\alpha]_D^{31}$ +25.78 ° (c 1.85, $CHCl_3$); IR (neat) 3410 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 - 1.40 (1H, m), 1.91 - 2.05 (1H, m), 2.05 - 2.19 (1H, m), 2.23 - 2.35 (1H, m), 2.35 - 2.49 (1H, m), 3.65 - 3.81 (1H, m), 4.46 - 4.58 (1H, m), 7.20 - 7.52 (5H, m); MS *m/z* 148 (M^+); HRMS calcd for $C_{10}H_{12}O$ 148.0888, found 148.0879.

(1S,2S)-(-)-2-Phenylcyclobutanol (21c): yield 65%; colorless oil: $[\alpha]_D^{27}$ -41.68 ° (c 0.82, $CHCl_3$); IR (neat) 3325 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 - 1.69 (1H, m), 1.78 - 1.96 (1H, m), 1.96 - 2.17 (2H, m), 2.22 - 2.35 (1H, m), 3.20 - 3.32 (1H, m), 4.17 (1H, m), 7.18 - 7.40 (5H, m); MS *m/z* 148 (M^+); HRMS calcd for $C_{10}H_{12}O$ 148.0888, found 148.0897.

Reduction of 15d

(1R,2S)-(+)-2-Methyl-2-phenylcyclobutanol (20d): yield 9%; colorless oil; $[\alpha]_D^{30}$ +78.18 ° (c 0.10, $CHCl_3$); IR (neat) 3350 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (3H, s), 1.55 (1H, br s), 1.59 - 1.76 (2H, m), 2.30 - 2.44 (1H, m), 2.48 - 2.62 (1H, m), 4.07 - 4.15 (1H, m), 7.22 - 7.44 (5H, m); MS *m/z* 162 (M^+); HRMS calcd for $C_{11}H_{14}O$ 162.1045, found 162.1069.

(1S,2S)-(-)-2-Methyl-2-phenylcyclobutanol (21d): yield 85%; colorless oil; $[\alpha]_D^{27}$ -15.41 ° (c 0.36, $CHCl_3$); IR (neat) 3352 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.80 - 1.89 (2H, m), 1.89 - 2.07 (2H, m), 2.25 - 2.37 (1H, m), 4.36 (1H, t, *J* = 7.8 Hz), 7.13 - 7.37 (5H, m); MS *m/z* 162 (M^+); HRMS calcd for $C_{11}H_{14}O$ 162.1045 (M^+), found 162.1020.

Reduction of 11

(1S,2S)-(-)-2-(2-*t*-Butyldimethylsiloxy-4-methylphenyl)-2-methylcyclobutanol (21e): yield 98%; colorless oil; $[\alpha]_D^{27}$ -30.5 ° (c 1.3, $CHCl_3$); IR (neat) 3355 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.23 and 0.24 (6H, each s), 0.93 (9H, s), 1.26 (3H, s), 1.67 - 1.97 (4H, m), 2.17 (3H, s), 4.27 (1H, t, *J* =7.5 Hz), 6.53 (1H, br s), 6.62 (1H, br d, *J* = 7.0 Hz), 6.90 (1H, d, *J* = 7.0 Hz); MS *m/z* 306 (M^+); HRMS calcd for $C_{18}H_{30}O_2Si$ 306.2015 (M^+), found 306.2023.

(2S,5S)-(-)-2-Methyl-15-nor-6,8,10,12-trichothecatetraene (26). A solution of the phenolic allyl alcohol **25** (14.1 mg, 0.06 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTs) in benzene (3 mL) was refluxed for 3 h under stirring with Dean-Stark apparatus. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane-Et_2O (9 : 1 v/v) as eluant to give the trichothecatetraene **26** (12.4 mg, 95%) as a colorless oil: $[\alpha]_D^{25}$ -13.0 ° (c 0.90, $CHCl_3$); IR (neat) 1602 (C=C) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.51 (3H, s), 1.57 (3H, s), 1.12 - 2.35 (4H, m), 2.23 (3H, s), 4.92 and 5.04 (2H, each s), 6.54 (1H, br s), 6.62 (1H, br d, *J* = 7.6 Hz), 6.98 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 21.0, 21.1, 37.4, 41.7, 45.3, 82.9, 100.7, 116.2, 120.7, 123.0, 130.8, 137.7, 153.1, 155.8; MS *m/z* 214 (M^+). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07, H, 8.47. Found: C, 83.92; H, 8.57.

(-)-Debromofiliformin (7a). The mixture of the trichothecatetraene **26** (20.4 mg, 0.15 mmol), a catalytic amount of 10% Pd-C, and AcOEt (4.5 mL) was stirred for 5 h at room temperature under the atmosphere of H_2. The reaction mixture was evaporated to leave the residue which was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) as eluant to give the trichothecatriene (debromofiliformin) **7a** (20.5 mg, 100%) as a colorless oil: $[\alpha]_D^{25}$ -11.6 ° (c 0.32, $CHCl_3$); IR (neat) 1602 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, d, *J* = 6.9 Hz), 1.34 (3H, s), 1.40 (3H, s), 1.24 - 2.14 (5H, m), 2.25 (3H, s), 6.53 (1H, br s), 6.64 (1H, br d, *J* = 7.5 Hz), 6.98 (1H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.6, 20.7, 21.1, 23.2, 37.4, 42.4, 44.8, 46.7, 85.2, 115.8, 120.7, 124.9, 127.5, 137.2, 153.1; MS *m/z* 216 (M^+); HRMS calcd for $C_{15}H_{20}O$ 216.1514 (M^+), found 216.1523.

(-)-Filiformin (7b). To a stirred mixture of debromofiliformin (**7a**) (5.0 mg, 0.023 mmol), $NaHCO_3$ (5.0 mg, 0.06 mmol) and $CHCl_3$ (1.5 mL) was added bromine (0.0014 mL, 0.028 mmol) at room temperature. The residue upon evaporation of the solvent was chromatographed on silica gel with hexane-Et_2O (41 : 1 v/v) as eluant to give (-)-filiformin (**7b**) (5.4 mg, 80%) as a colorless oil: $[\alpha]_D^{25}$ -16.4 ° (c 0.18, $CHCl_3$); IR (neat) 1600 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 6.9 Hz), 1.33 (3H, s), 1.39 (3H, s), 1.22 - 2.12 (5H, m), 2.28 (3H, s), 6.59 (1H, s), 7.19 (1H, s); MS *m/z* 296 (M^+ +2) and 294 (M^+); HRMS calcd for $C_{15}H_{19}OBr$ 296.0599 (M^+ +2) and 294.0620 (M^+), found 296.0608 and 294.0620.

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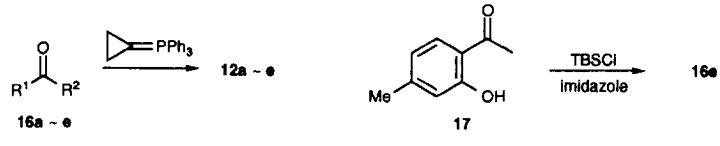
17. These cyclopropylidene derivatives **12a~e** were prepared in moderate to high yield by Wittig reaction of the corresponding aldehydes or ketones **16a~e** with cyclopropylidenetriphenylphosphorane under McMurry's conditions[18] (**12c** was already prepared[18] in this way). The substrate for **12e**, methyl 2-*t*-butyldimethylsiloxy-4-methylphenyl ketone (**16e**), was prepared by silylation of methyl 2-hydroxy-4-methylphenyl ketone (**17**)[19] with *t*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole.



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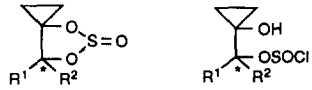
20. Although the monochlorosulfinates **19** could not be ruled out as the intermediates, it has been reported[16] that the cyclic sulfites like **18** were formed under these conditions.



18 **19**

21. The optical purity of the chiral diols **13** could not be determined because of these instabilities toward the derivatization (MTPA ester etc.) and chiral shift reagent [Eu(fod)$_3$ etc.] and because the conditions for resolving the enantiomers of **13** on the chiral HPLC could not be found. So, it is not clear whether the optical purity of **15** reflects the steps **12**→**13** or **13**→**15**.
22. These alcohols **21a~e** and its diastereomers **20a~e** were prepared by reduction ($NaBH_4$) of **15a~e**, respectively. The stereochemistries of these isomers were asssigned by the observation of the lower field signals attributable to R_2 of trans isomers **20** (2.32 - 2.43, 2.33 - 2.44, 3.65 - 3.81 and 1.49 ppm for **20a~d**, respectively) than the signals attributable to R_2 of cis isomers **21** (2.13 - 2.24, 2.12 - 2.24, 3.20 - 3.32 and 1.41 ppm for **21a~d**, respectively) due to the deshielding effect of neighboring hydroxy groups. The reduction of **11** afforded the only one isomer (deduced to be **21e** from the results of stereoselectivity in the reduction of **15a~d**) the stereochemistry of which could not be determined unambigously.

15a ~ e **20a ~ e** **21a ~ e**

23. The optically high grade of **11** (95% ee) was prepared by following the procedure described in ref. 9 and used in this study.
24. No optical data were described in ref. 11.

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