Pergamon

Tetrahedron, Vol. 52, No. 31, pp. 10363-10374, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00549-2

A Novel and General Route to Diverse A-Ring Aromatic Trichothecanes *via* Cyclobutanes

Hideo Nemoto, Junji Miyata, and Keiichiro Fukumoto*

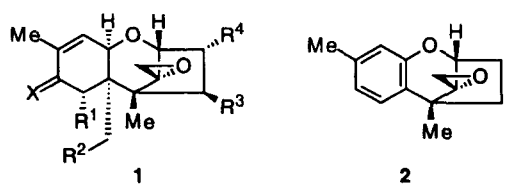
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract: A novel and generally applicable approach to A-ring aromatic trichothecane **2** was achieved by the regiocontrolled cyclization of **25**, **26**, **29**, and **30** as a key step, followed by stereoselective construction of the epoxide ring. This manuscript also described the regiocontrolled ring expansion of the olefinic cyclobutanols **19–22** to give the enones **23** and **24** which were the important intermediates in this approach. Copyright © 1996 Elsevier Science Ltd

Introduction

The trichothecane type of sesquiterpenes have been isolated from various species of fungi[1] and attracted much attention because of its significant biological activities such as antifungal, antibacterial, antiviral, insecticidal properties,[2] and inhibition of the growth of tumor cells.[3] These biological activities and unique structural feature have stimulated many organic chemists to make great deal of contributions for the synthesis of this class of compounds.[4] During our studies[5] directed toward the enantioselective construction of cyclobutanones and application to the synthesis of biologically desirable compounds, our recent interests have been focused on the development of the efficient synthesis of A-ring aromatic trichothecanes,[6] since such compounds have been shown to possess significant *in vivo* antileukemic activity[7] and also could be a potential intermediate for the synthesis of trichothecanes **1** (general structure of trichothecanes). Here we wish to report a novel route to A-ring aromatic trichothecane **2**, the methodology of which could be applied to the synthesis of diverse such compounds (Chart 1).

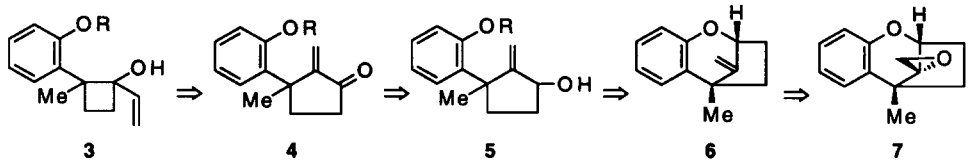
Chart 1



1 **2**

This synthesis involves the regiocontrolled ring expansion followed by the reduction of the cyclobutane **3** to the allyl alcohol **5** *via* the enone **4**, the regiocontrolled cyclization of **5** to **6** having the basic carbon framework of trichothecanes, and the stereoselective construction of the epoxide **7** (Scheme 1).

Scheme 1

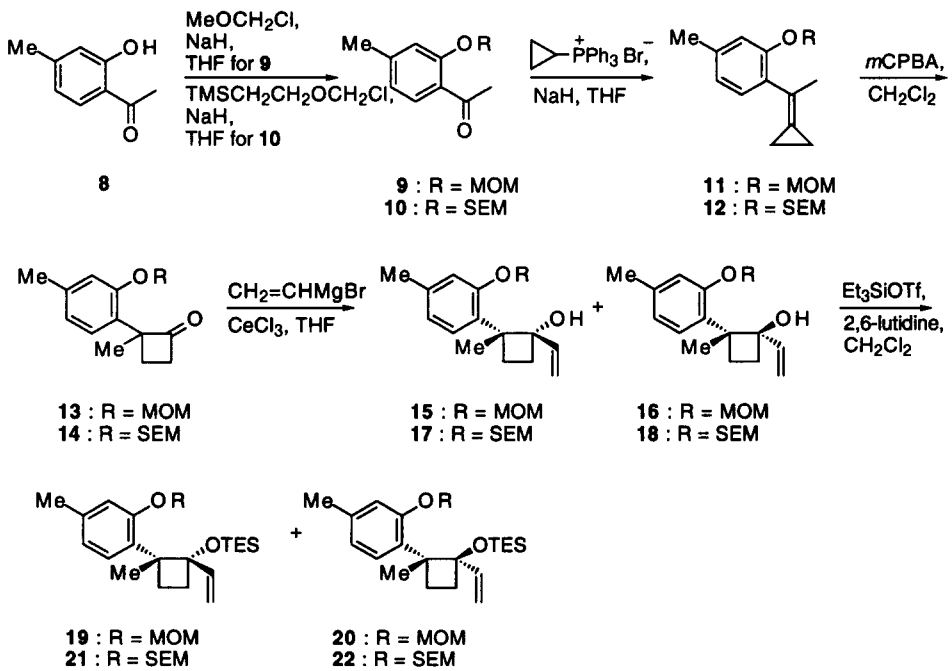


3 **4** **5** **6** **7**

Results and Discussion

As the preliminary studies, the cyclization of the type of the compound **5** (R=MOM in Scheme 1) at single stroke was examined under the deprotective conditions of R. The syntheses of 2,2-disubstituted cyclobutanone **13** and the substrates **19** and **20** for the regioselective ring expansion were straightforward and as follows (Scheme 2).

Scheme 2



8

9 : R = MOM
10 : R = SEM

11 : R = MOM
12 : R = SEM

13 : R = MOM
14 : R = SEM

15 : R = MOM
17 : R = SEM

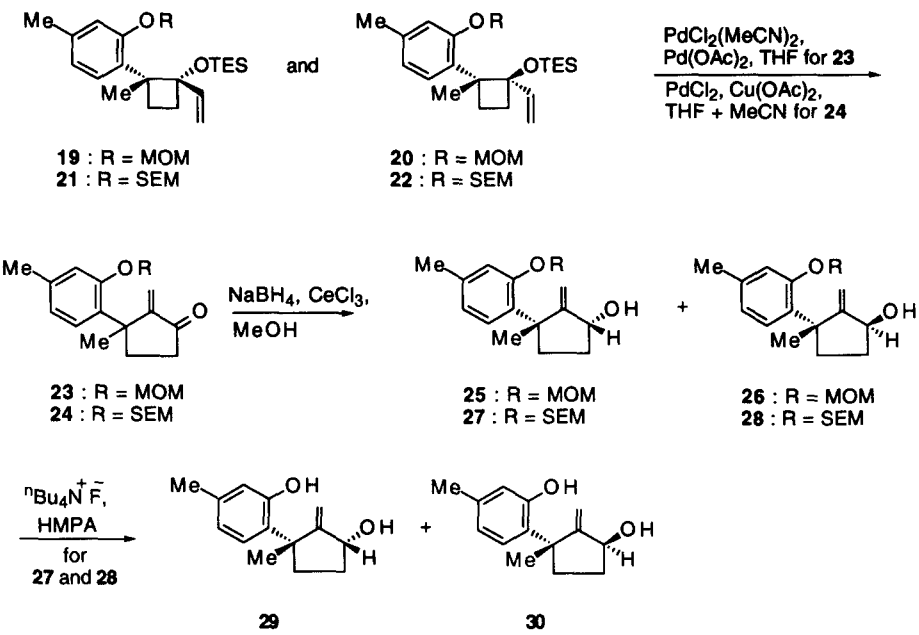
16 : R = MOM
18 : R = SEM

19 : R = MOM
21 : R = SEM

20 : R = MOM
22 : R = SEM

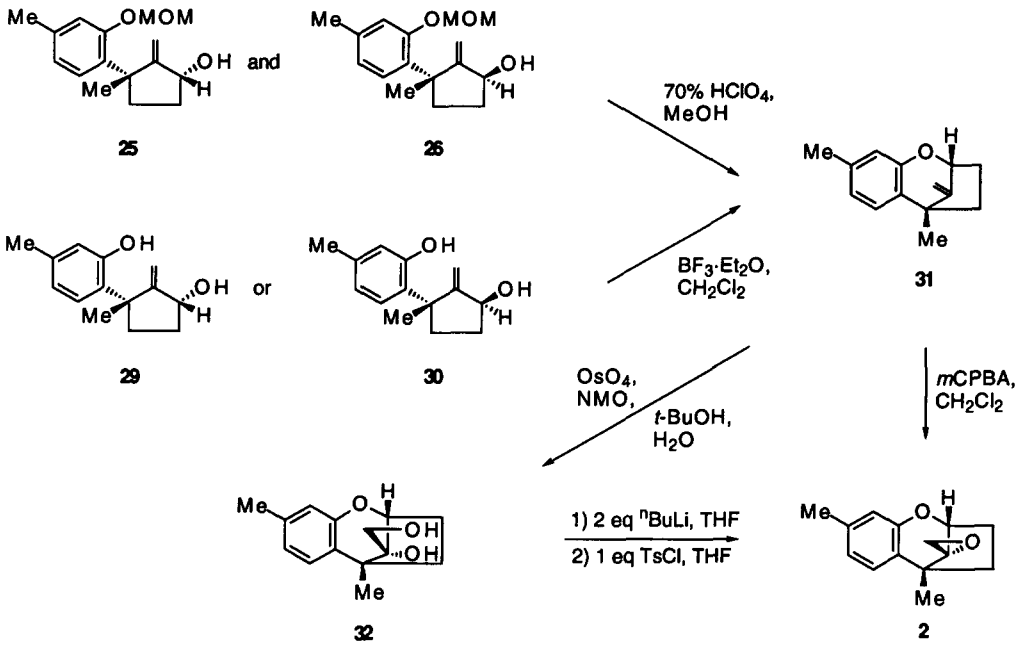
The ketone **9** prepared (76%) by methoxymethylation of **8**[8] was converted into the cyclopropylidene ether **11** (96%) by Wittig reaction with cyclopropylidenetriphenylphosphorane under the modified McMurry's conditions[9] and then into the cyclobutanone **13** (98%) by the tandem epoxidation and 1,2-rearrangement of **11**. The Grignard reaction of **13** afforded stereoselectively the allyl alcohols (93%, **15** : **16**/1 : 5.2)[10] which on silylation gave the triethylsilyl ethers **19** and **20** (99%). Next, the regiocontrolled ring expansion of **19** and **20** was examined (Scheme 3).

Scheme 3



Thus, the mixture of the silyl ethers **19** and **20** was subjected to the palladium mediated ring expansion[11] and it was found that the reaction proceeded regioselectively to give the ketone **23** (63%) as a sole product. The reduction of **23** with $NaBH_4$ in the presence of $CeCl_3$ afforded the allyl alcohols (88%, **25** : **26**/2 : 2.1).[12] Finally, the regiocontrolled cyclization of the mixture of **25** and **26** was examined resulting in the formation (29%) of the basic carbon framework **31** of trichothecanes. The direct introduction of epoxide ring into **31** was achieved by the oxidation (46%) of **31** with *m*-chloroperbenzoic acid to give the epoxide **2**[13] (Scheme 4). Thus, we could develop a novel route to A-ring aromatic trichothecanes. However, the last two steps including one (**26**→**31**) of the key steps in this approach did not proceed in satisfactory yields (13.4%). So, another efficient route to **2** was explored by using trimethylsilylethoxymethyl (SEM) group instead of methoxymethyl (MOM) group as the protecting group of phenol. The synthesis of the allyl alcohols **27** and **28** was achieved by following the almost same procedures described for **25** and **26** (see Schemes 2 and 3). The ketone **10**, prepared (100%) by silylethoxymethylation of **8**, was converted into the substrates (88% overall yield from **10**, **21** : **22**/1 : 6.2) for the ring expansion *via* the cyclopropylidene ether **12**, the cyclobutanone **14**, and the allyl alcohols **17** and **18**.[15] The regiocontrolled ring expansion of the mixture of **21** and **22** proceeded in 78% yield which was better than that of **19** and **20**. The allyl alcohols[16] {**27** (52%), **28** (47%)}, prepared by the reduction of the ketone **24**, were deprotected to give the phenols **29** (81%) and **30** (92%) respectively. The regiocontrolled cyclization of the both isomers **29** and **30** was effected by using BF_3·Et_2O as acid to give the compound **31** in 62 and 81% yields, respectively. Finally, the compound **31** was oxidized to the diol **32**[17] (93%) which was converted into the epoxide **2** (82%) in one pot operation (see Scheme 4).

Scheme 4



Thus, we could disclose a novel and generally applicable methodology for the synthesis of A-ring aromatic trichothecanes.

Experimental Section[18]

General Procedure: All reactions were carried out under 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, HMPA, CH_2Cl_2 and Et_3N were distilled from sodium hydride 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 Merck Kieselgel 60 Art. 7734, while Merck Kieselgel 60 Art. 9385 was used for flash chromatography.

[2-(Methoxymethyl)oxy-4-methyl]phenyl methyl ketone (9). To a stirred suspension of NaH (6.45 g, 60% oil suspension, 0.161 mol) in THF (120 mL) was added a solution of the ketone **8** (2.61 g, 0.134 mol) in THF (30 mL) at 0 °C and stirring was continued for 15 min at the same temperature. Chloromethyl methyl ether (MOMCl) (13.3 mL, 0.175 mol) was added dropwise and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (95 : 5 v/v) to give the ketone **9** (19.9 g, 76%) as a yellow oil: IR (neat) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 2.62 (3H, s), 3.52 (3H, s), 5.23 (2H, s), 6.83–6.89 (1H, m), 6.99(1H, br s), 7.66

(1H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz,$CDCl_3$) δ 21.72, 31.72, 56.41, 94.39, 115.40, 122.69, 126.31, 130.48, 144.89, 156.79, 199.45; MS *m/z* 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C,67.79; H, 7.05.

{2-[(2-Trimethylsilyl)ethoxymethyl]oxy-4-methyl}phenyl methyl ketone (10). By following the same procedure described for **9**, the ketone **10** was prepared from **8** and (2-trimethylsilyl)ethoxymethyl chloride: yield 100%; a yellow oil; IR (neat) 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (9H, s), 0.98 (2H, t, J = 8.3 Hz), 2.36 (3H, s), 2.61 (3H, s), 3.79 (2H, t, J = 8.3 Hz), 5.31 (2H, s), 6.84 (1H, br d, J = 7.5 Hz), 7.01 (1H, br s), 7.65 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.51, 17.88, 21.60, 31.60, 66.56, 92.63, 115.30, 122.18, 126.04, 130.14, 144.31, 156.70, 198.57; MS *m/z* 207 (M^+ –73). Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.32; H, 8.65.

1-Cyclopropylidene-1-[2-(methoxymethyl)oxy-4-methyl]phenylethane (11). To a stirred suspension of NaH (8.44 g, 60% oil suspension, 0.221 mol) in THF (100 mL) was added cyclopropyltriphenylphosphonium bromide (8.09 g, 0.211 mol) at rt. After the mixture was stirred for 12 h at 62 °C, a solution of the ketone **9** (24.1 g, 0.124 mol) in THF (20 mL) was added dropwise and stirring was continued for 2 h under reflux. The reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the cyclopropylidene ether **11** (25.9 g, 96%) as a colorless oil: IR (neat) 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.18 (2H, m), 2.19–2.23 (3H, m), 2.33 (3H, s), 3.47 (3H, s),5.16 (2H, s), 6.80 (1H, br d, J = 7.5 Hz), 6.94 (1H, br s), 7.14 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.37, 4.05, 21.27, 21.68, 55.81, 94.57, 115.68, 121.20, 122.33, 123.02, 129.50, 129.91, 137.63, 154.37; MS *m/z* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C,77.03; H, 8.31. Found: C, 76.99; H, 8.34.

1-Cyclopropylidene-1-{2-[(2-trimethylsilyl)ethoxymethyl]oxy-4-methyl}phenyl-ethane (12). By following the same procedure described for **11**, the cyclopropylidene ether **12** was prepared from **10**: yield 98%; a colorless oil; IR (neat) 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (9H, s), 0.96 (2H, t, J = 8.3 Hz), 1.13–1.18 (4H, m), 2.18–2.23 (3H, m), 2.33 (3H, s), 3.75 (2H, t, J = 8.3 Hz), 5.21 (2H, s), 6.76–6.81(1H, br d, J = 7.5 Hz), 6.97 (1H, br s), 7.13 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ –1.40, 2.41, 4.12, 18.02, 21.33, 21.74, 66.01, 92.97, 115.77, 121.05, 122.16, 123.11, 129.47, 129.91, 137.52, 154.56; MS *m/z* 304 (M^+). Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 71.01; H, 9.27.

2-[2-(Methoxymethyl)oxy-4-methyl]phenyl-2-methylcyclobutanone (13). To a stirred solution of the cyclopropylidene ether **11** (926 mg, 4.23 mmol) in CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA) (1.00 g, 80% active, 4.65 mmol) portionwise at 0 °C and stirring was continued for 30 min at the same temperature. The reaction mixture was extracted with CH_2Cl_2 and the extract was washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (98 : 2 v/v) to give the cyclobutanone **13** (973 mg, 98%) as a colorless oil: IR (neat) 1780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (3H, s), 1.92–2.08 (1H, m), 2.31 (3H, s), 2.35–2.47 (1H, m), 3.10–3.20 (2H, m), 3.47 (3H, s), 5.12–5.21 (2H, m), 6.77 (1H, br d, J = 8.0 Hz), 6.93 (1H, br s), 7.17(1H, d, J = 8.0 Hz); MS *m/z* 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.74; H, 7.80.

2-Methyl-2-{2-[(2-trimethylsilyl)ethoxymethyl]oxy-4-methyl}phenylcyclo-butanone (14). By following the same procedure described for **13**, the cyclobutanone **14** was prepared from **12**: yield 94%; a colorless oil; IR (neat) 1780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (9H, s), 0.95 (2H, t, *J* = 8.4 Hz), 1.55 (3H, s), 1.96–2.07 (1H, m), 2.32 (3H, s), 2.34–2.46 (1H, m), 3.14–3.20 (2H, m), 3.66–3.84(2H, m), 5.18–5.28 (2H, m), 6.74–6.83 (1H, br d, *J* = 7.8 Hz), 6.96 (1H, br s), 7.17 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.31, 18.07, 21.38, 21.94, 26.97, 52.52, 64.73, 66.42, 92.57, 114.83, 121.96, 126.24, 127.85, 138.27, 154.76, 212.76; MS *m/z* 320 (M^+). Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.35; H, 8.63.

(1S,2R)- and (1R,2R)-2-[2-(Methoxymethyl)oxy-4-methyl]phenyl-2-methyl-1-vinylcyclobutanols (15 and 16). To a stirred suspension of cerium chloride (12.6 g, 51.1 mmol) in THF (120 mL) was added a solution of vinylmagnesium bromide (62.2 mL, 1 M THF solution, 62.2 mmol) at 0 °C. After stirring was continued for 1 h, a solution of the cyclobutanone **13** (7.33 g, 31.3 mmol) in THF (100 mL) was added dropwise to this reaction mixture at the same temperature and the temperature was then raised to rt in 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (95 : 5 v/v) to give the mixture of the cyclobutanols **15** and **16** (7.66 g, 93%) as a colorless oil: IR (neat) 3560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (0.48H, s), 1.46 (2.52H, s), 1.78–2.00 (2H, m), 2.06–2.20 (1H, m), 2.25–2.46 (3.84H, m), 2.62–2.75 (0.16H, m), 2.81 (1H, br s), 3.47 (0.48H, s), 3.52 (2.52H, s), 4.83 (0.84H, br d, *J* = 10.6 Hz), 5.02–5.30 (3.16H, m), 5.91 (0.84H, dd, *J* = 10.6 and 16.8 Hz), 6.34 (0.14H, dd, *J* = 10.8 and 17.4 Hz), 6.74–7.00 (3H, m); MS *m/z* 262 (M^+); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569 (M^+), found 262.1562.

(1S,2R)- and (1R,2R)-2-Methyl-2-{2-[(2-trimethylsilyl)ethoxymethyl]oxy-4-methyl}-phenyl-1-vinylcyclobutanols (17 and 18). After following the same reaction conditions for **15** and **16**, the residue upon workup of the reaction mixture resulted from the ketone **14** was chromatographed on silica gel with hexane-AcOEt (99.5 : 0.5 v/v) to give the cyclobutanols **18** (4.68 g, 82%) from the first fraction and **17** (0.757 g, 13%) from the second fraction as a colorless oil each other. Data for **17**: IR (neat) 3580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.02 (9H, s), 0.90–0.97 (2H, m), 1.34 (3H, s), 1.81–1.91 (2H, m), 2.30 (3H, s), 2.31–2.39 (2H, m), 2.62–2.70 (1H, m), 3.63–3.75 (2H, m), 5.19 (1H, d, *J* = 7.0 Hz), 5.24 (1H, dd, *J* = 1.7 and 17.4 Hz), 6.32 (1H, dd, *J* = 11.0 and 17.4 Hz), 6.80 (1H, br d, *J* = 7.7 Hz), 6.91 (1H, br s), 6.96 (1H, d, *J* = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.35, 18.04, 21.33, 25.85, 28.40, 29.87, 50.73, 66.51, 80.88, 91.95, 112.34, 114.69, 123.00, 128.19, 132.33, 137.38, 142.17, 153.77; MS *m/z* 348 (M^+); HRMS calcd for $C_{20}H_{32}O_3Si$ 348.2119 (M^+), found 348.2089. Data for **18**: IR (neat) 3550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (9H, s), 0.98 (2H, t, *J* = 8.5 Hz), 1.44 (3H, s), 1.77–1.83 (1H, m), 1.90–1.95 (1H, m), 2.06–2.16 (1H, m), 2.28 (3H, s), 2.34–2.42 (1H, m), 2.90 (1H, br s), 3.69–3.83 (2H, m), 4.81 (1H, dd, *J* = 1.8 and 10.6 Hz), 5.08 (1H, d, *J* = 6.2 Hz), 5.25 (1H, d, *J* = 6.2 Hz), 5.23 (1H, dd, *J* = 1.8 and 16.9 Hz), 5.88 (1H, dd, *J* = 10.6 and 16.9 Hz), 6.73–6.78 (2H, m), 6.86 (1H, d, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.31, 18.26, 21.39, 22.87, 25.42, 30.10, 50.60, 67.25, 77.41, 93.41, 110.07, 114.32,

122.33, 126.43, 133.65, 136.84, 142.57, 154.09; MS *m/z* 348 (M^+); HRMS calcd for $C_{20}H_{32}O_3Si$ 348.2119, found 348.2100.

(1R,2S)- and (1R,2R)-1-[2-(Methoxymethyl)oxy-4-methyl]phenyl-1-methyl-2-triethylsiloxy-2-vinylcyclobutanes (19 and 20). To a stirred solution of the mixture of the cyclobutanols **15** and **16** (198 mg, 0.754 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.177 mL, 1.52 mmol) at rt. Triethylsilyl methanesulfonate (TESOTf) (0.207 mL, 0.914 mmol) was added at 0 °C and stirring was continued for 15 min at rt. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the mixture of the silyl ethers **19** and **20** (280 mg, 99%) as a colorless oil: IR (neat) 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.42 (0.96H, q, *J* = 7.5 Hz), 0.64 (5.04H, q, *J* = 7.8 Hz), 0.73 (1.44H, t, *J* = 7.5 Hz), 1.00 (7.56H, t, *J* = 7.8 Hz), 1.26 (0.48H, s), 1.46 (2.52H, s), 1.69–1.86 (1H, m), 1.99–2.35 (5.68H, m), 2.46–2.74 (0.32H, m), 3.47 (3H, s), 4.84 (0.84H, br d, *J* = 11.0 Hz), 5.03–5.20 (3.16H, m), 5.85 (0.84H, dd, *J* = 11.0 and 17.3 Hz), 6.25 (0.16H, dd, *J* = 11.3 and 17.3 Hz), 6.67–6.75 (1H, m), 6.83–6.91 (1.84H, m), 6.98 (0.16H, d, *J* = 7.5 Hz); MS *m/z* 376 (M^+); HRMS calcd for $C_{22}H_{36}O_3Si$ 376.2434 (M^+), found 376.2409.

(1S,2R)- and (1R,2R)-2-Methyl-1-triethylsiloxy-2-{2-[(2-trimethylsilyl)-ethoxymethyl]-oxy-4-methyl}phenyl-1-vinylcyclobutanes (21 and 22). By following the same procedure described for **19** and **20**, the cyclobutanes **21** and **22** were prepared from the mixture of **17** and **18**: yield 100%; a colorless oil; IR (neat) 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ –0.01–0.05 (9H, m), 0.42 (0.84H, q, *J* = 7.8 Hz), 0.64 (5.16H, q, *J* = 7.8 Hz), 0.74 (1.26H, t, *J* = 7.8 Hz), 0.93–1.06 (9.74H, m), 1.23 (0.42H, s), 1.44 (2.58H, s), 1.68–1.85 (1H, m), 1.98–2.34 (5.72H, m), 2.43–2.73 (0.28H, m), 3.67–3.82 (6H, m), 4.84 (0.86H, br d, *J* = 10.5 Hz), 5.07–5.23 (3.14H, m), 5.85 (0.86H, dd, *J* = 10.5 and 17.1 Hz), 6.26 (0.14H, dd, *J* = 11.3 and 17.0 Hz), 6.67–6.74 (1H, m), 6.81–7.00 (2H, m); MS *m/z* 348 (M^+ –114); HRMS calcd for $C_{20}H_{32}O_3Si$ 348.2121 (M^+ –114), found 348.2100.

3-[2-(Methoxymethyl)oxy-4-methyl]phenyl-3-methyl-2-methylenecyclopentanone (23). To a stirred solution of the mixture of the silyl ethers **19** and **20** (1.03 g, 2.73 mmol) in THF (30 mL) and MeCN (5 mL) were added $Pd(OAc)_2$ (400 mg, 1.78 mmol) and $PdCl_2$ (518 mg, 2.92 mmol) at rt and stirring was continued for 3 h under reflux. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with hexane-AcOEt (95 : 5) to give the cyclopentanone **23** (448 mg, 63%) as a yellow oil: IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, s), 1.78–1.90 (1H, m), 2.32 (3H, s), 2.39–2.64 (3H, m), 3.40 (3H, s), 4.98–5.17 (3H, m), 5.96 (1H, s), 6.77 (1H, br d, *J* = 8.0 Hz), 6.9 (1H, br s), 7.20 (1H, d, *J* = 8.0 Hz); MS *m/z* 260 (M^+); HRMS calcd for $C_{16}H_{20}O_3$ 260.1412 (M^+), found 260.1438.

3-Methyl-2-methylene-3-{2-[(2-trimethylsilyl)ethoxymethyl]oxy-4-methyl}-phenylcyclopentanone (24). To a stirred solution of the mixture of the silyl ethers **21** and **22** (1.02 g, 2.21 mmol) in THF (30 mL) and MeCN (6 mL) were added $PdCl_2$ (431 mg, 2.43 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.882 g, 4.42 mmol) at rt and stirring was continued for 5 h at 50 °C. The reaction mixture was filtered through short column of silica gel and the residue upon the evaporation of the solvent was chromatographed on silica gel with

hexane-AcOEt (98 : 2) to give the cyclopentanone **24** (595 mg, 78%) as a yellow oil: IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00(9H, s), 0.93 (2H, t, *J* = 8.4 Hz), 1.60 (3H, s), 1.73–1.88 (1H, m), 2.31 (3H, s), 2.40–2.48 (2H, m), 2.49–2.61 (1H, m), 3.56–3.73 (2H, m), 5.00 (1H, br s), 5.06–5.20 (2H, m), 5.96 (1H, br s), 6.76 (1H, br d, *J* = 7.8 Hz), 6.95 (1H, br s), 7.18 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.31, 18.05, 21.25, 28.09, 34.19, 36.29, 45.68, 66.38, 92.28, 115.45, 115.63, 121.51, 126.63, 133.22, 138.01, 154.67, 155.08, 207.59; MS *m/z* 346 (M^+). Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 69.32; H, 8.73. Found: C, 69.35; H, 8.70.

(1R,3S)- and (1S,3S)-3-[2-(Methoxymethyl)oxy-4-methyl]phenyl-3-methyl-2-methylene-cyclopentanols (25 and 26). To a stirred solution of the cyclopentanone **23** (122 mg, 0.469 mmol) in MeOH (3 mL) was added $CeCl_3 \cdot 7H_2O$ (227 mg , 0.609 mmol). Sodium borohydride ($NaBH_4$) (23.0 mg, 0.609 mmol) was added portionwise at 0 °C and stirring was continued for 15 min at the same temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (98 : 2 v/v) to give the cyclopentanol **26** (55.3 mg, 45%) and with hexane-AcOEt (93 : 7 v/v) to give the cyclopentanol **25** (52.8 mg, 43%) as a colorless oil each other. Data for **25**: IR (neat) 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (3H, s), 1.56–1.71 (2H, m), 1.72–1.83 (1H, m), 2.09–2.29 (2H, m), 2.31 (3H, s), 3.45 (3H, s), 4.68–4.78 (1H, m), 4.82 (1H, d, *J* = 2.4 Hz), 5.08–5.24 (3H, m), 6.74 (1H, br d, *J* = 8.0 Hz), 6.91 (1H, br s), 7.25 (1H, d, *J* = 8.0 Hz); MS *m/z* 262 (M^+); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569 (M^+), found 262.1613. Data for **26**: IR (neat) 3600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (3H, s), 1.55–1.67 (1H, m), 1.75–1.85 (1H, m), 1.96–2.08 (1H, m), 2.32 (3H, s), 2.47–2.59 (1H, m), 2.60–2.68 (1H, m), 3.48 (3H, s), 4.54–4.64 (1H, m), 4.76 (1H, br s), 5.12–5.25 (2H, m), 5.28 (1H, br s), 6.80 (1H, br d, *J* = 8.1 Hz), 6.91 (1H, br s), 7.33 (1H, d, *J* = 8.1 Hz); MS *m/z* 262 (M^+); HRMS calcd for $C_{16}H_{22}O_3$ 262.1569 (M^+), found 262.1617.

(1R,3S)- and (1S,3S)-3-Methyl-2-methylene-3-{2-[(2-trimethylsilyl)ethoxy-methyl]oxy-4-methyl}phenylcyclopentanols (27 and 28). By following the same procedure described for **25** and **26**, the cyclopentanols **28** (47%) and **27** (52%) were given from the reaction of the cyclopentanone **24** as a colorless oil each other. Data for **27**: IR (neat) 3390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.97 (2H, t, *J* = 8.1 Hz), 1.52 (3H, s), 1.58–1.70 (2H, m), 1.72–1.82 (1H, m), 2.08–2.27 (2H, m), 2.31 (3H, m), 3.68–3.80 (2H, m), 4.67–4.78 (1H, m), 4.82 (1H, d, *J* = 2.1 Hz), 5.13–5.27 (3H, m), 6.74 (1H, br d, *J* = 8.3 Hz), 6.94 (1H, br s), 7.25 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.29, 18.08, 21.24, 28.38, 33.98, 36.45, 47.17, 66.24, 75.73, 92.23, 106.05, 115.31, 121.40, 126.98, 133.74, 137.39, 155.10, 164.19; MS *m/z* 348 (M^+); HRMS calcd for $C_{20}H_{32}O_3Si$ 348.2121 (M+), found 348.2112. Data for **28**: IR (neat) 3430 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$) δ 0.00(9H, s), 0.93 (2H, t, *J* = 8.3 Hz), 1.43 (3H, s), 1.55–1.64 (1H, m), 1.65–1.75 (1H, m), 1.95–2.09 (1H, m), 2.32 (3H, s), 2.48–2.59 (1H, m), 2.70–2.76 (1H, m), 3.60–3.86 (2H, m), 4.55–4.66 (1H, m), 4.74 (1H, br s), 5.18–5.30 (3H, m), 6.79 (1H, br d, *J* = 8.0 Hz), 6.92 (1H, br s), 7.33 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.32, 18.02, 21.19, 28.53, 33.85, 37.71, 47.86, 66.94, 75.94, 92.75, 109.46, 115.57, 121.77, 127.97, 133.30, 137.49, 154.47, 163.81; MS *m/z* 348 (M^+); HRMS calcd for $C_{20}H_{32}O_3Si$ 348.2121, found 348.2135.

(1R,3S)-3-Methyl-2-methylene-3-(2-hydroxy-4-methyl)phenylcyclopentanol (29). To a stirred solution of the cyclopentanol **27** (168 mg, 0.482 mmol) in HMPA (10 mL) was added $^{n}Bu_4N^+F^-$ (227 mg, 0.867 mmol) at rt and stirring was continued for 3 h at 45 °C. To the reaction mixture was added water and the mixture was extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (90 : 10 v/v) to give the phenol **29** (85.0 mg, 81%) as colorless needles: mp 105.2–105.5 °C (from AcOEt-hexane); IR ($CHCl_3$) 3390, 3600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, s), 1.61–1.81 (2H, m), 1.84–1.95 (1H, m), 2.10–2.52 (5H, m), 4.70–4.81 (1H, m), 5.03 (1H, d, J = 2.3 Hz), 5.36 (1H, d, J = 2.3 Hz), 6.56–6.60 (1H, m), 6.66–6.73 (1H, m), 7.21 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.87, 27.74, 33.18, 36.43, 47.29, 75.07, 107.66, 118.03, 121.13, 127.27, 130.67, 137.68, 153.63, 163.37; MS *m/z* 218 (M^+); HRMS calcd for $C_{14}H_{18}O_2$ 218.1307 (M^+), found 218.1293

(1S,3S)-3-Methyl-2-methylene-3-(2-hydroxy-4-methyl)phenylcyclopentanol (30). By following the same procedure described for **29**, the phenol **30** was prepared from **28**: yield 92%; colorless needles; mp 143.8–144.0 °C (from AcOEt-hexane); IR ($CHCl_3$) 3390, 3600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (3H, s), 1.58–1.68 (1H, m), 1.88–2.09 (2H, m), 2.28 (3H, s), 2.53–2.68 (1H, m), 3.20–3.54 (1H, m), 4.72 (1H, m), 4.87 (1H, s), 5.29 (1H, s), 6.66–6.75 (2H, m), 7.28 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.83, 28.79, 33.20, 37.51, 46.51, 76.46, 112.16, 118.47, 120.55, 127.18, 130.40, 137.83, 153.28, 162.19; MS *m/z* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C,77.03; H, 8.31. Found: C, 77.00; H, 8.37.

(2R,5S)-15-Nor-6,8,10,12-trichothecatetraene (31) from the mixture of 25 and 26. To a stirred solution of the mixture of the cyclopentanols **25** and **26** (21.6 mg, 0.108 mmol) in MeOH (1 mL) was added 70% aqueous $HClO_4$ (1 mL) at rt and stirring was continued for 30 min at the same temperature. The reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the tricyclic compound **31** (4.8 mg, 29%) as a colorless oil: IR (neat) 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (3H, s), 1.66–1.80 (1H, m), 1.96–2.19 (3H, m), 2.24 (3H, s), 4.80 (1H, d, J = 5.4 Hz), 4.93 (1H, s), 5.11 (1H, s), 6.53–6.57 (1H, m), 6.61–6.68 (1H, m), 6.98 (1H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.70, 21.09, 31.23, 42.50, 43.81, 80.58, 103.26, 116.43, 120.90, 123.11, 130.86, 137.75, 152.21, 152.81; MS *m/z* 200 (M^+); HRMS calcd for $C_{14}H_{16}O$ 200.1201 (M^+), found 200.1190.

31 from 29. To a stirred solution of the cyclopentanol **29** (100 mg, 0.548 mmol) in CH_2Cl_2 (20 mL) was added $BF_3{\cdot}Et_2O$ (0.230 mL, 1.85 mmol) at 0 °C and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99.5 : 0.5 v/v) to give the tricyclic compound **31** (57 mg, 62%) as a colorless oil.

31 from 30. By following the same procedure described for **31** from **29**, the tricyclic compound **31** was prepared from **30**: yield 81%.

(2R,5R,12S)-15-Nor-6,8,10-trichothecatriene-12,13-diol (32). To a stirred solution of the tricyclic compound **31** (249 mg, 1.24 mmol) in ^{t}BuOH (2 mL) and water (2 mL) were added *N*-methylmorpholine-*N*-oxide (291 mg, 2.48 mmol) and a catalytic amount of OsO_4 at rt and stirring was continued for 12 h at the same temperature. To the reaction mixture was added saturated aqueous Na_2SO_4 and the solution was stirred for 30 min. The reaction mixture was extracted with Et_2O and the extract was washed with brine. The residue was chromatographed on silica gel with hexane-AcOEt (85 : 15 v/v) to give the diol **32** (270 mg, 93%) as colorless needles: mp 147.9–148.2 °C (from AcOEt-hexane); IR ($CHCl_3$) 3570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.84–1.98 (2H, m), 1.98–2.06 (1H, m), 2.08–2.24 (2H, m), 2.25 (3H, s), 2.81–2.92 (1H, m), 3.52 (1H, br d, J = 11.1 Hz), 3.85 (1H, br d, J = 11.1 Hz), 4.44 (1H, d, J = 5.1 Hz), 6.54 (1H, br s), 6.67 (1H, br d, J = 7.8 Hz), 6.97 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 21.02, 29.45, 42.08, 46.26, 61.86, 78.89, 81.20, 116.30, 121.58, 124.39, 129.18, 137.80, 151.68; MS *m/z* 234 (M^+); HRMS calcd for $C_{14}H_{18}O_3$ 234.1256 (M^+), found 234.1248.

(2R,5R,12S)-12,13-Epoxy-15-nor-6,8,10-trichothecatriene (2) from 31. To a stirred solution of the tricyclic compound **31** (18.7 mg, 0.0934 mmol) in CH_2Cl_2 (1 mL) was added *m*-CPBA (23.3 mg, 80% active, 0.135 mmol) at rt and stirring was continued for 17 h at the same temperature. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give epoxide **2** (9.3 mg, 46%) as a colorless oil: IR (neat) 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.97–2.25 (4H, m), 2.27 (3H, s), 2.91 (1H, d, J = 4.2 Hz), 3.11 (1H, d, J = 4.2 Hz), 4.14 (1H, d, J = 5.4 Hz), 6.59 (1H, br s), 6.69 (1H, br d, J = 7.8 Hz), 6.99 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.14, 20.94, 29.82, 41.16, 41.64, 47.69, 66.94, 81.32, 116.65, 121.48, 124.29, 129.46, 138.33, 152.59; MS *m/z* 216 (M^+); HRMS calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1142

2 from 32. To a stirred solution of the diol **32** (24.1 mg, 0.103 mmol) in THF (2 mL) was added a solution of ^{n}BuLi (0.141 mL, 1.5 M solution in hexane, 0.211 mmol) at –78 °C and the temperature was raised up to 0 °C in 1 h. A solution of *p*-toluenesulfonyl chloride (TsCl) (23.4 mg, 0.124 mmol) in THF (2 mL) was added to the above solution at 0 °C and stirring was continued for 1 h. To the reaction mixture was added brine and the mixture was extracted with Et_2O. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (97 : 3 v/v) to give the epoxide **2** (18.2 mg, 82%).

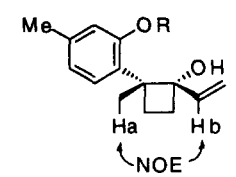
(2R,5R,12S)-12,13-Dimethylmethylenedioxy-15-nor-6,8,10-trichothecatriene (36). To a stirred solution of the diol **32** (151 mg, 0.644 mmol) in CH_2Cl_2 (5 mL) were added 2,2-dimethoxypropane (0.396 mL, 3.22 mmol) and a catalytic amount of camphorsulfonic acid at rt and stirring was continued for 9 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (99 : 1 v/v) to give the acetonide **36** (173 mg, 98%) as a colorless oil: IR (neat) 1620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (3H, s), 1.46 (6H, s), 1.88–2.04 (3H, m), 2.05–2.23 (1H, m), 2.25 (3H, s), 3.68 (1H, d, J = 9.2 Hz), 4.20 (1H, d, J = 9.2 Hz), 4.40 (1H, d, J = 5.5 Hz), 6.53 (1H, br s), 6.65 (1H, br d, J = 8.0 Hz), 6.98 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.09, 20.64, 25.95, 26.67, 29.43, 41.35, 45.19,

65.02, 81.93, 87.29, 109.76, 116.33, 121.25, 124.36, 129.01, 137.59, 152.05; MS *m/z* 274 (M^+); HRMS calcd for $C_{17}H_{22}O_3$ 274.1569 (M^+), found 274.1577.

References and Notes

1. (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds* Vol. II, *Terpenes*: Academic Press, New York, 1972, p 114. (b) *Terpenoids and Steroids*; The Chemical Society, London, Vol. 1–12. (c) Grove, J. F. *Nat. Prod. Rep.* **1988**, 187-209. (d) ApSimon, J. W.; Blackwell, B. A.; Blais, L.; Fielder, D. A.; Greenhalgh, R.; Kasitu, G.; Miller, J. D.; Savard, M. *Pure Appl. Chem.* **1990**, *62*, 1339-1346.
2. (a) Bamburg, J. R. *Clin. Toxicol.* **1972**, *5*, 495-515. (b) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63-117. (c) Purchase, I. F. H. Ed., *Mycotoxins*; American Elsevier, New York, 1974. (d) Kupchan, S. M.; Jarvis, B. B.; Dailey Jr., R. G.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, *98*, 7092-7093. (e) Ueno, Y. *Trichothecanes-Chemical, Biological and Toxicological Aspects, Developments in Food Science 4*, American Elsevier, New York, 1983.
3. Doyle, T. W.; Bradner, W. T. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M.; Douros, J. D., Eds.; Academic, New York, 1980, p 43.
4. (a) McDougal, P. G.; Schmuff, N. R. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch., Eds.; Springer-Verlag, New York, 1985. Vol. 47, p 153. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; John Wiley & Sons, Inc., New York, 1983, Vol. 5, p 238. (c) Boeckman, R. H.; Goldstein, M. *ibid.* 1988, Vol. 7, p 116. (d) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116-1118. (e) Trost, B.M.; McDougal, P. G. *ibid.* **1982**, *104*, 6110-6112. (f), Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *ibid.* **1982**, *104*, 1114-1116. (g) Rousch, W. R.; D'Ambra, T. E. *ibid.* **1983**, *105*, 1058-1060. (h) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *ibid.* **1983**, *105*, 4472-4473. (i) Gilbert, J. C.; Selliah, R. D. *Tetrahedron Lett.* **1992**, *33*, 6259-6262. (j) idem *J. Org. Chem.* **1993**, *58*, 6255-6265 and references cited therein.
5. (a) Nemoto, H.; Ishibashi, H.; Fukumoto, K. *Heterocycles*, **1992**, *33*, 549-552. (b) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707-1712. (c) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1992**, 1695-1697. (d) Nemoto, H.; Nagamochi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2329-2332. (e) Nemoto, H.; Tanabe, T.; Nagamochi, M.; Fukumoto, K. *Heterocycles* **1993**, *35*, 707-710. (f) Nemoto, H.; Shiraki, M.; Nagamochi, M.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 4939-4942. (g) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Synlett.* **1994**, 599-600. (h) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10391-10396. (i) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499-6502. (j) Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74-79. (k) Nemoto, H.; Tanabe, T.; Fukumoto, K. *ibid.* **1995**, *60*, 6785-6790. (l) Nemoto, H.; Shiraki, M.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 8799-8802.
6. (a) Nemoto, H.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Heterocycles* **1994**, *39*, 467-470. (b) Nemoto, H.; Miyata, J.; Hakamata, H.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 1055-1058. (c) Nemoto, H.; Miyata, J.; Hakamata, H.; Nagamochi, M.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 5511-5522.
7. Anderson, W. K.; Lee, G. E. *J. Med. Chem.* **1980**, *23*, 96-97.
8. Weber, H. W. *Fr.* 1, 511, 331 (*Chem. Abstr.* **1969**, *70*, 77767 h).
9. Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531-2534.
10. The stereochemistry of **15** was confirmed by the definite NOE enhancement between methyl (Ha) (1.35 ppm, s) and vinylic hydrogen (Hb) (6.34 ppm, dd, J = 10.8 and 17.4 Hz) in its ^{1}H NMR (300 MHz) spectrum. The ratio of **15** and **16** was determined by ^{1}H NMR integration of methyl signals (1.35 ppm for **15** and 1.46 ppm for **16**). These isomers could not be separated and used as a mixture (Figure 1).
11. This type of transformtion has been developed by us and others, see 5j and references cited therein.
12. The structures of **25** and **26** were determined mainly by ^{1}H NMR (300 MHz) studies as follows. Namely, the definite NOE enhancement between methyl (Ha) (1.56 ppm, s) and allylic 1hydrogen (Hb) (4.66–4.76 ppm,

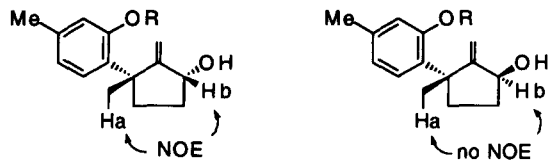
Figure 1



15 : R = MOM
17 : R = SEM

m) of **25** confirmed these two groups to be *cis*. On the other hand, no such enhancement between methyl (Ha) (1.44 ppm, s) and allylic hydrogen (Hb) (4.54–4.64 ppm, m) of **26** showed these two groups to be *trans* (Figure 2). Since the next cyclization process giving **31** seems to proceed *via* allylic cation, the both diastereomers **25** and **26** might be used for this reaction.

Figure 2

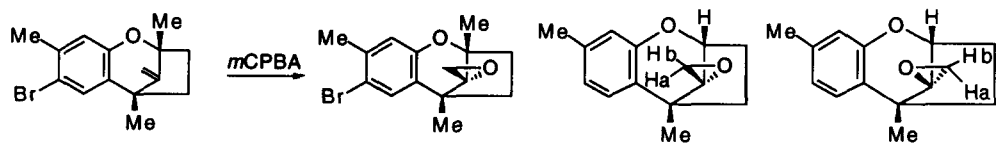


25 : R = MOM
27 : R = SEM

26 : R = MOM
28 : R = SEM

13. The stereochemistry of the epoxide **2** was tentatively assigned at the moment by the analogous reaction[14] of the compound **33** in which the epoxidation took place in the completely stereoselective manner to give the compound **34** with the *syn* relationship between the methylene hydrogens of the epoxide ring and the aromatic ring. This stereochemical outcome was explained by the effective size of the π system making the aromatic region of **33** to be more encumbered one. This stereochemical assignment was also supported by the somewhat large difference of the chemical shifts between the two hydrogens Ha (2.91 ppm, d, $J = 4.2$ Hz) and Hb (3.11 ppm, d, $J = 4.2$ Hz) of the epoxide **2** due to the deshielding effect of the phenoxy group and this seemed not to be the case for the isomeric epoxide **35**. This was also confirmed afterward by the identification with the sample obtained *via* the diol **32** (Figure 3).

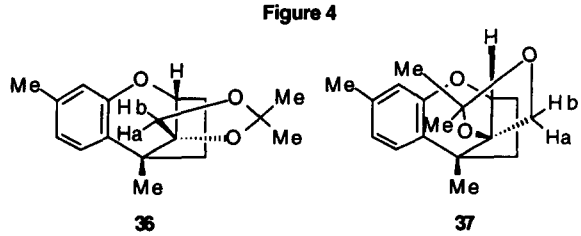
Figure 3



33 **34** **2** **35**

14. Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter III, G. R. *J. Org. Chem.* **1980**, *45*, 3989-3993.
15. The stereochemistry of **17** was confirmed by the definite NOE enhancement between methyl (Ha) (1.34 ppm, s) and vinylic hydrogen (Hb) (6.32 ppm, dd, $J = 11.0$ and 17.4 Hz) in its ^{1}H NMR (500 MHz) spectrum. The ratio of **17** and **18** was determined by ^{1}H NMR integration of methyl signals (1.34 ppm for **17** and 1.44 ppm for **18**) (see Figure 1).
16. The structure of **27** and **28** was determined mainly by ^{1}H NMR (300 MHz) studies as follows. The difinite NOE enhancement between methyl (Ha) (1.52 ppm, s) and allylic hydrogen (Hb) (4.67–4.78 ppm, m) of **27** showed these two groups to be *cis*. On the other hand, no such enhancement between methyl (Ha) (1.43 ppm, s) and allylic hydrogen (Hb) (4.55–4.66 ppm, m) of **28** confirmed these two groups to be *trans*. These two isomers were separated at this stage and used separately for further elaboration (see Figure 2).
17. The stereochemistry of the diol **32** was tentatively assigned by ^{1}H NMR (500 MHz) studies of the corresponding acetonide **36** as follows. The signals of the methylene hydrogens Ha and Hb were observed at 3.68 ppm (d, $J = 9.2$ Hz) and 4.20 ppm (d, $J = 9.2$ Hz) respectively with large difference (0.52 ppm) of chemical shifts which could be due to the deshielding effect of phenoxy group. On the other hand, the two methyl groups of acetonide were observed at 1.46 ppm with the same chemical shift. This showed the aromatic ring and the methylene group of dioxolane ring to be *syn* relationship. This could not be the case for the isomeric acetonide **37** (Figure 4).

Figure 4



36 **37**

18. All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.

(*Received in Japan* 16 *May* 1996; *accepted* 10 *June* 1996)