Convenient Synthesis of an A-Ring Aromatic Trichothecene Analog

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A short and convenient route to the synthesis of A-ring aromatic trichothecene analogue **2** is described, employing a cyclobutyl carbinol rearrangement as the key step. Cycloaddition of ethylene to the methoxychromone **6** furnished the oxetanol **7** along with some cycloadduct **8**, the latter arising from cleavage of **7**. Lithium aluminum hydride reduction of **7** to the diol **9** followed by acid-catalyzed rearrangement afforded the benzooxabicyclo[3.2.1]octanone **10**, through exclusive external bond migration. Interaction of **10** with dimethyloxosulfonium methylide furnished the desired anti-epoxide **2**, whereas dimethyl sulfonium methylide yielded the syn-epoxide **12**. Reduction of these epoxides provided the alcohols **13** and **14**, respectively. Addition of methylmagnesium iodide to ketone **10** furnished exclusively alcohol **14**, supporting the stereoassignments.

Introduction

The trichothecene family of sesquiterpenes contains a wide variety of biologically active antifungal, antitumor, cytotoxic, and phytotoxic molecules,[1] which are produced by various species of fungi like *Trichothecium*, *Trichoderma*, *Myrothecium*, *Fusarium*, etc. These compounds contain an unusual oxabicyclo[3.2.1]octane unit in their structural inlay incorporating also a methylene epoxide. Epoxytrichothecene **1** is the simplest representative of this group with other members arising from oxygenation at various carbon atoms. The highly intriguing structural features and the inherent wide ranging biological properties of these sesquiterpenes have attracted the considerable attention of organic chemists to bring them within the scope of synthesis as evidenced by the number of reports on their synthesis during the last two decades.[2] In our own efforts directed toward their synthesis we have previously reported[3] the synthesis of some bicyclic lactones as potential precursors. Subsequently we have targeted the A-ring aromatic trichothecene analogue **2** for synthesis since the aromatic ring can be suitably exploited for incorporating the necessary functionalities in that ring. Furthermore, A-ring aromatic trichothecene analogues themselves have been reported to display significant in vivo antileukemic activity.[4] Previous syntheses[5] of this ring system have involved multistep transformations with attendant low yields or use of expensive reagents. We have recently disclosed[6] a general, expeditious route to the benzooxabicyclo[3.2.1]octane system employing a cyclobutyl carbinol rearrangement and applied it to a short synthesis of the sesquiterpene filiformin. We report here an application of this methodology which delivers the desired A-ring aromatic trichothecene analogue **2** in a short number of steps and in good overall yield.

Results and Discussion

The required starting material for the synthesis of **2** employing our generalized approach was 3-methoxy-7-methylchromone **6**. This was prepared in good overall yield following the procedure of Moriarty et al.[7] for hydroxylation of ketones through hypervalent iodine oxidation. Thus, interaction of the readily available 7-methylchromone **3** with iodobenzene diacetate in methanol furnished the trimethoxychromanol **4** in 80% yield. The configuration of the C_2, C_3 substituents was inconsequential. Acid treatment of **4** led to deacetalization and concomitant methanol elimination to afford 3-hydroxy-7-methylchromone **5** in 90% yield which was methylated to the desired methoxychromone **6** in 87% yield (Scheme 1).

A benzene solution of the methoxychromone **6** was irradiated for 25 h during which time ethylene was bubbled through the solution. Removal of benzene followed by chromatography of the residue over silica gel furnished a mixture of the oxetanol **7**, arising from an intramolecular hydrogen abstraction from the methoxy substituent in the initial photoadduct followed by ring closure of the resulting 1,4-biradials[6] (Scheme 2) and the cycloadduct **8** in varying proportions. The yield of the desired oxetanol was about 55% even after extended hours of photolysis. The structure of the cycloadduct **8** was arrived at from analytical and spectral data, particularly the IR absorption at 1665 cm^{-1} indicative of the carbonyl group. The assigned structure and stereochem-

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(2) (a) McDougal, P. G.; Schmuff, N. R. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.;Springer-Verlag: New York, 1988; Vol. 47, p 153. (b) Colvin, E. W.; Egan, M. J.; Kerr, F. W. *J. Chem. Soc., Chem. Commun.* **1990**, 1200 and references cited. (c) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6225.

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(6) Nath, A.; Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1996**, *61*, 4391.

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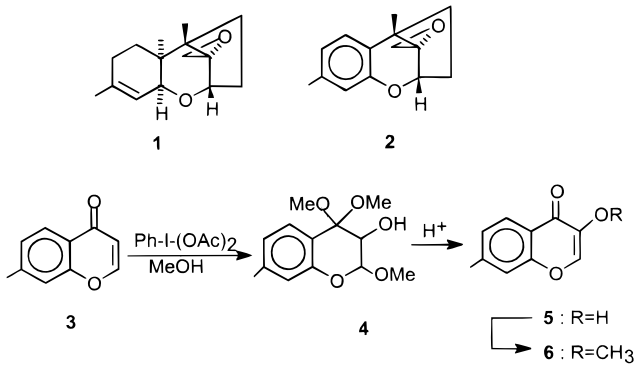
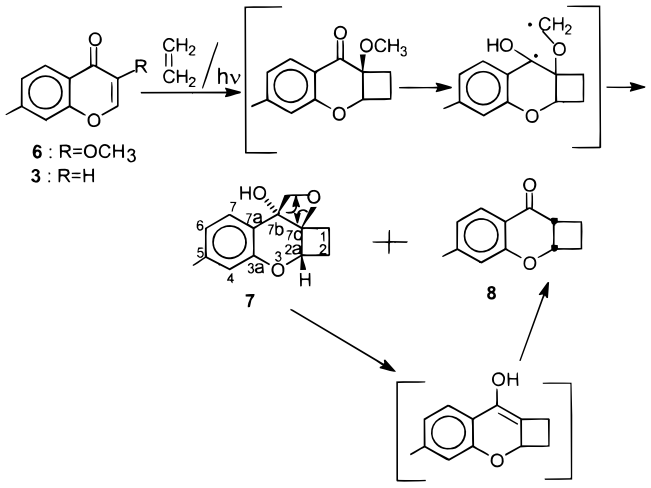
Scheme 1



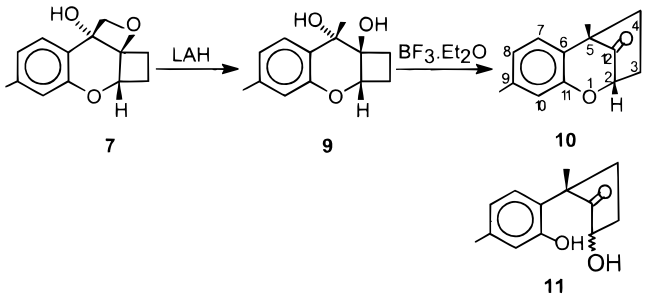
Scheme 2



istry were confirmed from spectroscopic identity with the same cycloadduct **8** obtained from photolytic addition of ethylene to 7-methylchromone **3** (Scheme 2). The adduct **8** may be deemed to arise from cleavage of the oxetanol **7** during chromatography (Scheme 2). This is akin to the reported cleavage of oxetanes under various conditions.[8] This assumption was supported by the fact that the product from photolysis did not show any absorption in the IR spectrum in the carbonyl region before chromatographic purification.

The oxetanol **7** displayed the expected analytical and spectral features, particularly the characteristic AB quartet for the oxetane methylene protons in the ^{1}H NMR spectrum. The stereochemistry was assigned based on analogy with previous results.[6] Efforts at rapid purification of the photolyzate also did not lead to any distinct improvement in the yield of the oxetanol **7** and the cleavage product **8** continued to plague the product profile. This cleavage of **7** was in sharp contrast to the nature of the previous oxetanols[6] which differed from **7** mainly in the presence of an additional methyl group at C-2a. Reduction of the oxetanol **7** with lithium aluminum hydride in refluxing tetrahydrofuran afforded the diol **9** as a crystalline solid in 97% yield, set up for the crucial pinacol−pinacolone type rearrangement. In the event, treatment of a benzene solution of **9** with a catalytic amount of boron trifluoride etherate at ambient

Scheme 3



temperature for 1 h furnished the desired benzooxabicyclo[3.2.1]octanone **10** as the only product in 87% yield, the rearrangement following our already established[6] pathway (Scheme 3). The structure of the bridged ketone **10** was adequately supported by the diagnostic features on its spectrum, particularly the IR absorption at 1765 cm^{-1} in conformity with previous results.[6] In the ^{1}H NMR spectrum, the bridgehead C-2a hydrogen appears as a doublet at δ 4.21 very close to the value for the same hydrogen in similar compounds[5a] differing only in substitutions pattern. The exclusive formation of **10** from rearrangement of **9** proved complementary to results from other diols synthesized by us[6] previously in course of synthesis of filiformin.

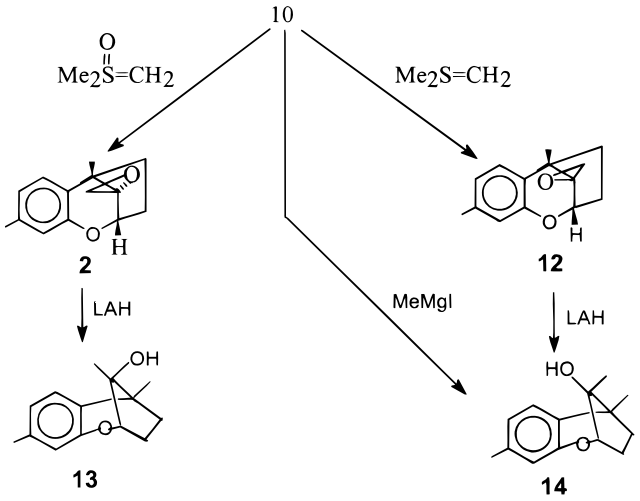
The bridged ketone **10** on storage was transformed to the keto diol **11**. This could have arisen by hydrolytic ring opening. The IR absorption was shifted from 1765 cm^{-1} for the bridged ketone to 1745 cm^{-1} for the keto diol, characteristic of simple cyclopentanone. A similar case of ring opening had been encountered by others.[5a] To gain additional support to the hydrolytic ring opening hypothesis, a tetrahydrofuran solution of the bridged ketone **10** was treated with a catalytic amount of dilute sulfuric acid and furnished the keto diol **11** in near quantitative yield. In view of this problem of hydrolytic cleavage, the diol **9** was rearranged as and when required and the bridged ketone **10** carried immediately to the next reaction. It must be mentioned that no such ring cleavage was observed in the previous synthesized benzooxabicyclo[3.2.1]octanones[6] in which the C-2 carbon atom was fully substituted. It now remained to convert the ketone **10** to the anti-epoxide **2** to complete the synthesis of our target compound. This was realized through the reaction of **10** with dimethyloxosulfonium methylide and furnished the desired anti epoxide **2** in 75% yield as a crystalline solid[9] (Scheme 4). The assignment of stereochemistry to epoxide **2** was based on analogy with the report of Goldsmith et al.[10] This was also corroborated from the matching ^{1}H NMR and ^{13}C NMR data for **2** with those for the same compound reported by Fukumoto et al.[5c] Interaction of **10** with dimethyl sulfonium methylide afforded an epoxide isomeric with **2** and by analogy,[10] was assigned the syn geometry **12**. The two epoxides **2** and **12** were differentiated in the ^{1}H NMR by the upfield shift of the AB quartet due to the epoxy methylene hydrogens in **2** relative to the same hydrogens in **12**. This upfield shift could be attributed to the greater shielding of these hydrogens in **2** by the benzene ring in consonance with previous observations.[10] To gain additional support in favor of the

(8) (a) Jones, G. (II); Schwartz, S. B.; Markon, M. T. *J. Chem. Soc., Chem. Commun.* **1973**, 374. (b) Jones, G. (II), Aquardo, M. A.; Carmody, M. A. *Ibid.* **1975**, 206. (c) Coyle, J. D. Ed. *Photochemistry in Organic Synthesis*; Royal Society of Chemistry Special Publications: London, 1986; p 101.

(9) Fukumoto et al. (ref 5c) have reported this to be an oil.

(10) Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R., III. *J. Org. Chem.* **1980**, *45*, 3989.

Scheme 4



assigned structures, the epoxides **2** and **12** were reduced with lithium aluminum hydride to alcohols **13** and **14** respectively in almost quantitative yields (Scheme 4). The ketone **10** on interaction with methylmagnesium iodide afforded a single alcohol in excellent yield, spectroscopically identical with **14**. By analogy with earlier report,[10] addition of reagents to the carbonyl group in **10** should be expected to display the same facial selectivity, taking place from the side opposite the benzene ring, with the Grignard reagent providing the alcohol **14**. This further confirmed the stereochemical assignment to the alcohols **13** and **14** and hence to the epoxides **2** and **12**.

The synthesis of epoxide **2** thus completed the objective of synthesis of an A-ring aromatic trichothecene analogue, employing cyclobutyl carbinol rearrangement as the key step. The somewhat lower yield at the initial photolysis step due to cleavage of the oxetanol notwithstanding, the overall process involving simple reaction conditions and short number of steps with attendant very good yields has provided a convenient and viable method for the synthesis of such compounds.

Experimental Section

General Procedure. All the compounds described herein possessing asymmetric centers are racemates. All reactions were performed under N_2. Compounds isolated by the reported purification procedures were sufficiently pure for the next reaction. However, for analytical purposes, solid compounds were crystallized from suitable solvents, and melting points of such crystallized samples have been reported and are uncorrected. Liquid products were subjected to bulb to bulb distillations, and the oven temperature is designated as ot. Solvents and reagents were reagent grade materials and were further purified by conventional methods. The petroleum ether that was used is that fraction of bp 60−80 °C and light petroleum ether of bp 40−60 °C. Et_2O refers to diethyl ether. Preparative TLC was performed with silica gel 60 HF_{254} plates of 1 mm thickness. Na_2SO_4 was used to dry organic extracts.

The IR spectra are of $CHCl_3$ solutions. ^1H NMR spectra of CCl_4 solutions were recorded at 60 MHz and that of $CDCl_3$ solutions at 200 MHz. ^{13}C NMR spectra were recorded at 50 MHz.

3-Methoxy-7-methylchromone (6). To a well stirred solution of KOH (10.08 g, 180 mmol) in dry methanol (150 mL) was added dropwise a solution of 7-methyl chromone[11] (10 g, 62.5 mmol) in absolute methanol (300 mL) over a period of 15 min at 5−10 °C, and the reaction mixture was stirred for 10 min. Then iodobenzenediacetate (21.27 g, 66 mmol) was added in 4−5 portions during 10 min, and the resulting mixture was allowed to stir overnight. Most of the methanol was evaporated in vacuo, and to the residue was added water (150 mL) and extracted with Et_2O (5 × 60 mL). The combined extracts were dried, filtered, and concentrated to yield crude **4**, which also contained iodobenzene. Column chromatography on silica gel with petroleum ether/ether (1:1) afforded trimethoxychromanol (**4**) as a pale yellow oil (12.88 g, 81%) ot, 120−125 °C (0.1 mmHg). ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.09 (s, 3H), 3.39 (s, 3H), 3.66 (s, 3H), 4.06 (d, J = 2 Hz, 1H), 5.14 (d, J = 2 Hz, 1H), 6.73−6.83 (m, 2H)), 7.45 (d, J = 9 Hz, 1H). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.08. Found: C, 61.38; H, 7.10

To a solution of **4** (12.8 g, 50 mmol) was added 20 mL of concentrated HCl, and the mixture was allowed to stand at room temperature for 4 h. Colorless crystals separated out from the solution. Filtration followed by washing with cold acetone (10 mL) and drying furnished the 3-hydroxychromone (**5**) (8 g, 90%), mp 178−180 °C (hot acetone).

A solution of the above 3-hydroxychromone (**5**) (8 g, 45 mmol), anhydrous K_2CO_3 (8.2 g, 60 mmol), and MeI (8.5 g, 60 mmol) in dry acetone (100 mL) was refluxed for 6 h. The reaction mixture was cooled. Most of the acetone was distilled off. The residue was poured into ice cold water and extracted with Et_2O. The combined layers were washed with sulfuric acid (2 N) and water, dried, and concentrated. The crude material was evaporatively distilled when it solidified to afford **6** (7.5 g, 87%) ot, 120−130 °C (0.5 mmHg), mp 110−112 °C (Et_2O/light petroleum ether); IR 1610, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 3.89 (s, 3H), 7.08−7.16 (m, 2H), 7.73 (s, 1H), 8.09 (d, J = 9 Hz, 1H)). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.20; H, 5.38

***cis*-1,2,2a,7c-Tetrahydro-5-methyl-7c-oxeto-9*H*-benzo[*b*]cyclobuta[*e*]pyran-7b-ol (7).** A solution of 3-methoxy-7-methylchromone (**6**) (500 mg) in dry thiophene free benzene (260 mL) was irradiated through a Pyrex filter with a Hanovia 450 W mercury lamp for 25 h, during which time ethylene was bubbled through the solution. Then the solvent was evaporated under reduced pressure to give a brown residue. The crude material was subjected to column chromatography over silica gel. Elution with petroleum ether/EtOAc (19:1) furnished the cycloadduct **8** as a colorless liquid (150 mg); ot 115−120 °C (0.15 mmHg); IR 1610, 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.91−2.71 (m, 4H), 2.34 (s, 3H), 3.08−3.46 (m, 1H), 4.91−5.29 (m, 1H), 6.66−6.86 (m, 2H), 7.76 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.59; H, 6.38. Found: C, 76.48; H, 6.39.

Further elution of the column with petroleum ether/EtOAc (17:3) afforded the desired oxetanol **7** (220 mg, 55%)) as a white crystalline solid; mp 145 °C (ether−light petroleum ether); IR 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 4.41 and 4.59 (AB_q, J = 6.6 Hz, 2H), 6.75 (s, 1H), 6.83 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.42. Found: C, 71.82; H, 6.50.

***cis*-1,2,2a,8a-Tetrahydro-5-methyl-8*H*-benzo[*b*]cyclobuta[*e*]pyran-8-one (8).** A solution of 7-methylchromone (700 mg) in dry thiophene free benzene (260 mL) was irradiated through a Pyrex filter with a Hanovia 450 W mercury lamp for 10 h, during which time ethylene was bubbled through the solution. Then the solvent was evaporated under reduced pressure to give a yellow oil. The crude material was subjected to column chromatography over silica gel. Elution with petroleum ether/EtOAc (19:1) furnished the photoadduct **8** (550 mg, 67%). This was found to be spectroscopically identical with the sample **8** obtained from photoaddition of 3-methoxy-7-methylchromone (**6**) to ethylene.

Further elution with petroleum ether/EtOAc (4:1) afforded the starting chromone (100 mg). Based on the recovered chromone the yield of the adduct **8** is 78%.

***cis*-1,2,2a,8a-Tetrahydro-5,8-dimethyl-8*H*-benzo[*b*]cyclobuta[e]pyran-8,8a-diol (9).** To a magnetically stirred solution of the oxetanol (**8**) (500 mg, 2.29 mmol) in dry THF (20 mL) was added lithium aluminum hydride (250 mg, 6.58 mmol), and it was refluxed vigorously for 5 h. The reaction mixture was cooled to 0 °C and decomposed by adding

(11) (a) Colonge, J.; Guyet, A. *Bull. Soc. Chim. Fr.* **1958**, 325. (b) Schonberg, A.; Sina, A. *J. Am. Chem. Soc.* **1950**, *72*, 3396.

saturated aqueous Na_2SO_4. The ether layer was separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried, and concentrated to afford the diol **9** as a crystalline solid (490 mg, 97%), mp 188−190 °C (acetone/light petroleum ether); ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 1.36 (s, 3H), 2.31 (s, 3H), 6.73−6.94 (m, 2H), 7.51 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.2. Found: C, 71.09; H, 7.37.

6-Nor-12-oxo-6,8,10-trichothecatriene (10). To a magnetically stirred solution of the diol **9** (100 mg, 0.45 mmol) in dry benzene (10 mL) at room temperature was added a drop of freshly distilled boron trifluoride etherate. The mixture was stirred for 1 h and then treated with saturated aqueous $NaHCO_3$. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water, dried, and concentrated. Preparative TLC [petroleum ether/EtOAc (49:1)] of the residue afforded **10** as a white crystalline solid (80 mg, 87%) (ether/light petroleum ether); mp 88−89 °C; IR 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 2.26 (s, 3H), 4.21 (d, J = 5.4 Hz, 1H), 6.60 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.22; H, 6.90. Found: C, 77.20; H, 6.77.

The bridged ketone **10** on keeping was transformed slowly into the keto diol **11**; mp 86−87 °C (ether/light petroleum ether); IR 1610, 1745 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.81 (s, 3H), 2.29 (s, 3H), 4.61−4.71 (m, 1H), 6.62−6.72 (m, 2H), 7.09 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.27. Found: C, 71.11; H, 6.98.

Acid-Catalyzed Cleavage of the Bridged Ketone (10). To a magnetically stirred solution of the bridged ketone **10** (40 mg) in THF (5 mL) containing water (1 mL) were added a few drops of dilute H_2SO_4 (10 N) and stirred at ambient tempeature for 24 h. It was diluted with water and extracted with Et_2O. The ether extracts were washed with water, dried, and concentrated to afford an oily residue which eventually solidified (40 mg). This was found to be identical (mp, ^{1}H NMR spectrum) with the keto diol **11** obtained above.

(2*R*,5*R*,12*S*)-6-Nor-12,13-epoxy-6,8,10-trichothecatriene (2). To a mixture of 0.27 mmol of dimethyloxosulfonium methylide (prepared from 10.8 mg (0.27 mmol, 60% in oil) NaH and 60 mg (0.27 mmol) of trimethyloxosulfonium iodide in 4 mL of Me_2SO) a solution of bridged ketone **10** (50 mg, 0.25 mmol) in Me_2SO (4 mL) was added dropwise. The mixture was heated at 55 °C under N_2 for 1.5 h. It was cooled to room temperature, poured into ice cold water, and extracted with ether. The combined organic layers were washed with water and dried. Evaporation of the solvent gave a light yellow oil which was subjected to chromatography (neutral Al_2O_3, petroleum ether) to afford the desired epoxide **2** (40 mg, 75%) as a crystalline solid; mp 56−58 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 2.27 (s, 3H), 2.91 and 3.12 (AB_q, J = 4 Hz, 2H), 4.15 (d, J = 5.4 Hz, 1H), 6.59 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.17, 20.98, 29.82, 41.12, 41.59, 47.68, 66.88, 81.21, 116.50, 121.34, 124.16, 129.29, 138.18, 152.37; *m*/*z* 216.1146 ($C_{14}H_{16}O_2$).

(2*R*,5*R*,12*R*)-6-Nor-12,13-epoxy-6,8,10-trichothecatriene (12). To a magnetically stirred solution of dimethylsulfonium methylide (0.27 mmol) in Me_2SO (5 mL) (containing sufficient THF to avoid freezing) at −10 °C was added dropwise a solution of the bridged ketone **10** (50 mg, 0.25 mmol). The resulting mixture was stirred at −10 °C for 15−20 min (if solidified, the reaction mixture is allowed to warm to room temperature) then at room temperature for 1 h, decomposed with saturated salt solution. The two liquid layers were separated. The aqueous layer was extracted with ether. The combined organic layers were washed with water, dried, and concentrated to afford a pale yellow oil, which was subjected to chromatography (neutral Al_2O_3, petroleum ether) to furnish **12** as a white solid (40 mg, 75%); mp 65−66 °C (light petroleum ether); ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 2.27 (s, 3H), 2.97 and 3.19 (AB_q, J = 4.4 Hz, 2H), 4.17 (m, 1H), 6.61 (s, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.19, 20.99, 28.54, 39.60, 40.20, 49.76, 65.53, 79.10, 116.75, 121.24, 124.23, 128.28, 137.99, 152.27; *m*/*z* 216.1143 ($C_{14}H_{16}O_2$).

(2*R*,5*R*,12*S*)-6-Nor-6,8,10-trichothecatrien-12-ol (13). To a magnetically stirred solution of LAH (5 mg, 0.137 mmol) in dry ether (10 mL) was added a solution of the epoxide **2** (30 mg, 0.138 mmol) in dry ether (5 mL). The resulting mixture was refluxed for 3 h, cooled to room temperature, and decomposed with saturated Na_2SO_4 solution. The ether layer was decanted and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried, and concentrated. The residual material was passed through a short column of neutral Al_2O_3 [petroleum ether/EtOAc (19:1)] to afford **13** as a crystalline solid (30 mg, 99%); mp 81−82 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.32 (s, 3H), 2.25 (s, 3H), 4.22 (d, J = 5.2 Hz, 1H), 6.53 (s, 1H), 6.66 (d, J = 6.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H). Anal. Calcd For $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 77.02 H, 8.14.

(2*R*,5*R*,12*R*)-6-Nor-6,8,10-trichothecatrien-12-ol (14). Method A: $LiAlH_4$ Reduction of Epoxide 12. The reduction of the syn-epoxide **12** (30 mg, 0.138 mol) with lithium aluminum hydride (5 mg, 0.137 mmol) in dry ether (5 mL) was carried out following the same procedure as for the anti-epoxide **2** to give the hydroxy compound **14** as a thick colorless oil (30 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.34 (s, 3H), 2.27 (s, 3H), 4.12−4.15 (m, 1H), 6.64 (s, 1H), 6.71 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H).

Analytical data of the above hydroxy compound could not be obtained. However, the homogeneity of the product was demonstrated by TLC and its ^{1}H NMR spectrum.

Method B: Grignard Reaction of the Bridged Ketone 10. To a magnetically stirred solution of MeMgI [prepared from Mg (7.2 mg, 0.0003 g atom), MeI (44 mg, 0.32 mmol) in dry Et_2O (10 mL)] at 0 °C was added a solution of bridged ketone **10** (50 mg, 0.25 mmol) in dry Et_2O (5 mL). The mixture was brought to room temperature and was stirred there for 15 min. Then it was refluxed for 1 h. The mixture was cooled to 0 °C and was decomposed by adding saturated aqueous NH_4Cl. The two liquid layers were separated. The aqueous layer was extracted with Et_2O. The organic layers were washed with water, dried, and concentrated to afford a thick colorless oil. The residue was passed through a short pad of silica gel [petroleum ether/EtOAc (19:1)] to give the hydroxy compound **14** (48 mg, 89%). This was found to be spectroscopically identical with the product **14** obtained from reduction of epoxide **12**.

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