

Total Synthesis of (\pm)-4-Deoxyverrucarol; A New Route to Trichothecanes via Ring Expansion of Small Ring Compounds

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Received 9 December 1998; revised 26 December 1998; accepted 28 December 1998

Abstract: Total synthesis of 4-deoxyverrucarol (**4**), a trichothecane-type sesquiterpene was achieved via two types of ring expansion reaction, 1,2-rearrangement of **18** and palladium mediated ring expansion reaction of **20**, as key steps providing a new route to trichothecanes.

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Trichothecanes are a group of tricyclic sesquiterpenes isolated from various species of fungi.¹ In general, these compounds comprise an A/B/C ring system and an *exo*-epoxy ring as the common features (Figure 1).

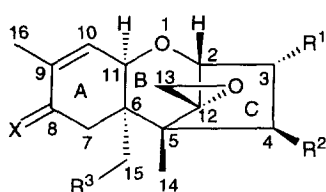
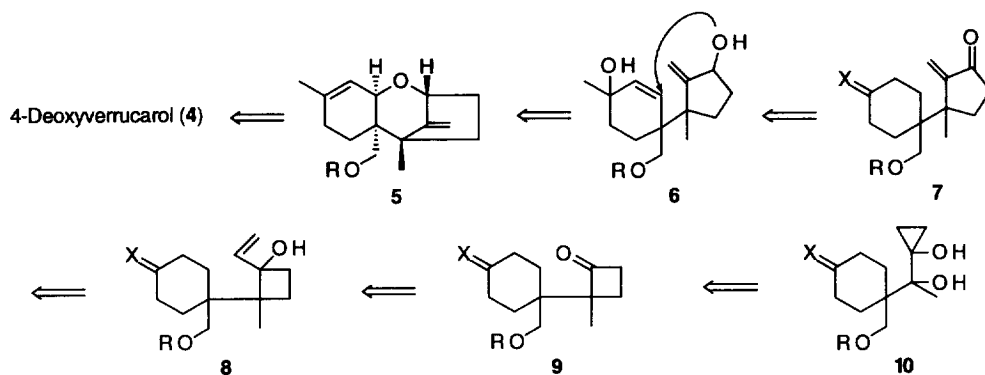


Figure 1

Trichothecinol A	1 : X = O, R ¹ = OH, R ² = OCOCH=CHCH ₃ , R ³ = H
Verrucarol	2 : X = H ₂ , R ¹ = H, R ² = R ³ = OH
Anguidine	3 : X = H ₂ , R ¹ = OH, R ² = R ³ = OAc
4-Deoxyverrucarol	4 : X = H ₂ , R ¹ = R ² = H, R ³ = OH

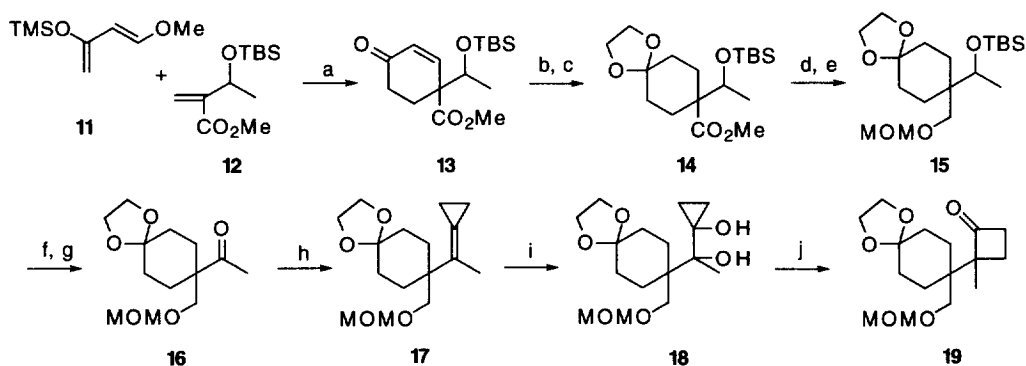
Members of this class exhibit significant biological activities such as antifungal, antiviral, antibacterial, and antitumor activities.² Recently, Iida and Tomioka have reported that trichothecinol A (**1**) exhibited not only potent inhibitory effect against the tumor promotor 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) but also tumor promotion effect in the absence of TPA.³ Therefore trichothecanes are expected to serve as a potential tool in disclosing the mechanism of carcinogenesis. 4-Deoxyverrucarol (**4**)⁴ has been synthesized from verrucarol (**2**)⁵ and anguidine (**3**) for studies on the preparation and development of monoclonal antibodies for trichothecanes. Here we report a new route to racemic 4-deoxyverrucarol via the ring expansion reactions^{6,7} of two types of small ring compounds **8** and **10** as key steps to form **7** and **9**, respectively. The tricyclic compound **5**, a key intermediate to 4-deoxyverrucarol (**4**), could be obtained by the regioselective acid

catalyzed cyclization of the allylic alcohol **6** which in turn could be readily prepared from the enone **7** (Scheme 1).



Scheme 1

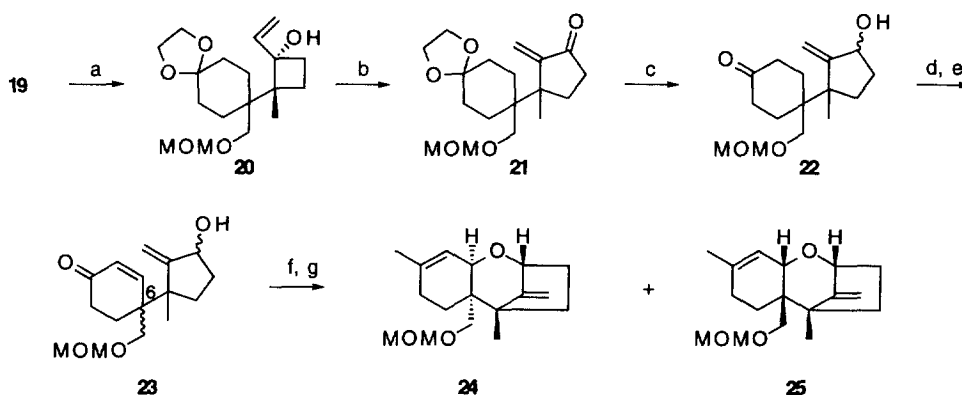
The unsaturated ketone **13** (ratio of diastereomers 2.6:1) corresponding to the A ring part of trichothecanes was obtained *via* Diels-Alder reaction of the silyloxydiene **11**⁸ and the methylenebutyric ester **12**.⁹ Hydrogenation of **13** and successive ketalization provided the ester **14**. The ester **14** was reduced with DIBAL-H and the resulting alcohol was protected as MOM ether **15**. Desilylation of **15**, followed by Swern oxidation, provided the ketone **16**. Wittig reaction of **16** with cyclopropylidetriphenylphosphorane¹⁰ afforded the cyclopropylidene **17**. This reaction proceeded in low yield, presumably due to the bulkiness of the substrate. Dihydroxylation of **17** afforded the diol **18**. We examined various conditions for 1,2-rearrangement⁶ of **18** and found the reaction of **18**, sulfuryl chloride¹¹ and imidazole, followed by addition of Florisil, to be the most effective procedure to obtain the cyclobutanone **19** (Scheme 2).



reagents: a. *o*-dichlorobenzene, 180 °C (96%); b. Pd-C, H₂; c. ethylene glycol, PPTS, heat (90% for 2 steps); d. DIBAL-H, -78 °C; e. MOMCl, *i*-Pr₂NEt (96% for 2 steps); f. TBAF, 50 °C (97%); g. Swern Oxidation (93%); h. cyclopropyltriphenylphosphonium bromide, NaH, heat (27%; 99% based on recovered **16**); i. cat. OsO₄, DABCO, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, *t*-BuOH, H₂O, 0 °C (85%); j. SO₂Cl₂, imidazole, then Florisil (91%).

Scheme 2

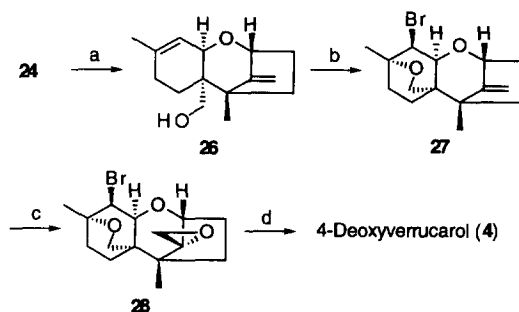
Next, the construction of the trichothecane framework *via* the second ring expansion⁷ was investigated (Scheme 3). The cyclobutanone **19** was stereoselectively converted to the vinylcyclobutanol **20** by treatment with vinylmagnesium bromide in the presence of CeCl_3 .¹² The ring expansion reaction of **20** was achieved by using palladium acetate as a mediator to give the cyclopentanone **21** in high yield. Reduction of **21**, followed by treatment with aqueous 10% HCl, provided a 5.2:1 mixture of the hydroxyketones **22**. The application of Saegusa's method,¹³ resulted in the conversion of hydroxyketones **22** to enones **23** as an inseparable mixture of four diastereoisomers. It was shown from the $^1\text{H-NMR}$ spectrum that the mixture is composed of stereoisomers at the quaternary stereogenic center of the cyclohexanone in the ratio of 1.3:1. The mixture thus obtained was treated with MeLi and the resulting diols were subjected to cyclization under acidic conditions to give a 1:1.3 mixture of the tricyclic compounds **24** and **25**.¹⁴



reagents: a. vinylmagnesium bromide, CeCl_3 , -78°C (97%); b. $\text{Pd}(\text{OAc})_2$ (90%); c. DIBAL-H, -78°C , then 10% HCl (92% for 2 steps); d. TMSCl , NEt_3 , 100°C ; e. $\text{Pd}(\text{OAc})_2$ (79% for 2 steps); f. MeLi, -78°C ; g. CSA (23% of **24** and 30% of **25** for 2 steps).

Scheme 3

The stereoselective introduction of the *exo*-epoxy group at C-12 and -13 positions was performed by the application of the Schlessinger's procedure.^{5a} The MOM group of **24** was deprotected to give 15-hydroxytrichothec-9,12-diene (**26**).¹⁵ Intramolecular bromoetherification with NBS afforded the bromoether **27**, which on treatment with *m*-CPBA stereoselectively provided the epoxide **28** because of the steric congestion between ethano bridge in ring A and *exo*-methylene. Finally, reductive ring opening of **28** with zinc and NH_4Cl furnished (\pm)-4-deoxyverrucarol (**4**) (Scheme 4). The spectral data of the synthetic compound were consistent with the reported ones.^{4a}



reagents: a. CSA, LiBF_4 , heat (50%); b. NBS, 0°C (67%); c. *m*-CPBA, NaHCO_3 (73%); d. Zn, NH_4Cl , 60°C (85%).

Scheme 4

Acknowledgment

J. M. acknowledges a support from the Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

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