CYCLOBUTANE STRATEGY FOR THE SYNTHESIS OF A-RING AROMATIC TRICHOTHECANES

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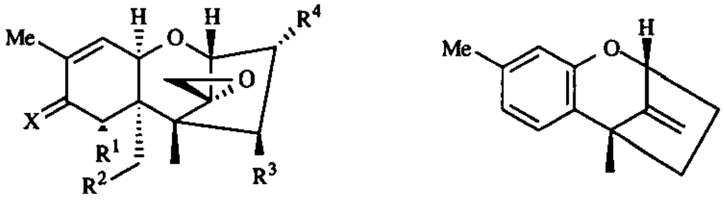
Abstract——A novel synthesis of A-ring aromatic trichothecane (**2**) by the regiocontrolled cyclization of 5-hydroxy-2-(2-methoxymethoxy-4-methylphenyl)-2-methyl-1-methylidenecyclopentane (**10**), which was prepared *via* the 2-phenylcyclobutanone (**6**) and cyclobutanols (**7** and **8**) and the 2-methylidene-3-phenylcyclopentanone (**9**), was achieved.

The trichothecanes are a group of structurally related sesquiterpenes isolated from various species of fungi.[1] 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 so far.[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] Here we wish to report the novel synthesis of A-ring aromatic trichothecane (**2**) which could be a potential intermediate for the synthesis of trichothecanes (depicted in Figure 1 together with the general structure (**1**) of trichothecanes) based on cyclobutane strategy.

Figure 1

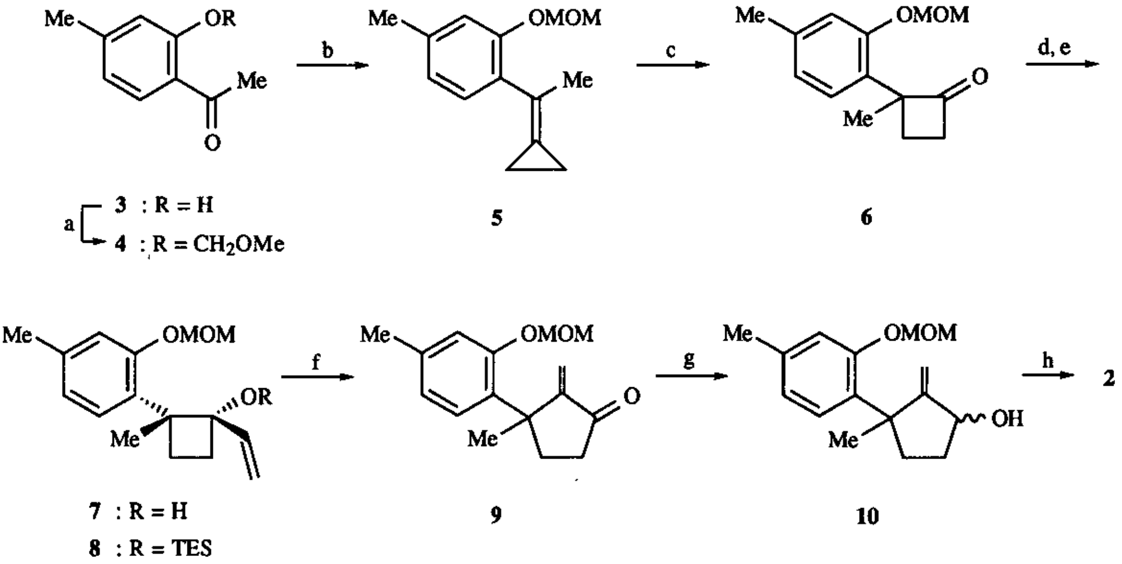


1 **2**

This paper is dedicated to the memory of the late Professor Yoshio Ban.

Thus,† the ketone (**4**) prepared (76%) by methoxymethylation of **3**[7] was converted into the cyclopropylidene derivative (**5**) (96%) by Wittig reaction with cyclopropylidenetriphenylphosphorane and then the cyclobutanone (**6**) (92%) by the tandem epoxidation and 1,2-rearrangement of **5**. Grignard reaction of **6** afforded stereoselectively the vinyl alcohol (**7**) (93%) as a sole product. The silyl ether (**8**) obtained (99%) by silylation of **7** was then subjected to the palladium mediated ring expansion[5j] to give the enone (**9**) (63%). Finally, the allyl alcohol (**10**) (*ca.* 1 : 1 diastereoisomeric mixture) prepared (88%) by the reduction of **9** was treated with acid to furnish the initial target (**2**) (29%) resulted from the deprotection followed by cyclization. Thus, we could develop a cyclobutane strategy for the synthesis of A-ring aromatic trichothecane (**2**) which could be a potential synthetic intermediate of trichothecanes (**1**).

Scheme 1



Reagents and conditions: a, $MeOCH_2Cl$ (MOMCl), NaH, THF, room temperature, 1 h; b, cyclopropyltriphenylphosphonium bromide, NaH, THF, 62 °C, 12 h; c, *m*-chloroperbenzoic acid (*m*-CPBA), CH_2Cl_2, 0 °C, 30 min; d, $CH_2=CHMgBr$, $CeCl_3$, THF, -78 °C→room temperature, 1 h; e, triethylsilyl trifluoromethanesulfonate (TESOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min; f, $PdCl_2(MeCN)_2$, $Pd(OAc)_2$, THF, reflux, 3 h; g, $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 15 min; h, 70%, $HClO_4$, MeOH, room temperature, 30 min.

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† All new substances exhibited spectroscopic data [ir, ^{1}H-nmr (300 mHz) and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data.

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