A NOVEL ROUTE TO DIVERSE FUSED OXABICYCLO[3.2.1]OCTANES——A RING MODIFIED TRICHOTHECANES

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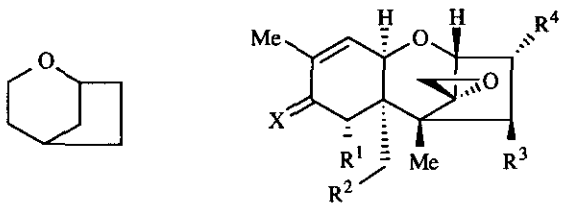
Abstract——The novel A-ring modified trichothecane type of compounds (**9a, b, 11, 13, 14a,b, 15a,b,** and **16a,b**), were synthesized starting from the A-ring aromatic diol (**6**).

Oxabicyclo[3.2.1]octane ring system (**1**) *constitutes a basic skeleton of various trichothecane type of* sesquiterpenes (**2**, general structure of trichothecanes) (Figure 1).

Figure 1



1 **2**

Members of this class have been known to exhibit significant biological activities such as antifungal, antibacterial, antiviral, and insecticidal properties[1] and also some of this family inhibit the growth of tumor cells.[2] Because of these biological activities and unique structural feature having oxabicyclo[3.2.1]octane ring system, a number of their synthesis have been published so far.[3] During our studies[4] 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 the benzooxabicyclo[3.2.1]octane ring system (**5**),[5] since such compounds have been shown to possess significant *in vivo* antileukemic activity.[6] This approach involves the regiocontrolled ring expansion of the vinylcyclobutanol (**3**) to the allyl alcohol (**4**) and the regiocontrolled cyclization of **4** to **5** having the basic

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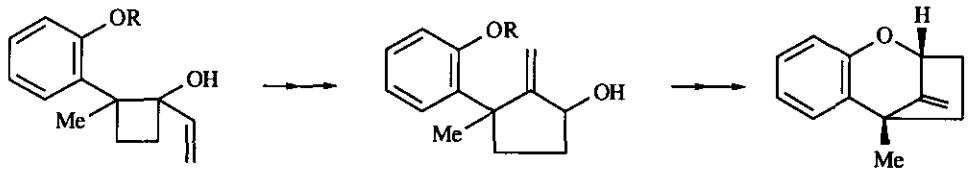
This paper is dedicated to prof. Shigeru Oae on the occasion of his 77th birthday

carbon framework of trichothecanes as key steps (Scheme 1).

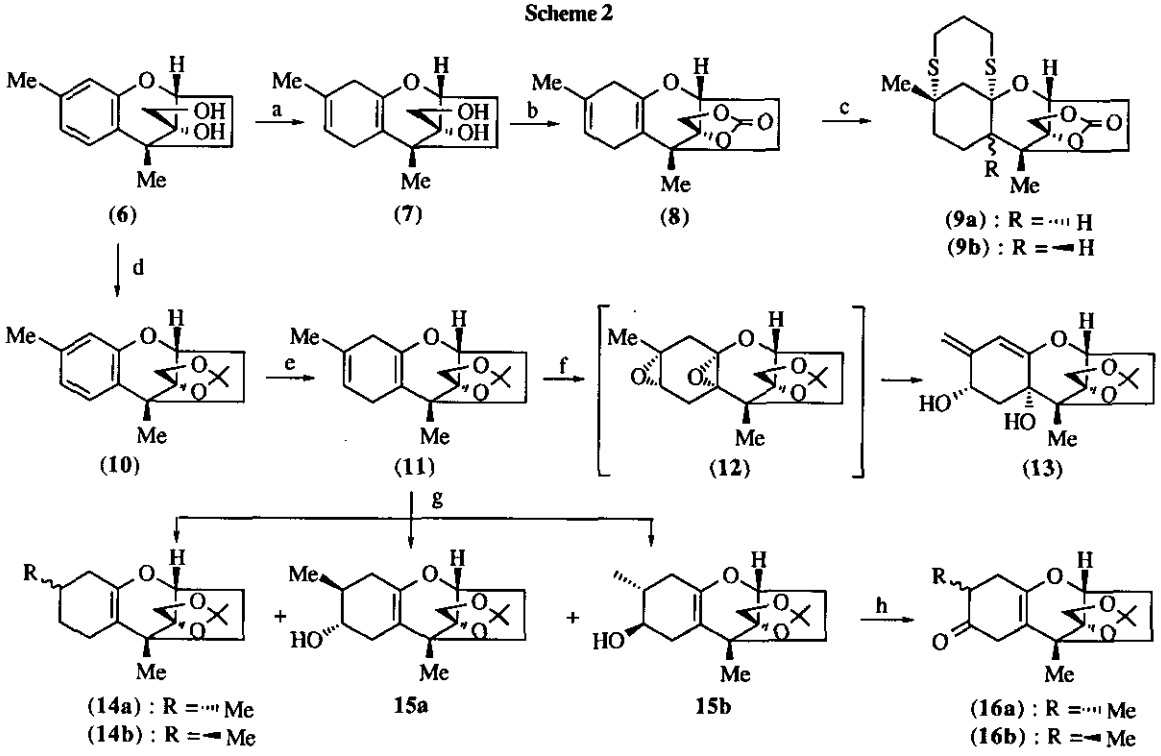
Scheme 1



3 4 5

Having these findings in hand, we have been involved in the synthesis of A-ring modified trichothecane type of compounds because of these biological interests. Here, we describe the synthesis of novel trichothecane analogues.† (Scheme 2)

Scheme 2



Reagents and Conditions: a, Li, liq. NH_3, EtOH, THF, –78 °C; b, $Cl_3CCOCCl_3$, Et_3N, CH_2Cl_2, room temperature, 1 h; c, $HSCH_2CH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temperature, 30 min; d, ref. 5e; e, Li, liq. NH_3, *t*-BuOH, THF, –78 °C, 2 h; f, *m*-Chloroperbenzoic acid (*m*-CPBA), $NaHCO_3$, CH_2Cl_2, room temperature, 1 h; g, $BH_3{\cdot}SMe_2$, THF, room temperature, 6 h; then 30% H_2O_2, 3N NaOH, room temperature, 24 h; h, $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 30 min; then Et_3N, 0 °C→room temperature, 2.5 h.

The benzooxabicyclo[3.2.1]octane (**6**)[5e] was subjected to Birch reduction (94%) to give the diene (**7**), the carbonate (**8**) (100%) of which was then treated with 1,3-propanedithiol in the presence of $BF_3 \cdot Et_2O$ to afford the mixture of the eight membered dithianes (**9a** and **9b**; 1 : 1) (71%). The diene (**11**), prepared (100%) from Birch reduction of the acetonide (**10**) was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to give the conjugate diene (**13**) (33%) as a sole product in place of the initially expected diepoxide (**12**). Next, the diene (**11**) was subjected to the hydroboration-oxidation process to give the mixture of the alcohols (**15a** and **15b**; 1 : 1) (38%) together with the mixture of **14a** and **14b** (1 : 1) (33%).[7] Finally, the mixture of the alcohols (**15a** and **15b**) was converted into the diastereoisomeric mixture of the ketones (**16a** and **16b**; 1 : 1) (80%) by Swern oxidation. Thus, we could prepare the novel A-ring modified trichothecanes.[8]

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7. At the moment, the reason for the formation of anomalous amount of **14a** and **14b** is not clear.

8. At the moment, the stereochemistries of all new compounds were tentatively assigned as shown mainly based on these spectroscopic data.

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