A FORMAL TOTAL SYNTHESIS OF XANTHORRHIZOL BASED ON NUCLEOPHILIC OPENING OF VINYLOXIRANE BY ARYLCOPPER REAGENT

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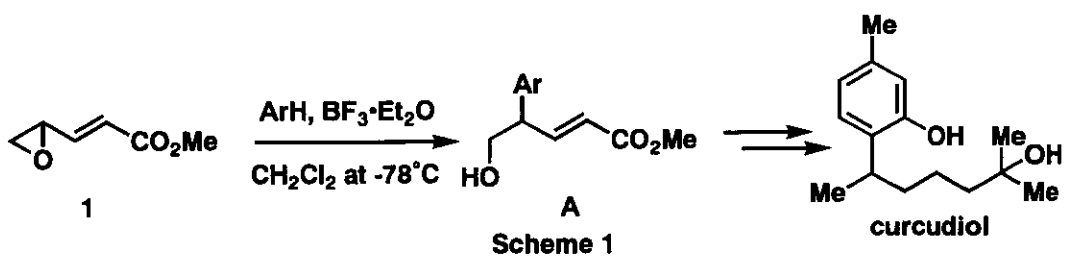
Abstract -A formal total synthesis of xanthorrhizol was achieved in short step sequence involving the nucleophilic opening of methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) by arylcopper reagent.

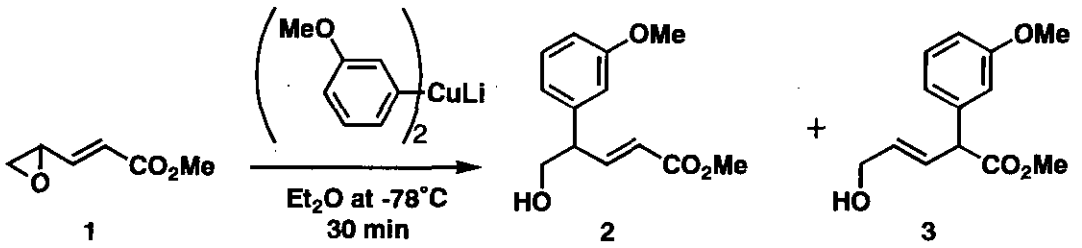
The phenolic bisabolane sesquiterpene, xanthorrhizol, was isolated from rhizomes of *Curcuma xanthorrhiza* Roxb. and used as a popular remedy in gall and liver disorders.[1] In the synthesis of this type bisabolane sesquiterpenes, the key step is the construction of desired connection between aromatic ring and side chain moiety. The first synthesis of xanthorrhizol requires eleven steps begining with aromatic ketone having desired functionality.[2] Meanwhile, we reported the novel syntheses of several bisabolane sesquiterpenes such as curcudiol from key intermediates (**A**), which was obtained by our developed nucleophilic opening of methyl 4,5-epoxy-(2*E*)-pentenoate (**1**) with polymethoxytoluene in the presence of $BF_3.Et_2O$.[3] In this synthesis, the key reaction proceeded in high yield and showed the generality by arenes. However, the reaction coud not be applied to the synthesis of xanthorrhizol because it was hard to achieve the C-C bond formation at *m*-position of electron-releasing function such as methoxyl or hydroxyl group (Scheme 1).



Scheme 1

More recently, we investigated the nucleophilic opening of **1** by various arylcopper reagents.[4] The reaction made it possible to form the C-C bond at the desired every position on benzene ring. For example, the reaction of Gilman copper reagent obtained from *m*-bromoanisole with **1** gave 4-arylated product (**2**) as a main product along with 2-arylated product (**3**) (Scheme 2).[5] In this paper, we wish to report the short step synthesis of xanthorrhizol by adopting our newly developed arylation of **1** by copper

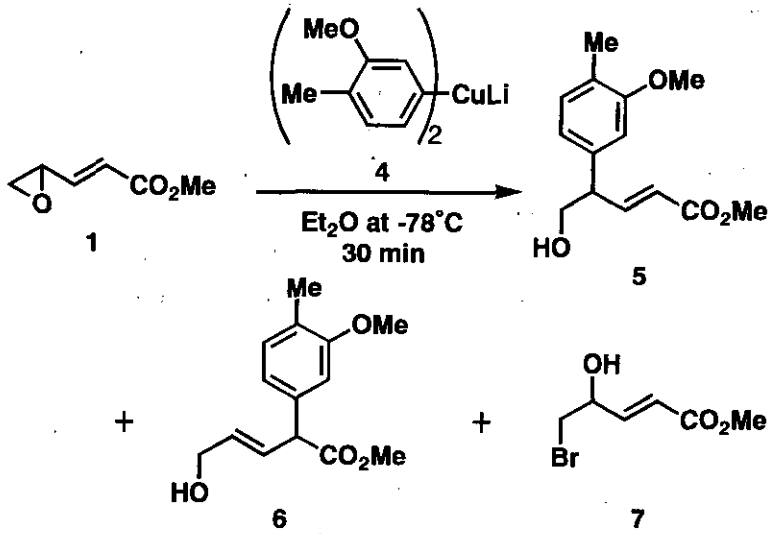
reagent as a key step and explanation of the unique role of an additional boron trifluoride in determining regioselectivity.



2 + 3 = 46%, 2 : 3 = 80 : 20

Scheme 2

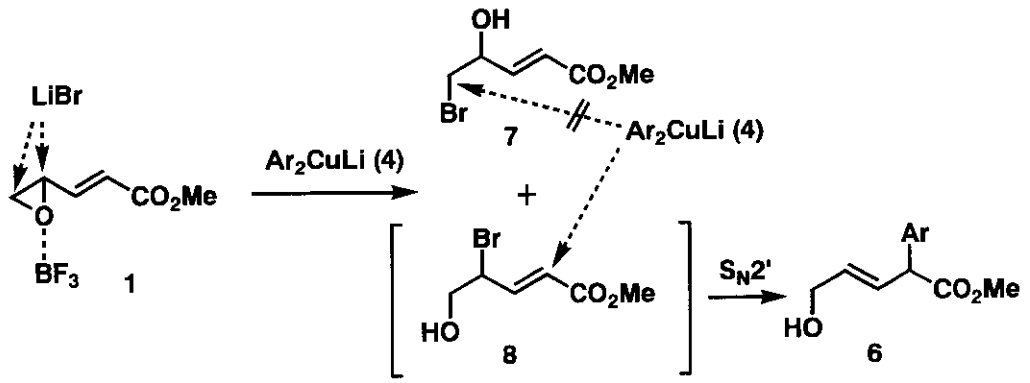
The nucleophilic opening of **1** by the Gilman copper reagent (**4**) obtained from 4-bromo-2-methoxytoluene[6] gave an unseparable mixture of 4-arylated product (**5**)[7,8] and 2-arylated product (**6**)[7,8] in 31% yield (Scheme 3). The regioselectivity (**5**:**6**=86:14) was estimated by comparing the corresponding integration intensities due to the olefinic protons in the ^{1}H-nmr spectrum of the mixture. The discontented yield encouraged us to add $BF_3.Et_2O$ to the reaction mixture because of an expectation of activation of epoxy ring followed by C-O bond cleavage at C_4-position. As a result, additional $BF_3.Et_2O$ caused the yield to increase but the regioselectivity to decline along with the unexpected bromohydrine (**7**).



5 + 6 (%)	5 : 6	7 (%)	
31	86 : 14	0	in the absence of BF_3•Et_2O
63	41 : 59	19	in the presence of BF_3•Et_2O

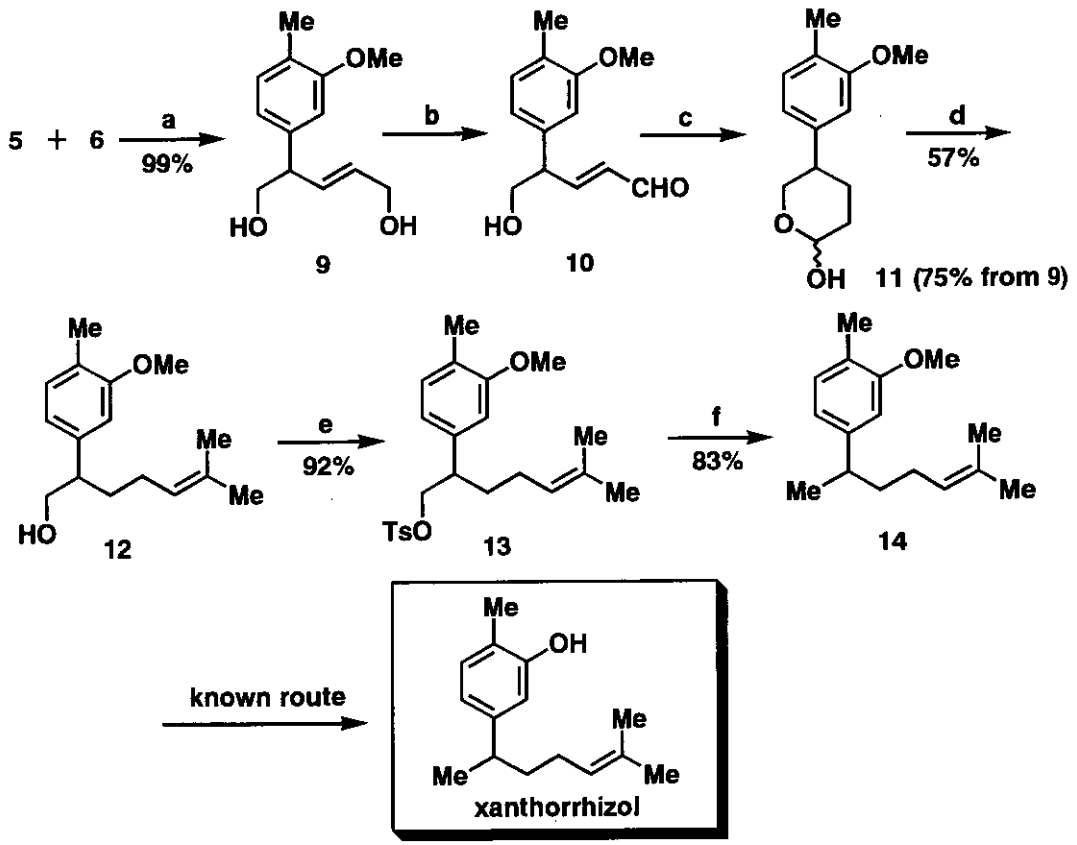
Scheme 3

The regioselectivity reversion and the formation of **7** can be explained by considering partial two steps conversion by way of bromohydrine (**8**) as described below (Scheme 4). In the absence of $BF_3.Et_2O$,



Possible reaction mechanism in the presence of BF_3•Et_2O

Scheme 4



Reagents and conditions: a) $LiAlH_4$, THF at 0°C (1 h); b) MnO_2, CH_2Cl_2, benzene (3 h); c) H_2, $Pd(OH)_2$, MeOH (2 h); d) *n*-BuLi, isopropyltriphenylphosphonium iodide (20 eq.), benzene at 0°C (12 h); e) TsCl, pyridine, (3 h); f) $NaBH_4$ (5 eq.) at 80°C (2 h).

Scheme 5

this reaction sequences compete with direct nucleophilic opening of **1** by **4** with high S_N2 regioselectivity. On the other hand, in the presence of $BF_3.Et_2O$, BF_3 assisted nucleophilic opening of **1** by LiBr derived from PhLi and CuBr in preparation step of copper reagent may occur with the formation of bromohydrins (**7**) and (**8**). Subsequently, the generated **8** reacts regioselectively with reagent (**4**) in S_N2' manner *in situ* to afford **6**. While, primary bromide (**7**) does not react with **4** at all and is consequently isolated after quenching.[9] However, the poor regioselectivity and the difficulty of separation between **5** and **6** were not serious problems for the synthesis of xanthorrhizol because both **5** and **6** could be converted to the same compound (**9**) as referred to later. Reduction of the mixture with $LiAlH_4$ gave diol (**9**) in 99% yield. Selective oxidation of **9** with activated MnO_2 followed by catalytic hydrogenation provided a 1:1 mixture of lactol (**11**) in 75% overall yield. Wittig reaction of **11** with excessive isopropylidene ylide afforded alcohol (**12**) in 57% yield. At final stage, tosylation (92%) of **12** followed by reduction (83%) with $NaBH_4$ in DMSO provided the deoxygenated compound (**14**). Conversion of **14** to xanthorrhizol has been already accomplished by Rao *et al.*[2] The spectroscopic data of the present **14** were in good agreement with the reported data [2] (Scheme 5).

In conclusion, nucleophilic opening of **1**, vinyloxirane linked to ester fuction, by arylcopper reagent provides a new efficient route to the synthesis of phenolic bisabolane sesquiterpenes.

ACKNOWLEDGEMENTS

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7) Satisfactory analytical data were obtained for all new compounds.

8) The ^1H nmr spectrum showed alkenic proton peaks for **5** at δ 7.13 (1 H, dd, J = 15.6, 7.0 Hz), 5.90 (1 H, d, J = 15.6 Hz), for **6** at δ 6.10 (1 H, dd, J = 15.6, 8.3 Hz), 5.72 (1 H, dt, J = 15.6, 5.4 Hz), C_2 proton peak for **6** at δ 4.28 (1 H, d, J = 8.3 Hz), C_5 proton peak for **6** at δ 4.12 (2 H, d, J = 5.4 Hz), C_5 proton peak for **5** at δ 3.88 (2 H, d, 7.0 Hz), and C_4 proton peak for **5** at δ 3.63 (1 H, q, J = 7.0 Hz). The ir absorption suggested the existence of hydroxy function (3440 cm^{-1}).

9) Detailed discussion based on an experimental proof concerning the same type reaction as the present arylation will be described in ref 5.

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