One-Step Synthesis of Norabietane Core and its Alkylation to Abietane Analogs

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Abietane is a tricyclic diterpenoid present in many types of alcohols, ketones, and acids. Since it has a wide variety of bioactivity effects, abietane synthetic methods have been extensively studied and now various types are present.

Carnosic acid type tricyclic diterpenoids are one kind of abietane including 10-carboxy group (carnosic acid, pisiferic acid) or 1-oxoferruginol (Figure 1).[1–3] They exhibit various biological activities such as antibacterial, antioxidant, anti-inflammatory, cytotoxic properties, and antimicrobial activity.[4,5] Although it has been known to be difficult to introduce the carboxy group at C-10 position, many groups have achieved it in four ways (Figure 2).

A simple approach is the A-B-C linear method. Meyer *et al*. reported the synthesis of carnosic acid series from decalone **a** and Uda *et al*. reported the synthesis of (+)-pisiferol from decalone **b** by employing Robinson annulation as a key.[6,7]

The second method is to start from B—C ring to construct C ring lastly. Tu *et al*. reported the intermediate of pisiferic acid starting from 2,7-dihydroxynaphthalene which was converted to β-ketoester **c**, by three-steps: Birch-reduction, hydrolysis, and carboxylation. The β-ketoester **c**, was cyclized with methyl vinyl ketone (MVK) and followed by functional group modifications to the intermediate of pisiferic acid.[8] Mukherjee *et al*. reported the synthesis of pisiferic acid series from tetralone **d**.[9,10]

The third method is to synthesize an abietane model skeleton from A to C ring **e** by connecting B ring by utilizing Friedel–Craft cycloalkylation. Pan *et al*. obtained carnosic acid analog from bicyclic intermediate **e** obtained from alkylation of 5,5-dimethyl-1,3-cyclohexanedione with 2-substituted aryl iodethane.[11a] Most of the cyclization methods are performed by intramolecular Friedel–Crafts cyclization using Lewis acid in Majetich's pioneering work.[11b]

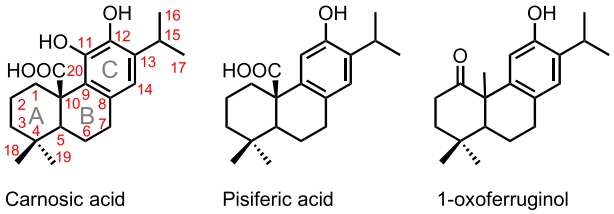

Figure 1. Carnosic acid type tricyclic diterpenoids.

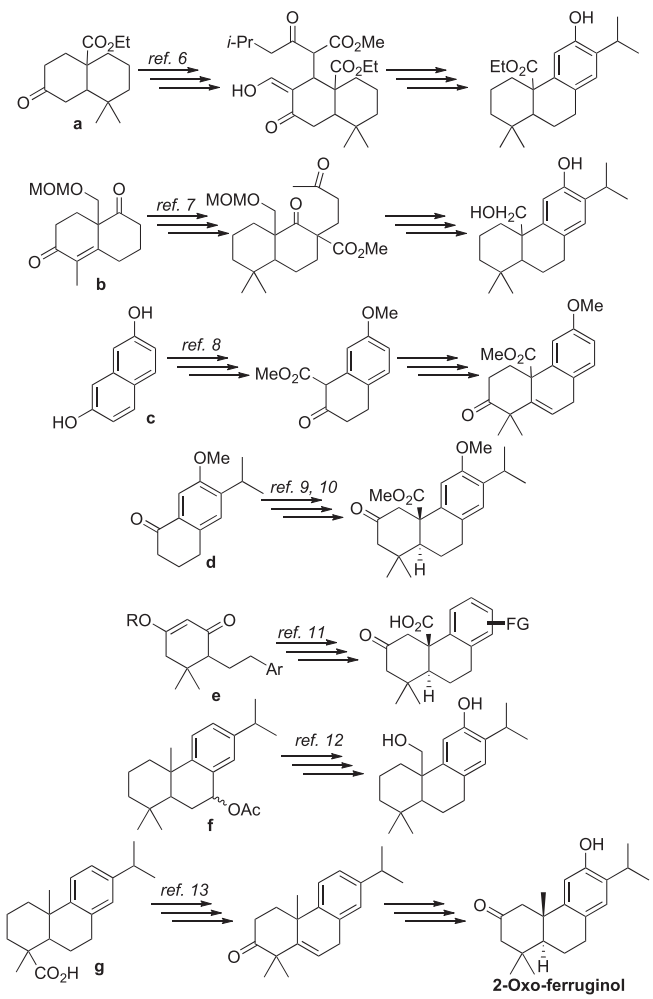

Figure 2. Typical synthetic approaches toward abietanes.

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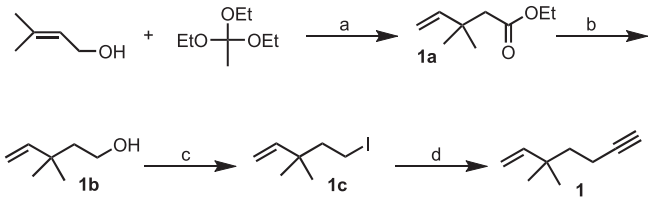
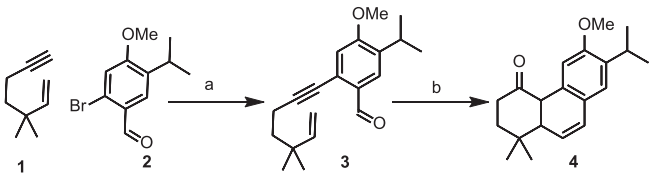


Scheme 1. Preparation of **1**. (a) Phenol, 85% (b) lithium aluminum hydride, DE, 99% (c) imidazole, triphenyl phosphine, iodine, DCM, 75% (d) lithium acetylide ethylenediamine complex, THF/DMSO solution, 85%.



Scheme 2. Preparation of **4**. (a) $PdCl_2(PPh_3)_2$, CuI, TBAI, Et_3N, 80 °C, 82%. (b) $Cu(OTf)_2$ (5 mol %), hydrogen atmosphere, DCE, rt, 65%.

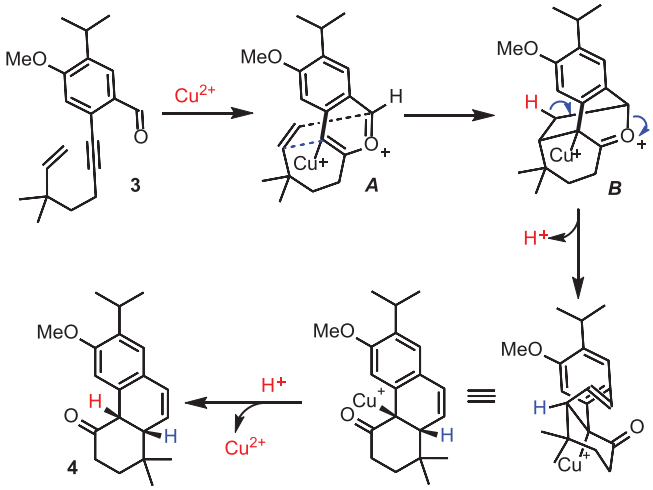
In the final case, several abietanes have been synthesized from pre-existing abietane cores (**f** or **g**) by functional group modification.

Matsumoto *et al*. reported the synthesis of (+)-pisiferol and (+)-2-oxoferruginol by from tricyclic compounds.[12,13]

In a previous study, we reported efficient synthesis of 1-oximiltirone and arucadiol using copper-catalyzed enynal cyclization as a key-step.[14] We used the approach of synthesizing C-ring first and constructed A and B-rings simultaneously. The approach using transition metals is a time-saving convenient method.[15–18] This method has a drawback lacking possibility in introducing C10-alkyl group in the key group in abietane natural products. Thus, we started to investigate introducing various functional groups at the C-10 position through LDA treatment at tricyclic compound. Our research goal is to functionalize norabietanes with C-10 position alkylation including hydroxymethylation.

First, substrates **1** and **2** should be prepared. Enyne **1** has been prepared by the well-known sequences (Scheme 1). After forming the ester **1a** from 3-methyl-2-buten-1-ol and triethyl orthoacetate by Johnson-Claisen rearrangement, reduction to **1b** and iodination to **1c** were performed. After that, enyne **1** was completed by attaching alkyne directly with a lithium acetylide ethylenediamine complex.[19] Substrate **2** was obtained through methylation, formylation, and bromination from 2-isopropyl phenol.[14] Enyanal **3** was successfully synthesized by Sonogashira coupling between the substrates **1** and **2**.

Second, cyclization of enynal **3** in the presence a catalytic amount of $Cu(OTf)_2$ was carried out under argon atmosphere. The reaction proceeded well but resulted in forming our product **4** along with the further oxidized product **5** as a by-product. This might be containing some oxygen under argon atmosphere. To eliminate the influence of oxygen from the reaction medium, we carried out this



Scheme 3. Mechanism of copper-catalyzed cyclization to *cis*-fused tricycle **4**.

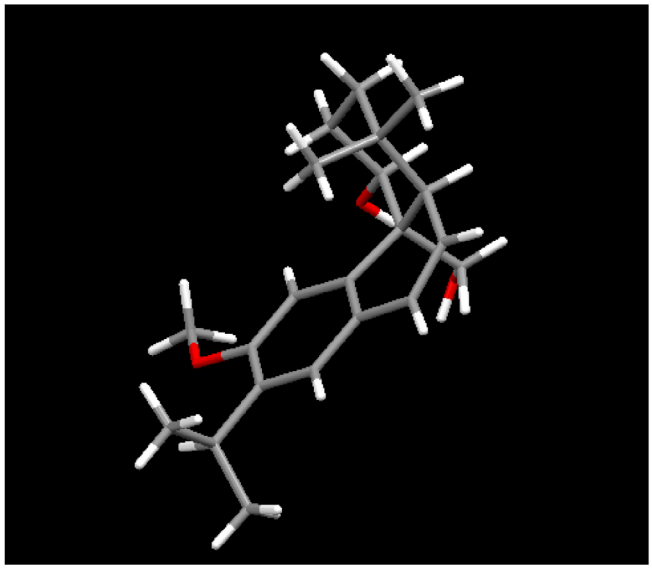


Figure 3. 3D structure of **5e**' (*cis*-type).

catalytic reaction under hydrogen atmosphere. As a result, only double bond is created at the target position of the B-ring giving only the product **4** (Scheme 2).

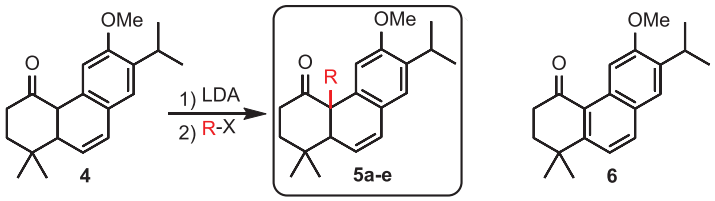
Copper catalyst effectively catalyzed the formation of 6-6-6 fused ring **4**. An efficient way to create a 6-6-6 fused ring is the intramolecular [4 + 2]-benzannulation of enyne or alkyne catalyzed by transition metal compounds.[15–16,20] Intramolecular cycloaddition reactions using rhodium, platinum, thallium and palladium catalysts have been extensively studied for a long time.[17,21] However, the applicability and diversity of copper or gold catalyst for intramolecular cycloaddition reaction have been few studied in the last 20 years.[14,18] Yamamoto *et al*. first reported the synthesis of naphthylketone via intramolecular [4 + 2]-benzannulation catalyzed by $AuBr_3$ or $Cu(OTf)_2$ catalysts. And they extended the study to a 6-6-6 fused ring system obtained by intramolecular cyclization.[22,23] According to the

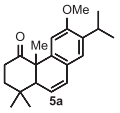
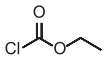
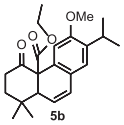
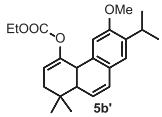
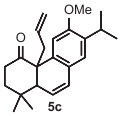
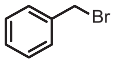
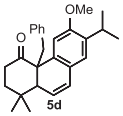
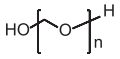
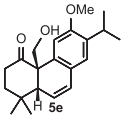
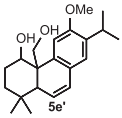
report by Yamamoto *et al*., 6-6-6 fused ring is initially synthesized through copper-catalyzed cyclization. Therefore, *cis*-type cyclic compounds were formed (Scheme 3).[24] Based on this, we could selectively obtain 6-6-6 tricyclic skeletons from enynal **3** in high yield via copper catalytic reaction.

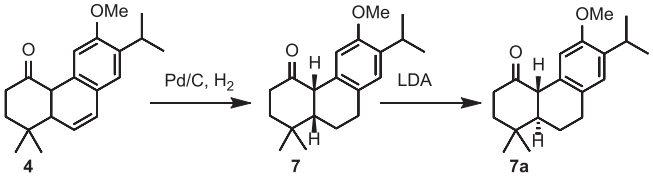
Third, we selected LDA as a base to effectively introduce several functional groups at the C-10 position of **4**. Due to the carbonyl group at C-1 position, it is possible to introduce functional group at C-10 position by LDA (Table 1). A simple functional group, methyl group, has been tried (entry 1). Methylation to **5a** was successful at the target location using LDA and methyl iodide. After confirming that methylation was successful, direct introduction of ester was attempted (entry 2). Acylation was performed using ethyl chloroformate with LDA. The result confirmed that *C*-acylation of LDA did not occur. However, *O*-acylation of the enolated keto group occurred to obtain **5b**'. After confirming that it was difficult to directly introduce ester, other alkylations have been accomplished by this method. Allyl is a useful functional group (entry 3), in which **5c** can be changed to other functional groups by Wacker oxidation or Prins reaction.[25,26] As a result of allylation using allyl bromide with LDA, the target compound **5c** was obtained along with its oxidation product **6** in 55% and 27% yields, respectively. Using a similar concept, an attempt was made to introduce a benzyl group, which can show a possibility to introduce other functional groups (entry 4). We performed benzylation using benzyl bromide and successfully obtained **5d** with a benzyl group at the C-10 position in 81% yield. Note that there was no oxidized compound **6** formed in benzylation. In addition, it has been reported that a carbonyl group can be introduced next to the phenyl group by using Ru catalyst.[27]

Because of the simple chain structure of the polymer paraformaldehyde, it could be predicted that alcohol group will be easily introduced (entry 5). Since paraformaldehyde is insoluble in organic solvents, it was added and stirred at the beginning of the reaction. As a result, **5e**' involving both *C*-alkylation and reduction was produced instead of the target

Table 1. Reaction table of LDA from **4**.



Entry	Reagent	Desired	Results	Isolated yield(%)
1	MeI		**5a**	65
2				71
3			**5c** : **6** = 2 : 1	55 for **5c**
4			**5d**	81
5				79
6	CH_3OCH_2-Cl	**SM recovered**	**No Rxn**	0



Scheme 4. Synthesis of **7a**.

compound **5e**. This **5e**' was obtained as a solid. Data from NMR, mass spectroscopy, and its X-ray crystallography could confirm the correct structure (Figure 3).[28] A sample for X-ray analysis was obtained by gradually crystallizing a compound separated by flash silica gel chromatography in ethyl acetate/hexane solution. According to X-ray crystallography, this structure was confirmed to harbor A-ring and C-ring as *cis*-type. Finally, we attempted to introduce a MOM group, because this is rather easy to convert to a free hydroxyl group but resulted in failure when we used MOM—Cl. Thus, sodium iodide was added to increase reactivity by changing chloride to iodide, but no reaction occurred at **4** (entry 6).

In other to extend the application of the norabitane core **4**, we have attempted hydrogenation to **7** and alkylated with MOM-Cl again. Hydrogenation using Pd/C under one atmosphere of hydrogen was conducted smoothly to afford **7** quantitatively. The LDA reaction of **7** with MOM-Cl and NaI as an additive confirmed the formation of a new compound instead of the target compound. As a result of analyzing new compound through NMR study, MOM-Cl did not participate in the reaction but epimerization did occur in the presence of LDA. The result confirmed that the protons of C-5 and C-10 in **7** were present in different directions of isomer, *trans*-type **7a** (Scheme 4).

The synthesis of **4** from enynal **3** was obtained under argon atmosphere using a transition metal copper catalyst along with a small amount of **6**. In the presence of oxygen atmosphere, a major product was a fully conjugated naphthalene substructure **6**. Thus, this reaction proceeded under hydrogen atmosphere that can effectively exclude oxygen, promoting the formation of target **4**. LDA base was used to introduce various functional groups at C-10 in tricyclic compound **4**. Methylation, allylation, and benzylation using LDA were successful. And *C*-alkylation and reduction occurred with paraformaldehyde. *O*-acylation occurred with ethyl chloroformate. Epimerization occurred under the LDA base, confirming the formation of **7** to **7a**. This increases the possibility of synthesizing additional types of abietane. In this regard, further study to extend the scope in natural product synthesis are in progress in our laboratory (Supporting Information SI).

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Supporting Information. Additional supporting information is available in the online version of this article.

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28. CCDC 2035343 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailingdata_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

