Communication to the Editor

Synthesis of 2,2-Dialkyl Chromanes by Intramolecular Ullmann C–O Coupling Reactions toward the Total Synthesis of D-α-Tocopherol

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The complete synthesis of D-α-tocopherol was achieved using our developed-Ullmann C–O coupling reaction as a key reaction. The synthesis of the core structure of D-α-tocopherol, which is a chiral chromane, has never been reported using intramolecular Ullmann C–O coupling reactions owing to the low reactivity of electron-rich iodoarenes with tertiary alcohols. Because the developed intramolecular C–O coupling reactions prefer electron-rich iodoarenes with tertiary alcohols, we successfully synthesized the chiral chromane core and achieved the total synthesis of D-α-tocopherol.

Key words Ullmann C–O coupling reaction; D-α-tocopherol; 2,2-dialkyl chromane

(2*R*,4′*R*,8′*R*)-α-Tocopherol[1,2] or D-α-tocopherol (**1**), a chemical form of vitamin E, is important for the human body owing to its biological activities.[3–6] It is known that vitamin E is an antioxidant protecting us from free radicals in the metabolic process.[4] In recent studies, the applications of the biological activities of the tocopherols were refocused. It was reported that an unnatural L-α-tocopherol derivative, *ent*-NP843, had inhibitory activity against L-MDM2-L-p53, while D-α-tocopherol derivative, NP843, did not.[7] Another DL-tocopherol derivative, γ-VE5, exhibited an anti-tumor efficacy in phosphatase and tensin homolog (PTEN)-negative cancer cells through PHLPP1-facilitated Akt inactivation.[8] Moreover, there are many reports on bioactive natural compounds containing chromane cores, which are the key structure of tocopherols. Tetrahydrocannabinol (THC),[9] cochlearol B,[10] and strongylophorine-2[11] are well-known examples (Fig. 1), and they showed biological activities such as those resulting from anti-Alzheimer's disease, anti-tumor, anti-inflammation, anti-cancer, and anti-liver fibrosis. Thus, the development of new methods for the synthesis of chromane cores is important.

The synthetic methodology of chromane cores was developed for vitamin E production. The artificial synthesis of *all-rac*-α-tocopherol was published in 1938.[12,13] Subsequently, researchers have focused on developing numerous different methodologies for the synthesis of chromanes.[14–20] However, we are currently interested in the application of Ullmann C–O coupling reactions to synthesize natural products containing cyclic ether.[21–23] This method could be used for the reaction with sterically hindered secondary alcohols using excess amounts of strongly coordinating monodentate ligands[23] (Chart 1). Therefore, we envisioned that our method could be applied to intramolecular C–O coupling reactions for tertiary alcohols with aryl iodides.[24,25] Recently, Reisman *et al.* reported the synthesis of 2,2-dialkylchromane prepared from a tertiary alcohol with bromoarene in the total synthesis of (+)-Psiguadial B[26] by copper-catalyzed coupling reactions, which were originally investigated by Satyanarayana and colleagues.[27,28] In the Satyanarayana's catalyst system, a bridgehead alcohol might be necessary[26] or substitutions in 4-positions[28] are required to enhance the reactivity by Thorpe–Ingold effect.[29] Furthermore, the product yields of reported compounds were unsatisfactory except in some cases. In this manner, reactions posed a challenge to prepare 2,2-dialkylchromane containing electron-donating groups in the benzene ring because of steric bulkiness, acidity of the ter-

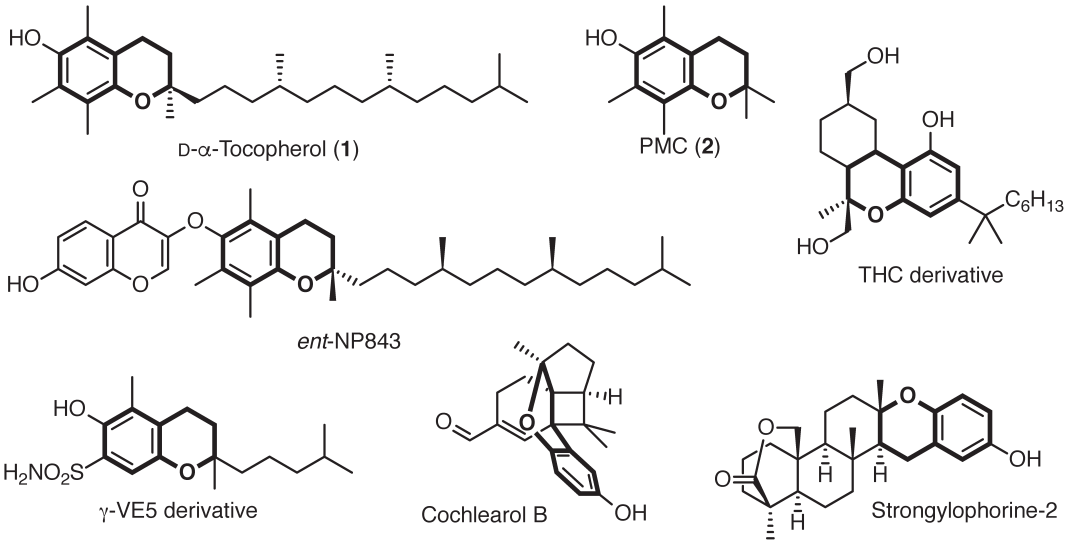

Fig. 1. D-α-Tocopherol, PMC, and Chromane Derivatives

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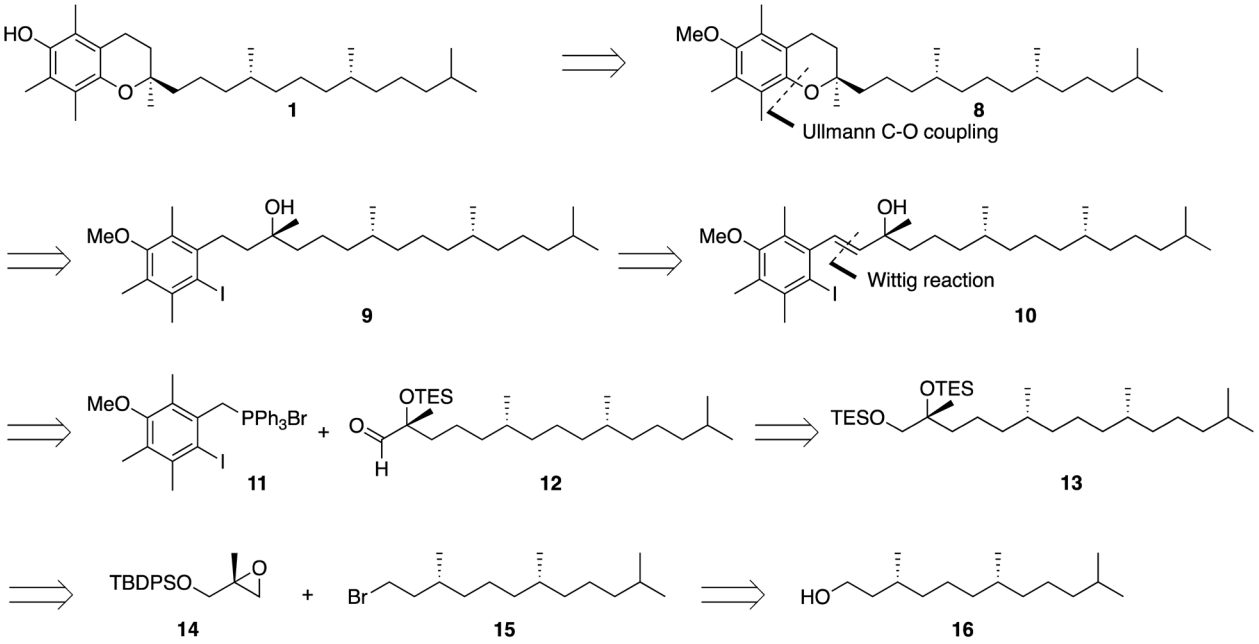


Fig. 2. Synthetic Strategy of D-α-Tocopherol

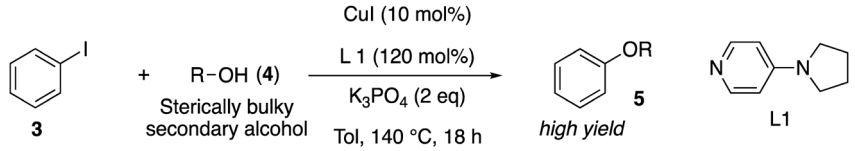


Chart 1. Ullmann C–O Coupling Reactions of Sterically Bulky Alcohols with Iodoarene **3**

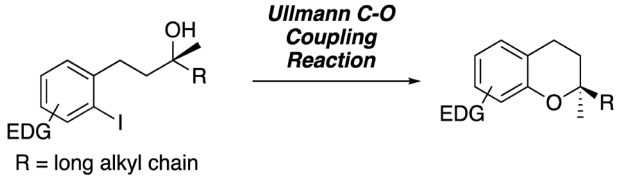


Chart 2. Synthetic Strategy for the Synthesis of D-α-Tocopherol

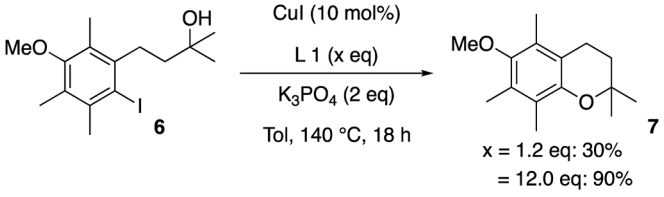


Chart 3. Ullmann C–O Coupling Reactions for the Synthesis of Protected PMC

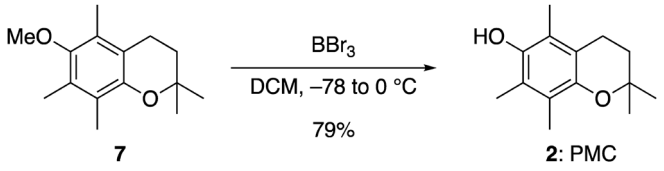
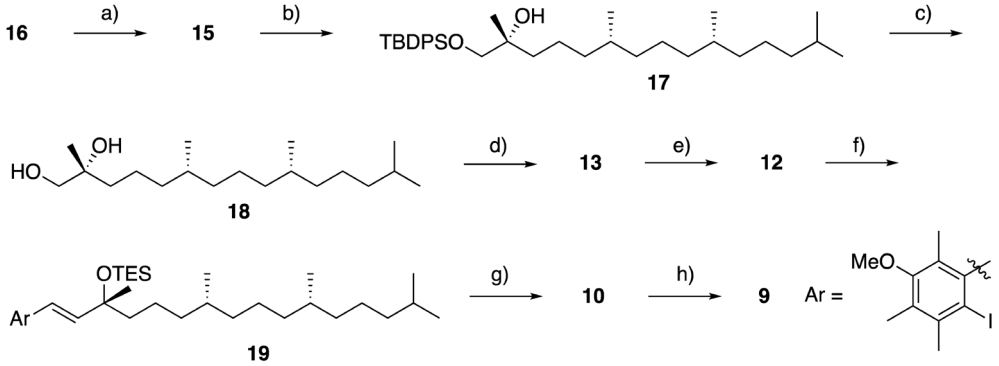


Chart 4. Deprotection of PMC

tiary alcohols, and electron richness of the iodoarenes. Therefore, we started to investigate intramolecular Ullmann C–O coupling reactions using our catalyst system for the synthesis of 2,2-dialkyl chromane cores containing an electron-donating group in the benzene ring and attempted to synthesize D-α-tocopherol starting from a tertiary alcohol (Chart 2).

First, we investigated the synthesis of PMC (2,2,5,7,8-pentamethyl-6-hydroxychromane, **2**),[30–34] which is a model compound of α-tocopherol. After several steps of transformation of phenol derivatives, we obtained the desired Ullmann precursor (**6**). As we mentioned before, arenes with electron-donating groups, such as iodoanisoles, are believed to be unsuitable for Ullmann coupling reactions owing to the difficulty of the oxidative addition step.[24,25] We assumed that activations of catalysts or substrates were needed to address this issue; hence, we decided to add a ligand to enhance the catalytic activity further. It was found that a significant excess ligand amount affected the reaction system dramatically, and we consequently obtained the desired protected PMC (**7**) with an excellent yield (Chart 3). We considered that the formation of inactive copper complexes was suppressed and consequently accelerated the reaction rate to improve the yield.[23–25] Other reported reaction conditions, such as using 1,10-phenanthroline[35] or 2,2′-bipyridyl with copper iodide,[26–28] gave low product yields. Finally, a deprotection process was conducted by treating the protected PMC (**7**) with BBr_3 to give the desired PMC (**2**) with a good yield (Chart 4).

Since we successfully synthesized PMC, we proceeded to synthesize chiral D-α-tocopherol (**1**). A synthetic strategy of D-α-tocopherol is shown in Fig. 2. To prepare D-α-tocopherol, we encountered a problem to construct a chiral side chain, which is hexahydrofarnesol (**16**). Current solution is to use



Reagent and conditions: a) PPh_3, NBS, DCM, 0°C, 90%; b) Mg, THF then **14**, CuI, THF, −40°C, 85%; c) TBAF, THF, 0°C to RT, 95%; d) TESCl, Imidazol, DMF, 80°C, 97%; e) $(COCl)_2$, DMSO, DCM, −78 to −40°C then Et_3N, 85%; f) **11**, ^{t}BuOK, Dioxane, 100°C, quant; g) TBAF, THF, RT, 77%; h) $TsNHNH_2$, NaOAc, THF/H_2O, reflux, 40% (repeated three times).

Chart 5. Synthesis of Ullmann C–O Coupling Precursor

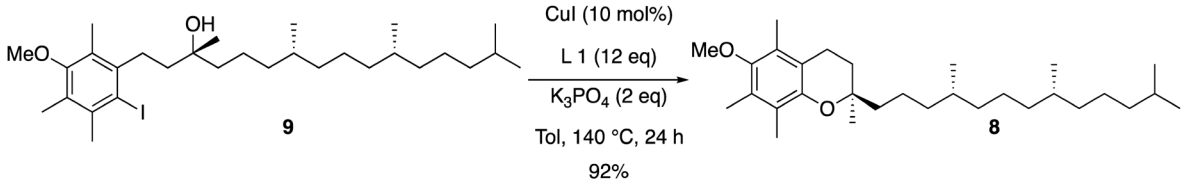


Chart 6. Ullmann C–O Coupling Reaction for the Synthesis of Methyl-Protected D-α-Tocopherol Core Structure

chiral phytol instead,[10–13] but its scarcity poses a huge problem. Therefore, we decided to prepare hexahydrofarnesol (**16**) by using a modified Negishi's method[36] starting from protected 2-methyl-1,4-butanediol. Although their original work used a zirconium-catalyzed asymmetric carbo-alumination (ZACA)-lipase-catalyzed acetylation protocol, we planned to pick up the kinetic resolution with lipase[37] in their second step owing to the availability of the chiral zirconium catalyst. Moreover, we selected a benzyl protective group[37] in the alcohol because the handling would be easier. Then, we planned to follow their copper-catalyzed cross-coupling reactions of the C-5 units. After obtaining hexahydrofarnesol (**16**), it would be converted to alkyl magnesium bromide to couple with the chiral epoxide **14**[38] prepared by Sharpress asymmetric epoxidation.[39,40] The formed diol was protected as its triethylsilyl (TES) ethers form and oxidized to aldehyde **12**.[41,42] Aldehyde **12** would be coupled with Wittig reagent to transfer allyl alcohol **10**. Allyl alcohol **10** would be hydrogenated[43] to Ullmann precursor **9**. Finally, Ullmann coupling reaction could be conducted to form the protected D-α-tocopherol (**8**). After obtaining the protected D-α-tocopherol, we planned a deprotection of the phenol, and the desired D-α-tocopherol (**1**) could be subsequently formed. Based on this strategy, we started to study the synthesis pathway.

Initially, the bromination reaction of alcohol **16**[44] was conducted to produce the desired alkyl bromide **15** (Chart 5). After preparation of the Grignard reagent, the copper-catalyzed ring opening reaction of epoxide **14** was conducted to obtain chiral alcohol **17**. To conduct selective oxidation of primary alcohol, diol **18** was protected as its TES ether groups. Initially, we attempted to conduct Swern oxidation of diol **18**; however, the desired α-hydroxy aldehyde could not be obtained. However, the deprotective process using Swern oxidation[41,42] worked well for this substrate. Then, Wittig reaction was conducted to obtain protected allyl alcohol **19**.

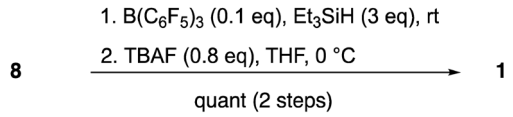


Chart 7. Deprotection of Protected D-α-Tocopherol

After treatment with tetrabutylammonium fluoride (TBAF), we continued with the reduction of **10** with tosyl hydrazide thrice to obtain Ullmann precursor **9**. Although we attempted several conditions for the hydrogenation of **10**,[18] the yield of **9** was very low; thus, we repeated the same reaction three times, and the yield was improved to 40%.

Finally, we conducted the Ullmann C–O coupling reaction using our catalyst system in the PMC synthesis. As a result, the desired methyl-protected D-α-tocopherol (**8**) could be obtained with high yield (Chart 6). After deprotection of the methyl group[45] (Chart 7), we completed the total synthesis of D-α-tocopherol (**1**). The NMR spectrum of the synthesized D-α-tocopherol (**1**) was consistent with that of the natural compound.[46] Furthermore, it was confirmed that the optical purity of the 2-position[47] was not decreased during the Ullmann C–O coupling and deprotection processes.

In summary, we have completed the synthesis of PMC (2,2,5,7,8-pentamethyl-6-hydroxychromane) and D-α-tocopherol using intramolecular Ullmann C–O coupling reactions as the key step. Furthermore, the optical purity was not decreased during the Ullmann C–O coupling reaction. Our catalyst system modified by adding the amount of the ligand worked well for less reactive substrates (*i.e.*, electron-rich iodoarenes) to achieve high yields. This result might open a new strategy for the synthesis of chiral chromane structure of other natural compounds. The synthesis of those types of natural compounds and further investigations of Ullmann C–O coupling reactions are now in progress.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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