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Total Synthesis of Termicalcicolanone A via Organocatalysis and Regioselective Claisen Rearrangement

Saki Ito,[†] Taiki Kitamura,[‡] Sundaram Arulmozhiraja,[*,§,∥] Kei Manabe,[‡] Hiroaki Tokiwa,[§,∥] and Yumiko Suzuki[*,†]

[†]Department of Materials and Life Sciences, Faculty of Science and Technology, Sophia University, 7-1 Kioicho, Chiyoda-ku, Tokyo 102-8554, Japan

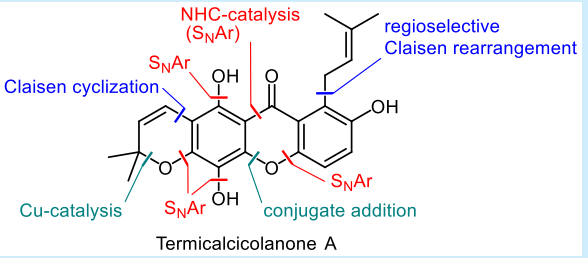
[‡]School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

[§]Department of Chemistry, Rikkyo University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

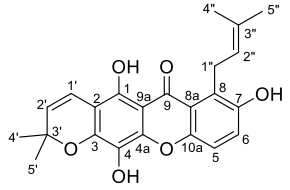
[∥]Research Center for Smart Molecules, Rikkyo University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

Supporting Information

ABSTRACT: A total synthesis of an anticancer xanthone natural product termicalcicolanone A utilizing multiple nucleophilic aromatic substitutions and pericyclic reactions has been developed. The pyrano[3,2-*b*]xanthen-6-one scaffold was constructed via NHC-catalyzed aroylation to produce the benzophenone intermediate, Claisen cyclization to form the pyran ring, and intramolecular 1,4-addition to construct the xanthone framework. The prenyl group was introduced in the final stages of the synthesis through regioselective Claisen rearrangement. The synthesis has been achieved in 19 steps.



Termicalcicolanone A (**1**) (Figure 1) is a natural product isolated from the Madagascan plant *Terminalia calcicola*



termicalcicolanone A (**1**)

Figure 1. Structure of termicalcicolanone A (**1**).

H. Perrier through an activity-guided fractionation of the ethanol extract.[1] This natural product is classified as a xanthonoid because of its xanthone core bearing phenolic hydroxy groups. Xanthonoids have various biological activities, e.g., antitumor,[2] antibacterial,[3] and antivirus.[4] In fact, xanthonoide **1** exhibits antiproliferative activity against the A2780 human ovarian cancer cell line with an IC_{50} value of 40.6 μM.[1] Despite the importance of this class of natural products, the total synthesis of **1** has not been reported. Herein, we report the first total synthesis of this important natural product **1** and present the synthetic scheme for this class of natural products.

It is often not straightforward to construct highly substituted xanthones with functionalities at specific positions. Common methods to access xanthone frameworks are based on the Friedel−Crafts reaction, which is used either to construct xanthones from diphenyl ether intermediates[5] or to prepare benzophenones as starting materials for cyclization to xanthones by reactions such as Ullmann-type reaction and nucleophilic aromatic substitution (S_NAr).[6] One of the recently introduced methods is the one-step synthesis of xanthones from easily accessible benzaldehydes and benzenes.[7] However, none of these methods is universal for the synthesis of highly functionalized xanthones that were found in naturally occurring compounds[8] due to problems such as accessibility to the starting materials and orientation effects of the substituents. Thus, synthetic chemists search for efficient ways to construct xanthones with functionalities at specific positions. In this study, we demonstrated an alternative synthetic route to produce multioxygenated xanthone natural products that consists of *N*-heterocyclic carbene (NHC)-catalyzed aroylation (to prepare the benzophenone intermediate),[9] nucleophilic aromatic substitutions, and an intramolecular 1,4-addition to the quinone moiety.

As outlined in Scheme 1, our retrosynthetic strategy involves the introduction of a prenyl group to the core by Claisen rearrangement in the final step, and the pyran ring could be formed through Claisen cyclization. The xanthone framework could be constructed via successive S_NAr reactions with *O*-nucleophiles from the fluorinated benzophenone **3**,[10] which were prepared from 3,4,5-trifluoronitrobenzene **4** and 2-fluorobenzaldehyde derivative **5** through NHC-catalyzed

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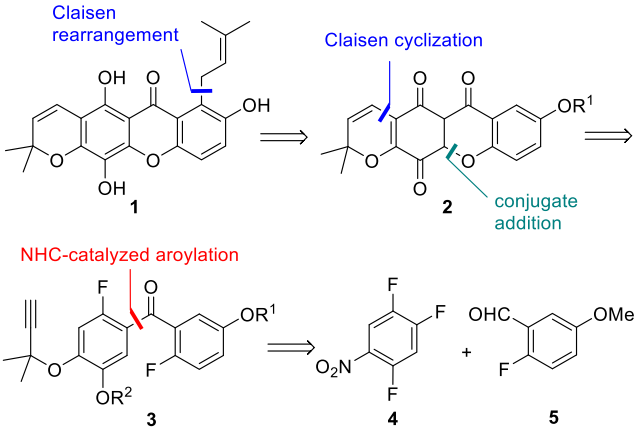
Scheme 1. Retrosynthesis of 1

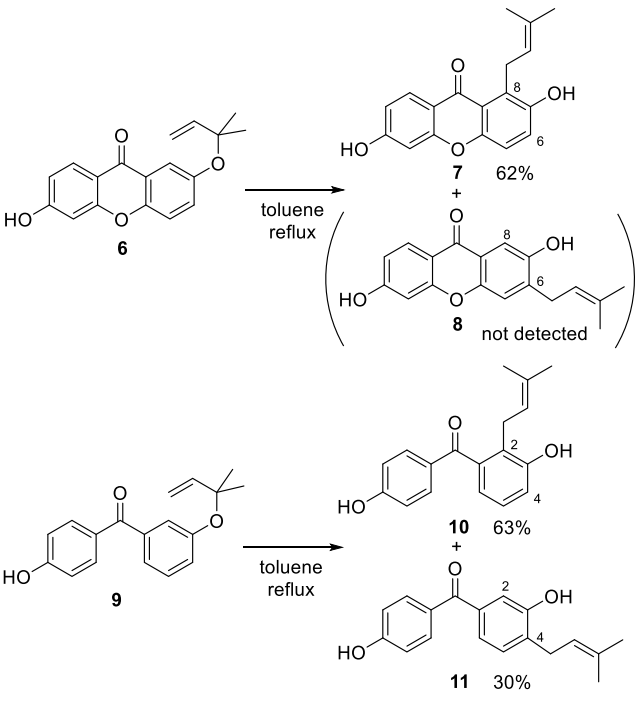


nucleophilic aroylation reaction and other transformations. Unlike the scheme normally employed in traditional natural product synthesis, this synthetic strategy is similar to the one used in medicinal chemistry, i.e., employing S_NAr reactions multiple times using the fluorine groups and the nitro group as leaving groups.

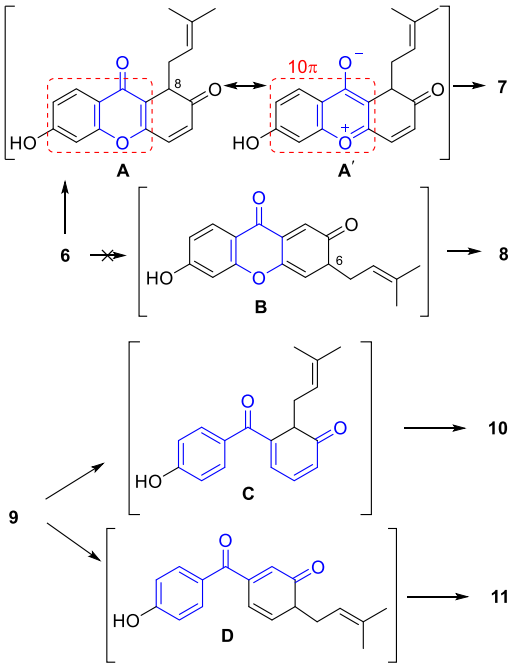
Our main concern, before initiating the synthesis, was the regioselective introduction of the prenyl group at position 8 of **1**. Therefore, we first conducted model reactions to confirm our synthetic strategy. The Claisen rearrangement of the model compound—xanthone **6**—proceeded in refluxing toluene regioselectively to afford 8-prenylated product **7** in 62% yield (Scheme 2). The regioisomer **8** was not detected. In contrast, the rearrangement of benzophenone **9** afforded 2-prenylated **10** in 63% yield and 4-prenylated product **11** in 30% yield.

The regioselectivity in the reaction of the model compounds can be explained through the stability of the reaction intermediates **A**–**D** (Scheme 3).[11,12] In the reaction of

Scheme 2. Claisen Rearrangement of Model Compounds



Scheme 3. Intermediates in Claisen Rearrangements of 7 and 10



xanthone **6**, 8-prenylxanthone **7** was obtained via intermediate **A**. The rearrangement to the 6-position would afford **8** via intermediate **B**. The intermediate **A** has a 10π aromatic system involving a 4-pyrone ring (in blue) as shown in the resonance structure **A′**. In contrast, the pyrone ring of **B** is not incorporated in the aromatic system, and therefore, the reaction involving the formation of **B** is unfavorable compared with that of **A**. On the other hand, both benzophenone products **10** and **11** were, respectively, generated through intermediates **C** and **D** having the conjugated diketone structures (in blue).

To understand the regioselectivity further, a putative step of the Claisen rearrangement of the model compounds involving the reactants (**6** and **9**), transition states (TS^A, TS^B, TS^C, and TS^D), and intermediates (**A**–**D**) was theoretically studied using density functional theory (DFT), and the relative energies are depicted in Figure 2. Two conformers each (**6**, **6′** and **9**, **9′**) for the reactants were considered. As the experiments were conducted in refluxing toluene, all of the calculations were performed at 383.15 K incorporating solvent (toluene) effects. The calculations clearly show (Figure 2) that formation of products **7** (from the reactant **6** via intermediate **A**) and **10** (from **9** via **C**) should be energetically favored as they are connected to the energetically more stable conformers of the reactants (**6** and **9**) via transition states (TS^A and TS^C) with smaller activation barriers (23.2 and 25.3 kcal/mol) through the energetically favored intermediates **A** (3.78 kcal/mol) and **C** (6.67 kcal/mol). Therefore, aromatic Claisen rearrangements via the intermediates **A** and **C** are both thermodynamically and kinetically favored. As expected, the intermediate **A** is more stable than **B** by 8.81 kcal/mol, and **C** is energetically more favored than **D** by 0.95 kcal/mol. These findings support our experimental results on Claisen rearrangements. It should also be mentioned that there is a good correlation between the calculated results and the experimentally observed regioselectivity: the difference in activation energy in favor of **A** over **B** (7.37 kcal/mol) is larger than that

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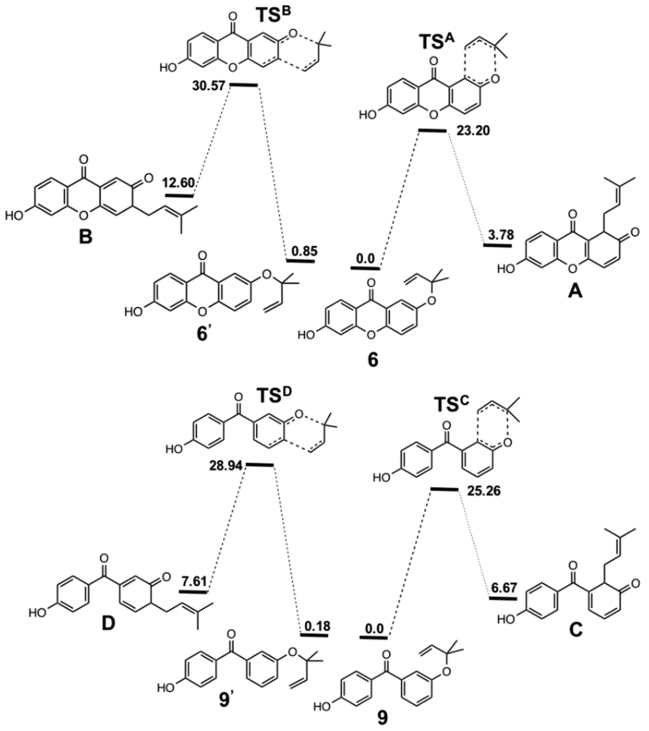
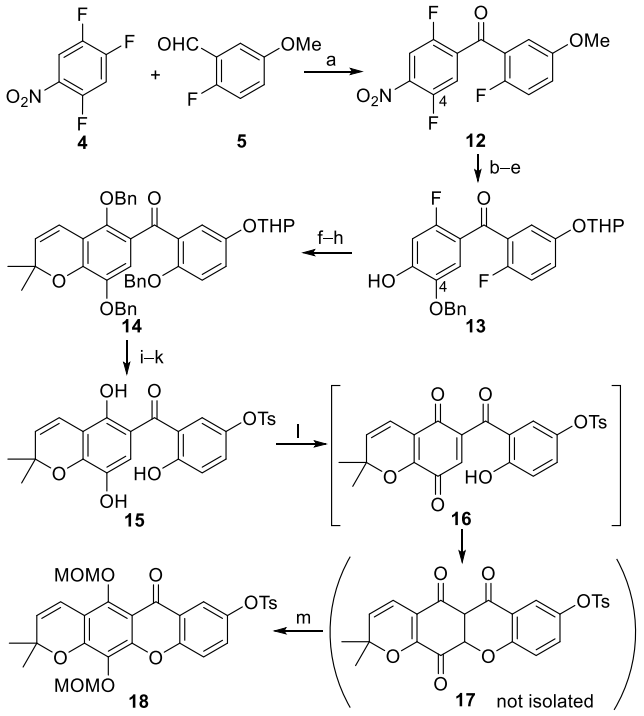


Figure 2. B3LYP/6-311+G(2d,p) relative energies (in kcal/mol) of Claisen rearrangements involving the model reactants **6** and **9**.

in favor of **C** over **D** (3.68 kcal/mol), and similarly, as mentioned above, the energy difference between **A** and **B** is larger than that between **C** and **D**; in parallel, product **11** with a yield of 30% was observed, whereas **8** was not observed. The foregoing facts suggest introducing the prenyl group after the construction of the xanthone framework in the total synthesis is necessary. In addition, the results of the model reactions indicate that the Claisen rearrangement in the actual total synthesis would proceed with complete regioselectivity.

The synthesis commenced with NHC-catalyzed aroylation in which the 4-fluoro group of trifluoronitrobenzene **4** was selectively substituted with the aroyl group originating from aldehyde **5** to produce benzophenone **12** (Scheme 4).[10] After conversion of the methyl ether **12** to the tetrahydropyran (THP) ether, the fluoro group at position 4 (numbering in termicalcicolanone A) was substituted with the benzyloxy group. Then the nitro group was converted to the hydroxy group via S_NAr reaction using benzaldoxime anion[10,13] affording hydroxybenzophenone **13**, which was then propargylated. Since the resulting propargyl ether is unstable, it was subjected to Claisen cyclization directly after the isolation by column chromatography without any further purification. The substitution of the remaining fluoro groups with the benzyloxy groups produced tribenzyloxylated **14**. After conversion of the THP ether of **14** to the acid-tolerant tosylate, the debenzylation in acidic condition was performed to yield trihydroxylated **15**, which was then subjected to oxidation with manganese dioxide. In this reaction, the quinone intermediate **16** was supposedly generated in situ and then subsequently underwent intramolecular 1,4-addition to produce tetracyclic triketone **17** with a slight amount of its tautomer **18**. The mixture of **17** and **18** was treated with tetrabutylammonium iodide in refluxing toluene[10] to obtain **18** quantitatively from **15** in two steps. Thus, the construction of the core framework, pyrano[3,2-*b*]xanthen-6-one scaffold, was accomplished.

Scheme 4. Construction of the Pyrano[3,2-*b*]xanthen-6-one Scaffold[a]



[a]Reagents and conditions: (a) 1,3-dimethylimidazolium iodide, NaH, DMF, 0 °C to rt, 2 h; 76%; (b) HBr aq, AcOH, reflux, 20 h; quant; (c) DHP, CSA, CH_2Cl_2, rt, 30 min.; 93%; (d) K_2CO_3, BnOH, rt, 48 h; 82%; (e) benzaldoxime, NaH, DMSO, 0 °C to rt, 4 h; 87%; (f) 3-chloro-3-methyl-1-butyne, DBU, $CuCl_2$, CH_2Cl_2, 0 °C to rt, 2.5 h; 84%; (g) toluene, reflux, 24 h; quant; (h) BnOH, NaH, DMF, 0 °C to rt, 21 h; 90%; (i) *p*-TsOH, CH_2Cl_2, MeOH, rt, 30 min.; quant; (j) TsCl, K_2CO_3, acetone, reflux, 7 h; 92%; (k) HBr aq, AcOH, reflux, 4 h; 78%; (l) MnO_2, CH_2Cl_2, rt, 24 h; (m) TBI, toluene, reflux, 3 h; quant (two steps).

For the regioselective Claisen rearrangement to introduce the prenyl group at position 8 of the core, the oxygen atom attached at position 7 needed to be propenylated. Therefore, after protecting group manipulation, 1,1-dimethypropenyl ether **21** was prepared from **19** (Scheme 5) in the reaction with ester **20** catalyzed by palladium(0). The Claisen rearrangement of this doubly MOM-protected intermediate **21** suffered from the instability of prenylated product **23**: Either of the MOM ethers was gradually cleaved as time proceeded. The attempted Claisen rearrangement from **21** led to a complicated mixture containing **23**, which gradually decomposed and could not be separated from undesired products. Hence, one of the MOM ethers was cleaved using zinc chloride to produce **22**. Only one product was observed; however, the exact structure was not determined, and the product was then subjected to Claisen rearrangement followed by removal of the remaining MOM group. Thus, the total synthesis of **1** was accomplished.

In conclusion, the total synthesis of anticancer natural product termicalcicolanone A (**1**) was achieved for the first time in 19 steps in a 4.2% overall yield. The feature of our synthesis is the regioselective Claisen rearrangement and the multiple use of S_NAr reaction including organocatalysis–NHC-catalyzed aroylation. We have demonstrated that the NHC-catalyzed preparation of a highly functionalized benzophenone

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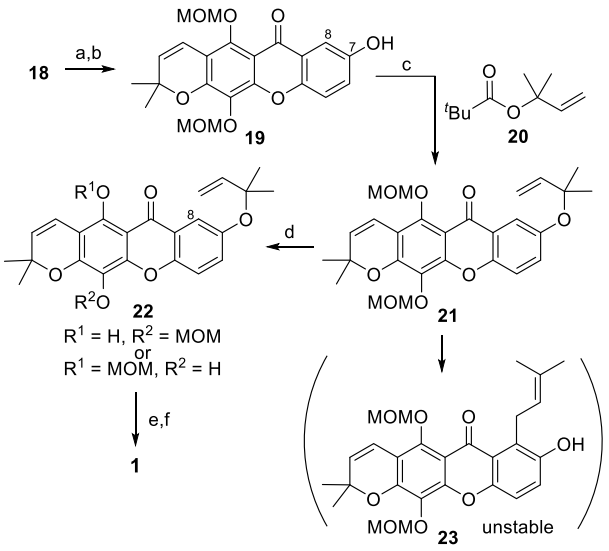
Scheme 5. Synthesis of 1 from 19: Introduction of the Prenyl Group[a]



[a]Reagents and conditions: (a) MOMCl, NaH, DMF, rt, 3.5 h; 71%; (b) KOH, EtOH, H_2O, reflux, 3 h; 80%; (c) **20**, $Pd(PPh_3)_4$, THF, 5 °C, 30 min.; 73%; (d) $ZnCl_2$, THF, 40 °C, 22 h; (e) toluene, 100 °C, 5 h; (f) *p*-TsOH, EtOH, CH_2Cl_2, reflux, 4 h; 37% (three steps).

is beneficial for the eventual access to polyphenolic xanthone **1**, and that S_NAr reactions are viable not only for the synthesis in the medicinal chemistry field but also for the total synthesis of natural products. The strategy used here can be employed for the synthesis of other natural products of this class. In fact, synthetic studies on other xanthone natural products using related strategy are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00731.

Detailed experimental procedures, computational details, optimized structures, characterization data (PDF)

^1H and ^{13}C NMR spectra of all purified compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: raja@rikkyo.ac.jp.

*E-mail: yumiko_suzuki@sophia.ac.jp.

ORCID

Kei Manabe: 0000-0002-9759-1526

Hiroaki Tokiwa: 0000-0002-3790-1799

Yumiko Suzuki: 0000-0002-8226-5867

Notes

The authors declare no competing financial interest.

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