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A Concise Synthesis of a Highly Strained Cyclobutane in Solanoeclepin A by Radical Cyclization

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Tin- and samarium(II)-mediated 4-*exo-trig* radical cyclizations enable the synthesis of highly strained cyclobutane-containing tricyclic compounds related to the right-hand nucleus of solanoeclepin A, a hatching agent of potato cyst nematode.

Solanoeclepin A (**1**) was isolated as a compound exhibiting significant hatching-stimulating activity in potato cyst nematode (*Globodera rostochiensis* and *G. pallida*) from a potato cultivation by Mulder and co-workers in 1986.[1] The structure was elucidated by X-ray crystallographic analysis in 1999[2] to be a distinctive triterpenoid similar to glycinoeclepin A,[3] another hatching-stimulating substrate for soybean cyst nematode. The structure of **1** consists of an unprecedented heptacycle including all ring sizes ranging from three to seven. In particular, a tricyclo[5.2.1.$0^{1,6}$]decane skeleton, corresponding to the right-hand nucleus, includes a highly strained cyclobutanone with three contiguous quaternary stereogenic centers (Figure 1). Because of the noticeable biological activity, **1** would be a feasible lead compound in the development of agrochemicals against potato cyst nematode. However, the limited availability of **1** from natural sources has prevented us from studying the mechanism of the hatching phenomenon on a molecular level and the structure–activity relationship for the development of agrochemicals. Thus, supply by chemical synthesis of **1** has been highly desired, we embark on the synthetic studies on solanoeclepin A. Recently, the first total synthesis of **1** was reported by Tanino and Miyashita.[4]

In the synthesis of **1**, construction of the unprecedented tricyclo[5.2.1.$0^{1,6}$]decane skeleton is one of the most challenging synthetic issues because of the inherent high ring strain.[5,6] So far, only three syntheses of the tricyclodecane core skeleton have been reported;[4,7,8] (i) intramolecular [2 + 2]-photochemical cycloaddition of dioxenone derivative,[7a] (ii) intramolecular cyclization of epoxynitrile,[4] and (iii) ring contraction by the Wolff rearrangement.[8] We disclose herein an alternative and expeditious synthesis of compound **A** as a model of the tricyclic ring systems including cyclobutane by radical cyclization.

Our synthetic plan for the model compound **A** is based on the radical cyclization in a 4-*exo-trig* manner (Scheme 1). Radical cyclization has not been frequently employed for the construction of a cyclobutane, probably because it seems that strain of the product reverses the reaction back to the acyclic product.[9] In the few existing reports of the radical cyclization for the synthesis of cyclobutane, the precursors included ester or sulfone for stabilization of the cyclized radical as well as *gem*-disubstituents with the aim of enhancing the reaction velocity in the intramolecular cyclization.[10–12] However, if 4-*exo* radical conjugate addition[13] depicted in Scheme 1 would be possible, construction of the tricyclo[5.2.1.$0^{1,6}$]decane skeleton of solanoeclepin A (**1**) as well as preparation of the precursor would be exceedingly simple. On the basis of this consideration, we planned to synthesize cyclobutane-containing tricyclic compounds **B** and **C** as synthetic equivalents of the model compound **A** by 4-*exo-trig* radical cyclization with two different radical intermediates; (a) vinyl radical **D** generated from acetylene **E** with *n*-Bu_3SnH, and (b) ketyl radical **F** generated from aldehyde **G** with SmI_2[14] (Scheme 1). These two precursors **E** and **G** could be readily prepared from the Hajos–Parrish ketone.

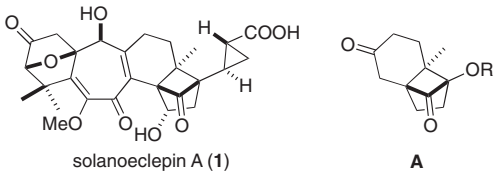
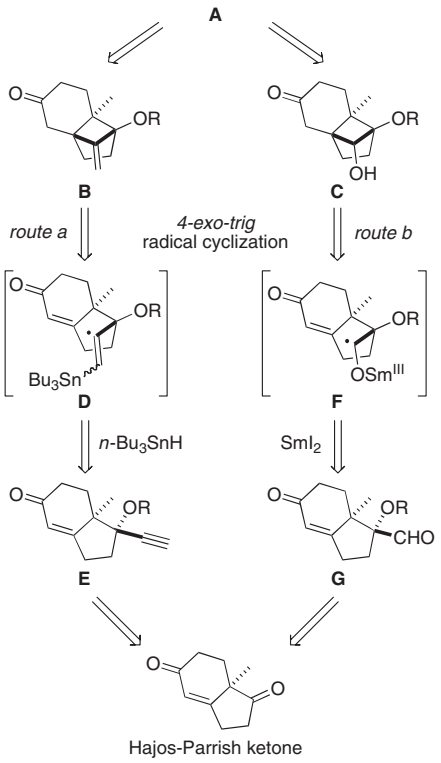
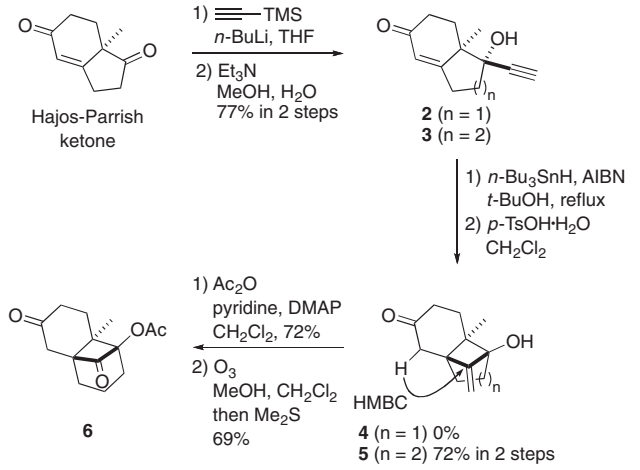


Figure 1. Structure of solanoeclepin A and model compound **A** for the right-hand nucleus.

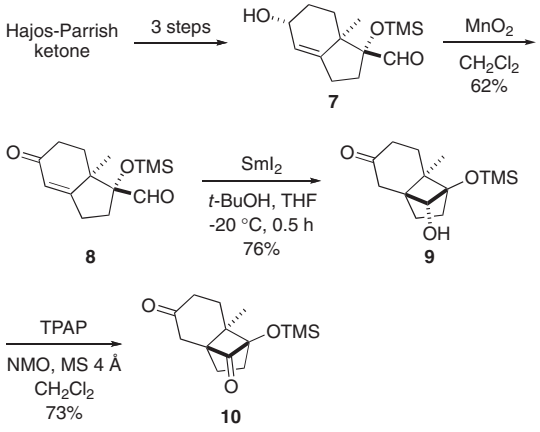


Scheme 1. Synthetic strategy for cyclobutane by radical process.

We first examined the route (a) by utilizing 4-*exo-trig* radical cyclization of vinyl radical **D**. The precursor **2** (=**E**) was



Scheme 2. Synthesis of tricyclic compound **5** by tin-mediated radical cyclization.



Scheme 3. Synthesis of tricyclo[5.2.1.0^{1,6}]decane **9** by samarium(II)-mediated radical cyclization.

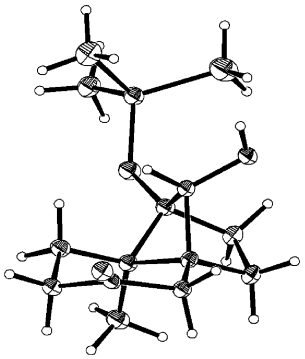


Figure 2. Perspective ORTEP drawing for **9**.

prepared from the Hajos–Parrish ketone in two steps including addition of lithium trimethylsilylacetylide followed by deprotection of the trimethylsilyl group (Scheme 2). When alkynylenone **2** was treated with *n*-Bu_3SnH in the presence of AIBN under reflux of *t*-BuOH,[15] the desired cyclization product **4** was not obtained at all. In sharp contrast, the similar precursor **3**, prepared from the Wieland–Miescher ketone, reacted under identical conditions to provide a tricyclic product **5** in good yield after protodestannylation by treatment with *p*-toluenesulfonic acid.[16] The structure of **5** was determined through extensive NMR analysis; the newly formed carbon–carbon bond was confirmed by HMBC correlation as shown in Scheme 2. E*xo*-olefin **5** was further transformed into ketone **6** by acetylation followed by ozonolysis. The marked contrasting results of the above cyclization might be explained by a difference of ring strains of the cyclized radical intermediates from **2** and **3**. Steric hindrance between the Bu_3Sn substituent and the cyclohexenone moiety might also influence the reactivity in cyclization.

We next examined the route (b) by utilizing 4-*exo-trig* radical cyclization of radical species **F** with less steric hindrance. The precursor **8** (=**G**) was obtained by MnO_2 oxidation of allylic alcohol **7**, readily prepared from the Hajos–Parrish ketone in three steps as reported by our laboratory (Scheme 3).[17] Upon treatment of ald-enone **8** with SmI_2 and *t*-BuOH in THF at $-20\,^{\circ}C$, 4-*exo-trig* radical cyclization proceeded smoothly to give the desired tricyclodecane **9** in 76% yield as a single product.[18,19] The structure of **9** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2).[20] Compared with the tin-mediated cyclization of **2** via the sp^2 vinyl radical, sp^3 ketyl radical generated from **8** with SmI_2 may give a better overlap with a π-orbital of the enone in the transition state, resulting in the successful radical cyclization. Finally, oxidation of **9** with TPAP afforded cyclobutanone **10**, which possesses the highly strained tricyclo[5.2.1.0^{1,6}]decane skeleton found in solanoeclepin A (**1**).

In summary, we have demonstrated the power of 4-*exo-trig* radical cyclization for construction of the highly strained cyclobutane found in solanoeclepin A. Since the substrate is readily prepared from the Hajos–Parrish ketone, samarium(II)-mediated 4-*exo-trig* radical cyclization could provide one of the most straightforward accessible routes to the tricyclo[5.2.1.0^{1,6}]-decane skeleton of solanoeclepin A. Tin-mediated radical cyclization leading to tricyclic compound **5** should also be useful for preparation of the analogues for use in structure–activity relationship studies. These 4-*exo* radical cyclizations may allow us to synthesize other natural products possessing tricyclic ring system including cyclobutane such as astellatol[21] and plumisclerin A.[22] Continuing effort toward the synthesis of solanoeclepin A is now in progress.

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20 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-855640. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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