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Novel Synthesis of Right Segment of Solanoeclepin A

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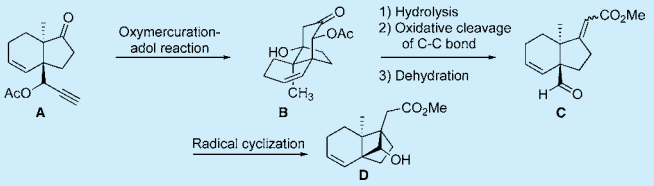
Supporting Information

ABSTRACT: The highly strained tricyclo[5.2.1.0^{1,6}]decene skeleton of solanoeclepin A was synthesized through two key C−C bond forming processes; thus, a Hg(TFA)$_2$-mediated oxymercuration followed an intramolecular aldol reaction to B and a SmI$_2$-mediated cyclization of C between an aldehyde and an unsaturated ester to form the cyclobutane D having a tricyclo[5.2.1.0^{1,6}]dodecene.



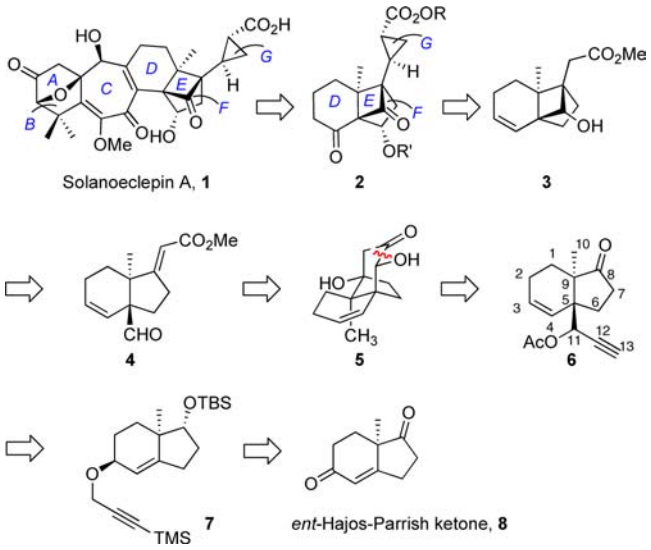
Solaneclepin A is a natural hatching stimulant of potato cyst nematodes (PCN; *Globodera rostochiensis* and *G. pallida*),[1] which causes serious damage to food crops over the world. It was first isolated by Mulder in 1986,[1] and its structure was elucidated by Schenk and co-workers from X-ray crystallographic analysis.[2] Solanoeclepin A stimulates the hatching of PCN with its highly specific selectivity and is expected to be an environmentally friendly natural product. The difficulty in acquisition from natural sources and the complexity of the molecular structure have gained the attention of synthetic organic chemists.

Solanoeclepin A contains a tricyclo[5.2.1.0^{1,6}]decene bearing a highly strained cyclobutanone substructure and a 7-oxabicyclo[2.2.1]heptanone moiety. Several groups have reported partial syntheses of this molecule such as Hiemstra et al.,[3] Isobe,[4] and Adachi−Nishikawa.[5] In 2011, Tanino and Miyashita reported the first asymmetric synthesis of solanoeclepin A.[6] We applied a convergent synthetic strategy for the synthesis of this natural product by coupling the AB ring system (left segment) with the DEFG ring system (right segment) to construct a seven-membered C-ring.

One synthetic challenge toward this natural product is the construction of a highly strained tricylo[5.2.1.0^{1,6}]decene moiety. There have been only three methods reported for the synthesis of the tricyclo[5.2.1.0^{1,6}]decene skeleton of solanoeclepin A: (i) intramolecular [2 + 2]-photocycloaddition of an allene butanolide,[3] (ii) base-induced intramolecular cyclization reaction of an epoxy nitrile,[6] (iii) and a SmI$_2$-mediated 4-*exo*-*trig* cyclization between an aldehyde and α,β-unsaturated ketone.[5] In 2012, our group reported the fourth method by formation of cyclobutane via a cationic mechanism stabilized by the Nicholas effect and a Hosomi−Sakurai type nucleophile between an allylsilane and an acetylene-dicobalthexacarbonyl complex.[7] Herein we report the fifth method by formation of a cyclobutane ring through SmI$_2$-mediated 4-*exo*-*trig* ketyl radical cyclization between an aldeyde and α,β-unsaturated ester (such as **4**) to afford the highly strained tricyclo[5.2.1.0^{1,6}]decene ring system.

In our retrosynthetic analysis (Scheme 1), the seven-membered carbocyclic C-ring would be formed by coupling between the AB-ring system and the DEFG ring system. The cyclopropane G-ring would be introduced after the formation of cyclobutane **3** from aldehyde precusor **4**, which should be obtainable by oxidative cleavage of α-hydroxyl ketone **5**. This ketone **5** must be prepared by oxymercuration followed by an intramolecular aldol reaction, and the quaternary center C-5 was introduced by [2,3]-Wittig rearrangement[7] from allyl propargyl ether **7** at low temperature.

Scheme 1. Synthetic Strategy for Synthesis of DEFG Ring of Solanoeclepin A



As shown in Scheme 2, *ent*-Hajos−Parrish ketone **8** was reduced under Luche conditions at −78 °C to give diol **9** in 79% yield.[8] A selective Mitsunobu inversion of the 3-α-hydroxyl group to β-benzoate **10** without protecting the 8-α-hydroxyl group by carefully treating diol **9** with 1.2 equiv of triphenyl phosphine, DEAD, and benzoic acid gave 65% β-benzoate **10**. Protection of the 8-α-hydroxyl group by TBSOTf and 2,6-

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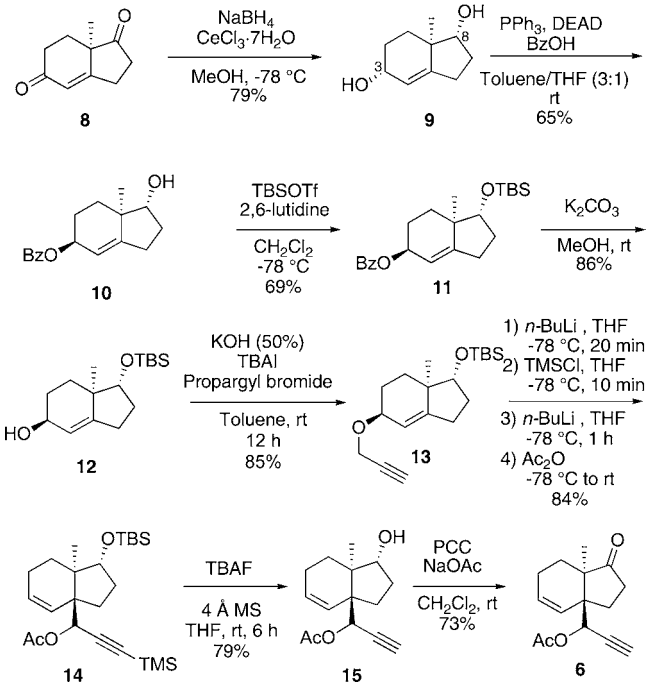
Scheme 2. Preparation of Alkyne 6 from *ent*-Hajos–Parrish Ketone

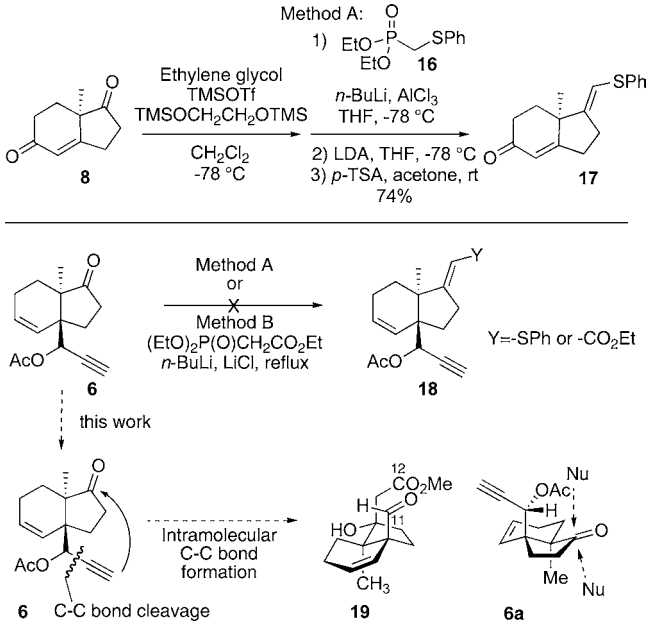


lutidine at −78 °C afforded 69% of silyl ether **11**, which was treated with potassium carbonate in methanol to hydrolyze the benzoate in 86% yield. Etherification of allyl alcohol **12** in a two-phase reaction afforded allyl propargyl ether **13** in 85% yield. A one-pot silylation and simultaneous [2,3]-Wittig rearrangement were employed by treating allyl propargyl ether **13** with *n*-BuLi at −78 °C followed by the addition of TMSCl at −78 °C,[7] and the rearrangement proceeded at −78 °C for 1 h. The reaction was quenched by the addition of acetic anhydride to afford rearrangement product **14** in an overall 84% yield. The silyl protection was removed by TBAF, which was followed by PCC oxidation in the presence of sodium acetate buffer to obtain the corresponding ketone **6** in 79% yield.

Nucleophilic addition of a carbon nucleophile to easily enolizable ketones such as **6** (as steroid C-17) has always been a challenge for synthetic chemists.[9] An acid–base combination condition would provide a solution which can reduce the basicity of the carbanion by employing an additional Lewis acid to a nucleophile allowing it to still retain its nucleophilicity. As shown in Scheme 3, we have recently developed a new method which combined the phosphonate carbanion of **16** with aluminum trichloride, and then LDA to achieve the olefination at the easily enolizable ketone. The α,β-unsaturated ketone (*ent*-Hajos–Parrish diketone) **8** was selectively protected,[10] and the phosphonate-carbanion plus aluminum trichloride condition was used to provide the addition product. This intermediate was treated with LDA to complete the olefination, which was followed by a deprotection of the ethylene-ketal to give (*E*)-phenyl vinyl sulfide **17** in 74% yield in four steps (Scheme 3).

However, in the olefination of ketone **6**, neither method A nor method B was successful in affording **18** due to steric blocking of both of the two faces of the carbonyl group. Fortunately, we explored indirect conversion via intramolecular C13–C8 bond formation under activation of the acetylenic

Scheme 3. C–C Bond Formation at Easily Enolizable Ketone



group to facilitate the cyclization as **19**. Then cleavage of C11 and C12 afforded **4**, which could serve in the samarium diiodide cyclization (Scheme 3).

Hydration of alkyne **6** to a methyl ketone with mercury(II) trifluoroacetate in a mixture of acetic acid and water (6:1) gave cyclization product **21** in 49% yield together with a minor product diketone **20** in 12% yield.[11] After isolation, diketone **20** was converted to β-hydroxyl ketone **21** in 82% yield by treatment with 1 equiv of pyrrolidine at 65 °C. The structure of tricyclic product **21** was confirmed by X-ray crystallographic analysis as shown in Scheme 4. We proposed the formation of β-hydroxyl ketone **21** involving two transformations: (i) hydration of alkyne to methyl ketone, and (ii) an intramolecular aldol reaction under Lewis acid conditions. On the other hand, gold-catalyzed hydration of an alkyne has been well studied to form methyl ketone.[8] So we attempted the hydration reaction by employing a similar method. When alkyne **6** was treated with methyl(triphenylphosphine)gold(I) and 1.1 equiv of water, 17% of β-hydroxyl ketone **21** and 56% of cyclopropane **22** were obtained, respectively. The structure of cyclopropane **22** was confirmed by X-ray crystallographic analysis (Scheme 4).[13]

As shown in Table 1, several conditions have been examined for the mercury-mediated cyclization. Mercury(II) oxide and mercury(II) acetate gave neither product nor recovery of starting material, respectively. In entries 3 and 4, addition of mercury(II) trifluoroacetate at room temperature and 0 °C in acetic acid gave a 49% and 53% yield of the hydration/cyclization product, respectively. Methyl ketone **20** was observed under the conditions of mercury trifluoroacetate in acetic acid solvent. In entry 5, the solvent was replaced with a stronger acid trifluoroacetic acid which gave 60% of cyclization product **21** without formation of methyl ketone **20**.

An attempted hydrolysis of the acetyl group of **21** failed in obtaining alcohol **5** using potassium carbonate in methanol or LiOH conditions. Milder conditions using dihydrogen peroxide and sodium bicarbonate in THF at room temperature afforded alcohol **5** in 64% yield. Oxidative C–C bond cleavage of diol-

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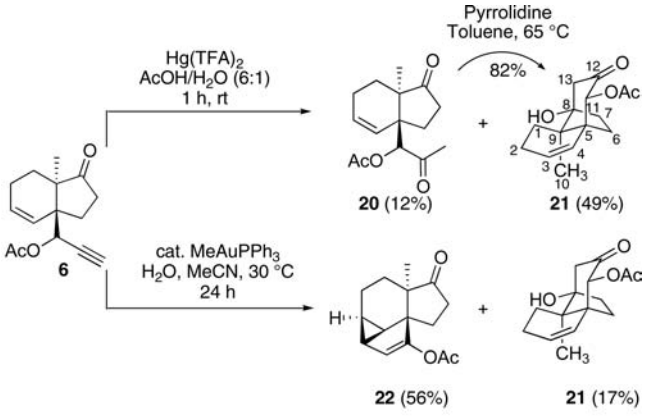
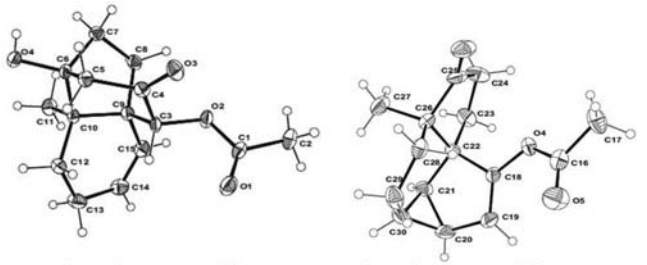
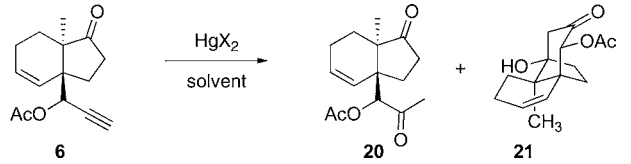
Scheme 4. Comparison between Hg-Mediated Cyclization and Au-Mediated Cyclization; X-ray Structures of 21 and 22





Crystal structure of **21** Crystal structure of **22**

Table 1. Hg-Mediated Oxymercuration/Cyclization

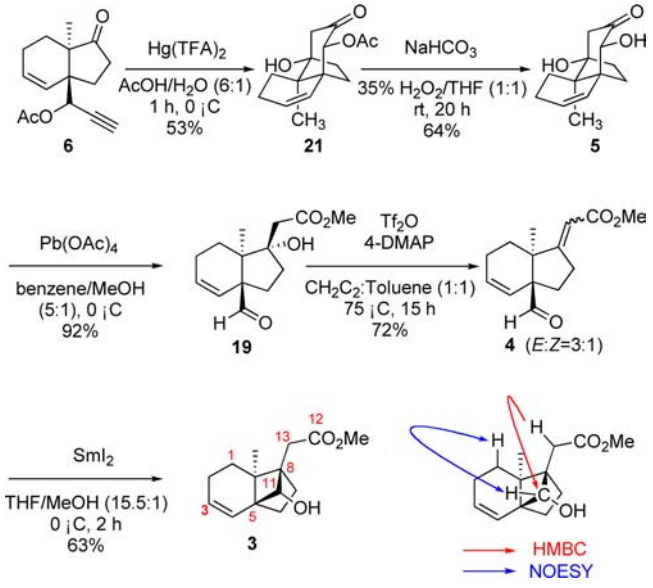


entry	reagent solvent	temp	yield **20**/**21**
1	HgO (1 equiv) H_2SO_4/H_2O/acetone	60 °C	0%/0%
2	$Hg(OAc)_2$ (1 equiv) $AcOH/H_2O$ (6:1)	0 °C to rt	0%/0%
3	$Hg(TFA)_2$ (1 equiv) $AcOH/H_2O$ (6:1)	rt, 1 h	14%/49%
4	$Hg(TFA)_2$ (1 equiv) $AcOH/H_2O$ (1.7:1)	0 °C, 1 h	17%/53%
5	$Hg(TFA)_2$ (1 equiv) TFA/H_2O (1.7:1)	0 °C, 1 h	0%/60%

ketone **5** with lead tetraacetate in methanol solvent yielded 92% of methyl ester **19**. The tertiary hydroxyl group of **19** was subsequently eliminated by treatment with trifluoromethanesulfonic anhydride and 4-DMAP at 75 °C to give *α,β*-unsaturated ester **4** with a mixture of (*E*)- and (*Z*)-olefin (3:1). The cyclobutane ring formation to **3** was achieved by treating *α,β*-unsaturated ester **4** with SmI_2 in a mixture of THF and methanol as cosolvents at 0 °C for 2 h to obtain cyclobutane **3** in 63% yield. The structure of cyclobutane **3** was confirmed by HMBC correlation between C-11 and H-13 as shown in Scheme 5. The 11-*S* configuration was established from the cross peaks between H-1 and H-11 in an NOESY experiment (Scheme 5).

In conclusion, we have accomplished the synthesis of highly strained tricyclo[5.2.1.$0^{1,6}$]decene core **3** of solanoeclepin A

Scheme 5. SmI_2-Mediated Synthesis of Tricyclo[5.2.1.$0^{1,6}$]decene Moiety 5 and HMBC and NOESY Experiments of Cyclobutane 3



through two important carbon−carbon bond forming processes: (i) $Hg(TFA)_2$-mediated hydration and an intramolecular aldol reaction forming *β*-hydroxyl ketone **19** and (ii) SmI_2-mediated 4-*exo*-*trig* cyclization of a constituent achieving cyclobutane. The methyl (triphenylphosphine) gold(I)-catalyzed 1,5-enyne cyclization reaction formed cyclopropane **22** from 1,5-enyne **6**. This synthetic method will be applied to the asymmetric total synthesis of solanoeclepin A.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR, ^{13}C NMR, 2D NMR, X-ray crystallographic data, and typical experimental details are supplied as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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(13) The mechanism for the formation of **22** is currently under investigation.

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