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Cobalt-Mediated Synthesis of the Tricyclo[5.2.1.0^{1,6}]decene Framework in Solanoeclepin A

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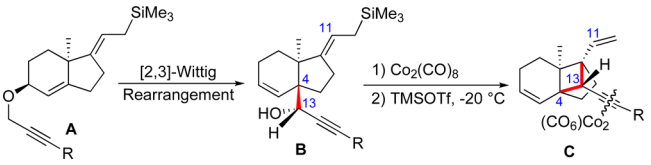
ABSTRACT



The stereocontrolled synthesis of the highly strained, tricyclo[5.2.1.0^{1,6}]decene skeleton (C) of solanoeclepin A has been achieved through two key transformations: a [2,3]-Wittig rearrangement of allylpropargyl ether (A) to propargyl alcohol (B) having a *trans*-fused perhydroindane framework and the formation of the cyclobutane via a cobalt-mediated Hosomi−Sakurai type cyclization of an acetylene dicobalthexacarbonyl complex.

Solanoeclepin A (**1**; Figure 1) was first isolated by Mulder in 1986 as the hatching stimulant principle particularly against the cyst nematodes (PCN; *Globodera rostochiensis* and *G. pallida*).[1] Its structure was elucidated by Schenk in 1999 from X-ray crystallographic analysis.[2] This molecule has a tricyclo[5.2.1.0^{1,6}]decene unit which includes a highly strained cyclobutane, and a 7-oxabicyclo-[2.2.1]heptanone moiety. PCNs can survive in the cyst over years, and once they hatch in the field bearing crops, there would be significant damage to the host plant (potato). Damages to crops due to PCN have been reported in over 50 countries in the world. However, if **1** is first applied to potato fields as a treatment prior to planting, the hatching process will be initiated, followed by PCN death in 8 weeks without any feeding on the host plants. While **1** is available from nature in very small quantities (0.245 mg from thousands of potato roots),[1b] organic synthesis of **1** would contribute to solving this source problem.

In the process of synthesizing solanoeclepin A and its derivatives, it will be possible to assemble a structure−activity relationship profile and find the most critical

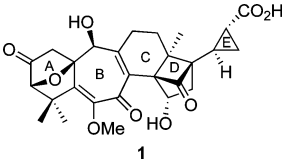


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Figure 1. Solanoeclepin A, nematode hatching stimulant.

structure or framework that displays biological activity. Many organic synthetic chemists such as the groups of Hiemstra,[3] Isobe,[4] and Adachi−Nishikawa[5] have made efforts in the challenge of synthesizing **1**. Tanino, Miyashita

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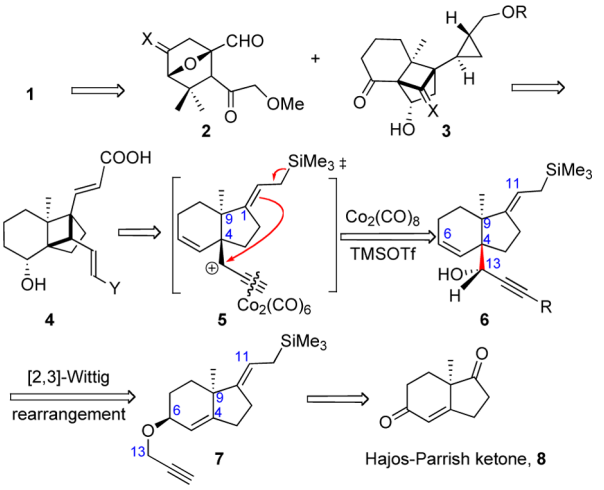
and co-workers achieved the first asymmetric total synthesis of solanoeclepin A in 2011.[6]

One of the challenges of synthesizing solanoeclepin A is the construction of the highly strained tricyclo-[5.2.1.$0^{1,6}$]decene skeleton **4**, which includes four-, five-, and six-membered rings and bears three contiguous quaternary stereogenic centers. There have only been three reports of the syntheses of the tricyclo[5.2.1.$0^{1,6}$]decane core of solanoeclepin A to date: (i) intramolecular [2 + 2] photocycloaddition of alkene-dioxenone or allene butenolide,[3] (ii) base-induced intramolecular cyclization of an epoxynitrile,[6] and (iii) 4-*exo-trig* radical cyclization of the cyclobutane.[5] In this letter, we showcase a fourth example as an alternative synthesis of the tricyclic, cyclobutane-containing framework **4** by exploiting a Hosomi−Sakurai type cyclization of an acetylene−dicobalthexacarbonyl complex. The key step is generation of the Nicholas type carbenium ion,[7] which had been employed in our previous work as the main strategy for the cyclization of seven-, eight-, and nine-membered ether rings, in the total synthesis of ciguatoxin.[8]

In our retrosynthetic analysis of solanoeclepin A, the functionalized seven-membered carbocyclic B-ring is cleaved into two segments (Scheme 1): the 7-oxabicyclo-[2.2.1]heptanone **2** and the highly strained tricyclic moiety **3** bearing three quaternary centers. We intended to develop a stereocontrolled synthesis of the tricyclic subunit **4** and envisaged that its cyclobutane moiety could be acquired by a Hosomi−Sakurai type cyclization through a Nicolas cation **5** generated *in situ* from an acetylene−dicobalthexacarbonyl complex under Lewis acidic conditions. According to the stereochemistry of the cyclobutyl moiety, a *trans*-stereochemistry at the fused rings of **6** is required. Therefore, the propargyl group at the C4 bridgehead position was required to be *trans* with respect to the methyl group at the C9 junction. This stereochemically defined intermediate **6** could be procured through a [2,3]-Wittig rearrangement[9] of *β*-propargyl ether **7**, which could be prepared in turn from Hajos−Parrish ketone **8**.

The incorporation of substituents to generate the quaternary C4 with the correct stereochemistry at the bridgehead for producing the *trans*-fused octahydroindane ring in solanoeclepin A was a synthetic challenge. Conjugate addition of cuprates to **8** is known to produce the *cis*-fused bicyclo[4.3.0] framework, except in the case of the Nagata-hydrocyanation reaction,[10] which also yielded a minor amount of the *trans*-fused product. All attempts to use [3,3]-sigmatropic rearrangements (e.g., the Ireland−Claisen rearrangement) failed to build the *trans*-fused ring junction, including the use of 6-*β*-thiophenyl acetate.[11] On the other hand, the use of a [2,3]-Wittig rearrangement (Scheme 2) was found to generate the requisite *trans*-fused rings in model experiments on **9a** (X = H, Y = OTBS). The terminal acetylenic moiety of **9a** was first deprotonated with *n*BuLi and protected with TMSCl. Then a smooth deprotonation of the propargylic proton took place with the addition of a second equivalent of *n*BuLi in THF at −78 °C (Conditions A), and a spontaneous [2,3]-Wittig rearrangement proceeded at the same temperature to provide the propargylic alcohol **10a** as a single stereoisomer in one pot with an 85% overall yield. Furthermore, after methylation and removal of the TMS group, the NMR analysis of **12** revealed that the newly generated stereogenic C11 was of an *R*-configuration.[12] These experiments also confirmed that the A/B rings of the hexahydroindene derivative **10** was *trans*-fused.

Scheme 1. Retrosynthetic Analysis of Solanoeclepin A



In the [2,3]-Wittig rearrangement of **9b** having a *β*-substituent on C1 (X = —C≡C—$SiMe_3$, Y = OTBS), the rearrangement was impeded by the bulky *β*-TMS acetylenic group. Under the same reaction conditions, only a very small amount of the desired rearrangement product **10b** was observed by TLC. When the reaction temperature was raised from −78 to 28 °C for 3.5 h (Conditions B), a 9% yield of **10b** was obtained, along with elimination product **11b** (75% yield) as the major product. On the other hand, the reaction of **9c** bearing an exocyclic olefin (X = Y = —C=$CHCH_2$OTBS) at C1 provided the desired [2,3]-Wittig rearrangement product **10c** in 70% yield over two steps (Conditions A).

Having accomplished the [2,3]-Wittig rearrangement to give the desired *trans*-octahydroindene system, we proceeded to synthesize the right-hand segment **4** of solanoeclepin A from Hajos−Parrish ketone **8** (Scheme 3). First, the α,*β*-unsaturated ketone was selectively protected to give monoethylene-ketal **13** in 90% yield following Wicha's method using 1,2-bis(trimethylsiloxy)ethane and

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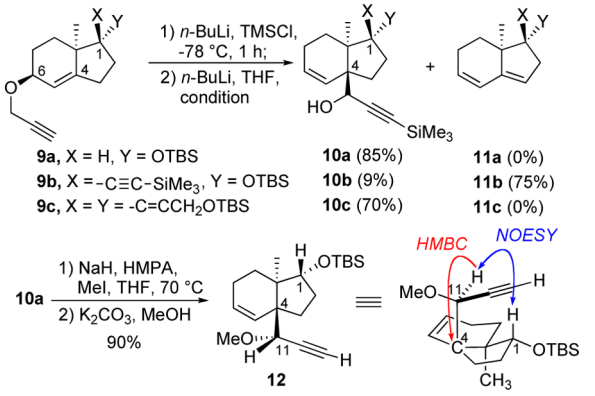
(10) Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255–476.
(11) See the Supporting Information.

(12) It is mechanistically assumed from Nakai et al. (ref 9) and from similar [2.3]Wittig rearrangement product **22** and crystalline compound **23**.

Scheme 2. Model Studies of [2,3]-Wittig Rearrangement

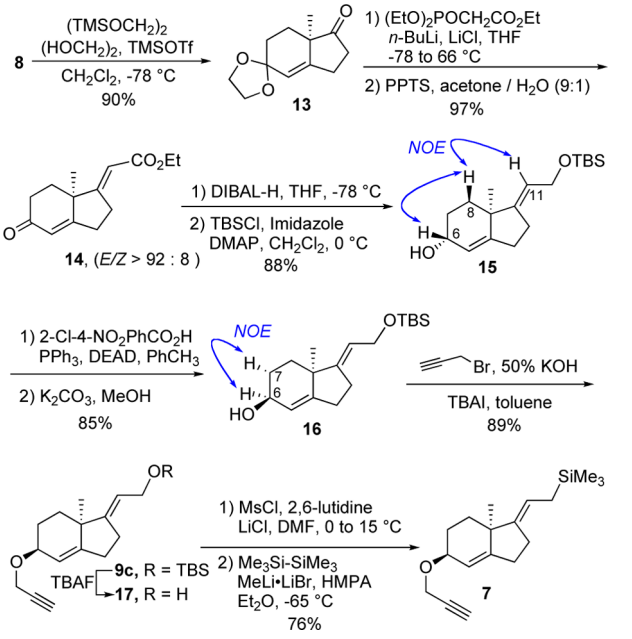


Conditions A (**9a** and **9c**): -78 °C, 1 h.
Conditions B (**9b**): -78 to 28 °C, 3.5 h.

TMSOTf at −78 °C.[13] Horner−Wadsworth−Emmons (HWE) olefination of **13** proceeded in high yield and predominantly provided the *E*-unsaturated ester (*E*/*Z* = 92:8) upon treatment with triethyl phosphonoacetate in the presence of lithium chloride,[14] which not only avoided antagonizing the base-sensitive substrate but also increased the reactivity of the phosphonium ylide. The unstable ester was subsequently treated with pyridinium *p*-toluenesulfonate to deprotect the ketal group to give the corresponding ketone **14** in 97% overall yield over two steps.

Both carbonyl groups in **14** were reduced simultaneously by treatment with DIBAL-H in THF at −78 °C to afford a single isomer of a bis-allylic alcohol, in which the hydroxyl group at C6 was exclusively α. The primary alcohol was then protected with 1.05 equiv of TBSCl to give monosilyl ether **15** selectively (92% yield in two steps). The stereochemistries of the HWE olefination and reduction at C6 were determined by the NOESY correlations of β-H8 with H11 and H6, respectively. A Mitsunobu reaction was employed to invert the stereochemistry at C6 of **15**. This was followed by hydrolysis (K_2CO_3, MeOH) to give the epimeric allyl alcohol **16** in 85% yield, and the stereochemistry of **16** was confirmed by the NOESY correlation between H6 and α-H7. An *O*-alkylation with propargyl bromide provided β-propargyl ether **9c** in 89% yield. Desilylation of **9c** with TBAF in the presence of Et_3N and 4 Å molecular sieves produced allyl alcohol **17** in 92% yield. To furnish **7**, the precursor to the [2,3]-Wittig rearrangement, **17** was converted to the corresponding allylsilane according to Smith's method[15] (76% yield in two steps).

Scheme 3. Synthesis of the Precursor **7** of [2,3]-Wittig Rearrangement



Compound **7** was subjected to the same reaction conditions at −78 °C as in the model reaction of **9c** to furnish β-propargyl alcohol **18** as the expected product bearing the *trans*-fusion and quaternary C4 in 83% yield (Scheme 4). Removal of the TMS group from the acetylenic moiety with K_2CO_3 in MeOH was followed by complexation with dicobaltoctacarbonyl at room temperature to afford acetylene dicobalthexacarbonyl complex **19** in 87% yield over two steps.

Subsequently, **19** was treated with excess TMSOTf at −20 °C, which generated the cobalt-stabilized propargyl cation **5** *in situ* in dichloroethane solvent. To this reaction mixture was further added THF as a cosolvent[8] to scavenge the excess TMSOTf that prompted the Hosomi−Sakurai type cyclization to yield the strained tricyclic cyclobutane **20** in 76% yield as a single isomer having the three quaternary stereocenters.

Eventually, **20** was further transformed by hydrosilylation ($HSiMe_2Ph$, bis(trimethylsilyl)acetylene) to *trans*-vinylsilane **21** (85%) stereoselectively.[16] Formation of the tricyclic **21** was verified by three sets of HMBC correlations as shown in Scheme 5. The 13-*R* configuration was proven from NOESY cross peaks between H13 and H11 as well as H13 and H8.

Gold-catalyzed propargylic substitution with the nucleophile of allyltrimethylsilane was reported by the Campagne group.[17] Therefore, we attempted the gold-catalyzed cyclization of propargylic alcohol **19** bearing allyltrimethylsilane for comparison with the above-mentioned results

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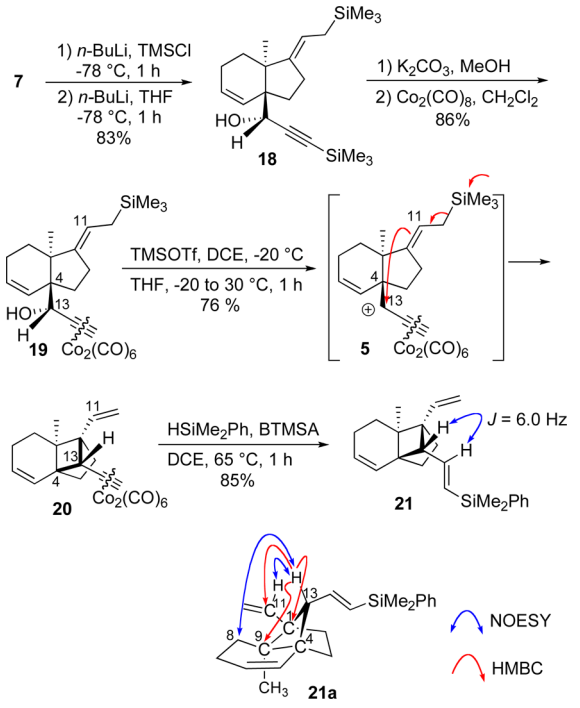
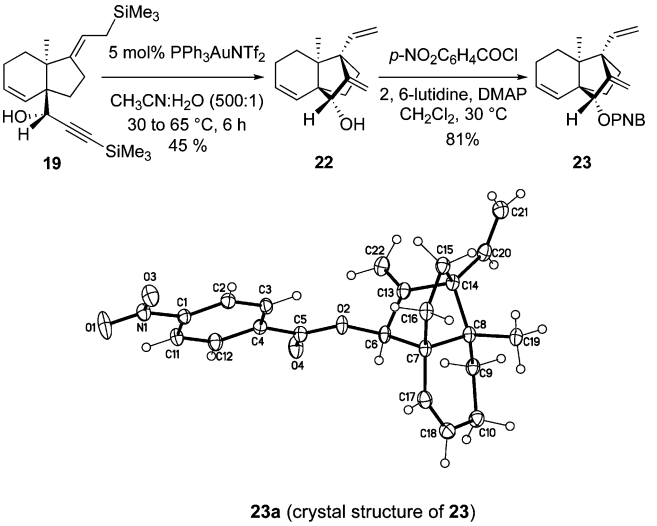
Scheme 4. Cobalt Mediated Synthesis of Tricyclo-[5.2.1.0^{1,6}]decene **20** and HMBC and NOESY Experiments of Vinyl **21a**



Scheme 5. Gold Catalyzed Cyclization to Tricyclic Compound **23**



23a (crystal structure of **23**)

(Scheme 4). The treatment of **19** with 5 mol % of PPh_3AuNTf_2 provided the unexpected formation of a five-membered ring instead of four-membered ring (Scheme 5). The absolute stereochemistry was established from X-ray crystallographic analysis of corresponding *p*-nitrobenzoate derivatives **23**.[18]

In summary, we have achieved the stereocontrolled synthesis of the highly strained tricyclo[5.2.1.0^{1,6}]decene **21** through two vital strategies: (i) [2,3]-Wittig rearrangement that enabled the installation of the β-propargyl alcohol on C4 *trans* with respect to the C9 methyl group and (ii) cobalt-mediated Hosomi−Sakurai type cyclization of an acetylene dicobalthexacarbonyl complex to construct the four-membered carbocyclic ring. The cyclization was in effect accomplished via the Nicholas type cobalt-stabilized propargylic cation with the bulky ligands, which facilitated the intramolecular attack by the allytrimethylsilane. The methodology is also amenable for gram-scale preparation toward the synthesis of solanoeclepin A in our laboratory. This research is in progress.

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Supporting Information Available. ^{1}H 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.

(18) Crystallographic data are also included in the Supporting Information and have been deposited with the Cambridge Crystallographic Data Center as CCDC No. 887423.

The authors declare no competing financial interest.