Organic LETTERS

Letter

pubs.acs.org/OrgLett

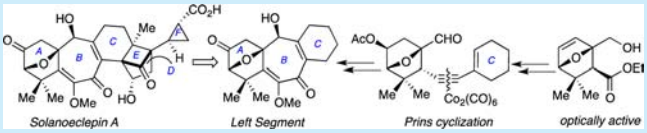
Novel Synthesis of the ABC Rings of Solanoeclepin A

Ya-Ting Lin, Feng-Yi Lin, and Minoru Isobe*

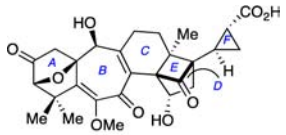
Department of Chemistry, National Tsing Hua University, 101, Section 2, Kuang-Fu Road, Hsinchu 30013, Taiwan

Supporting Information

ABSTRACT: A stereocontrolled synthesis of the ABC rings of solanoeclepin A has been achieved. The seven-membered ring B was synthesized by an intramolecular Prins-ene reaction between an aldehyde and an enyne-dicobalthexacarbonyl complex. The acetylene in this synthesis plays multiple roles: to join the A and C rings, to allow stereoselective cyclization via dicobalthexacarbonyl complexation, and to facilitate Nicholas cation stabilization followed by deprotonation to form an *endo*-cyclic olefin (Nicholas–Prins cyclization).



Solanoeclepin A (**1**) is a cyst nematode-hatching stimulant isolated from potato roots, and its structure was elucidated by Schenk et al. through X-ray crystallographic analysis.[1] Hiemstra et al. have reported their efforts on advanced intermediates toward this natural product,[2,3] while Tanino and Miyashita elegantly accomplished the first total synthesis of **1**.[4] Adachi and Nishikawa reported on a concept demonstrated by a model synthesis.[5] We are also interested in the total synthesis of **1** and have already described some new methodology toward this molecule, including strategies for the cyclobutane ring formation.[6] We have succeeded in using two different routes to construct the tricyclo[5.2.1.0^{1,6}]decene unit through cationic, as well as radical, cyclizations.[7]

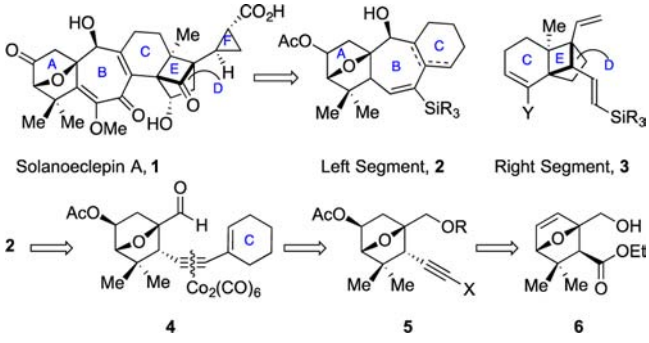


Our retrosynthetic analysis of solanoeclepin A divides the target molecule into two hemispheres for our studies, modeled by **2** and **3** (Scheme 1). As illustrated in Scheme 1, the C-ring in **1** was simplified to a cyclohexene in **2**.

We planned the synthesis of **2** to include three essential steps: (i) the cyclization of **4** to form the seven-membered ring, (ii) the coupling of **6** to yield **5** (where X = cyclohexenyl or the equivalent of rings CDE), and (iii) formation of the 7-oxabicyclo[2.2.1]heptanone **6**.

For our preparation of **6**, the precursor oxabicyclic lactam **17** has been synthesized by Mukaiyama[9] and by Hiemstra,[2b] using an intramolecular Diels–Alder strategy.[8] Both groups used the same chiral amine as an auxiliary to obtain the cycloadducts as a mixture of diastereoisomers (**14**:**15**:**16** = 1:2:1), which were separated and used in the next step. We employed a slightly different chiral amine **13**, which was commercially available (Scheme 2). After separating the desired **15** from the reaction mixture by silica gel flash column chromatography, **14** and **16** were recycled and heated to promote the retro-Diels–Alder/

Scheme 1. Retrosynthetic Strategy for Synthesis of the Left Segment of Solanoeclepin A



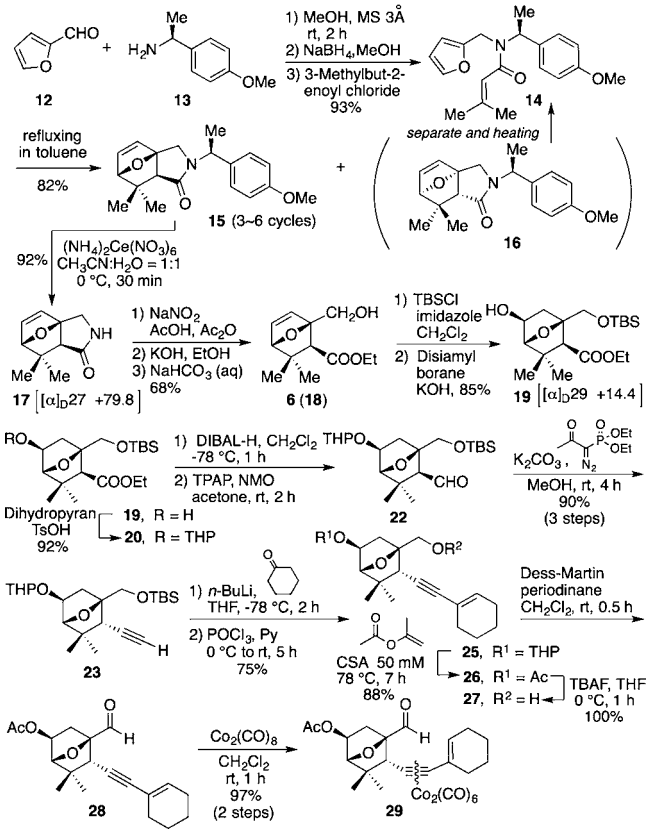
Diels–Alder reaction to obtain another diastereomeric mixture in a similar ratio (1:2:1). Repeating this process for 3 to 6 cycles provided us with **15** in 82% yield on a 10–15 g scale. Following Mukaiyama's synthesis, we then secured lactam **17** in 92% yield; mp 150.3 °C, $[\alpha]_D^{27}$ +79.8 (*c* 1.0, $CHCl_3$); lit. mp 154.2 °C, $[\alpha]_D^{22}$ +52.4 (*c* 0.82, $CHCl_3$);[2b] mp 153.5 °C, $[\alpha]_D^{28}$ +88.3 (*c* 3.94, EtOH).[8] This route from **12** to **17** was more efficient (70% yield over 5 steps) compared to another earlier strategy[3a] (55% yield over 7 steps). It was further hydrolyzed to afford hydroxyester **6** following the reported method.[9]

Hydroboration of the double bond of **6** generated the *β*-alcohol **19** in 94% yield, along with 2% of its regioisomer. Alcohol **19** was protected as THP ether **20** in 92% yield. Ester **20** was reduced to alcohol **21**, and without further purification, it was oxidized in quantitative yield to aldehyde **22**. Compound **22** was subjected to the Bestman–Ohira reaction[10] to obtain *α*-acetylene **23** with concomitant epimerization at C-5, in 90% overall yield over 3 steps. The alkynyl group was found to be in an *α*-orientation due to the epimerization of the aldehyde group under the basic conditions prior to acetylene formation.[11]

Received: October 9, 2014
Published: November 6, 2014

dx.doi.org/10.1021/ol5029755 | *Org. Lett.* 2014, 16, 5948–5951

Scheme 2. Synthesis of the Chiral Precursor 29 for the Seven-Membered Ring Cyclization

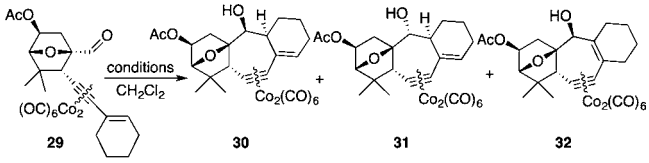


Acetylene **23** was lithiated and then added to a C-ring model, cyclohexanone, to obtain a propargyl alcohol that was subjected to dehydration. A direct exchange of the *O*-THP group for the *O*-acetate provided **26**, which was shown to be a single compound and obtained in 51% overall yield from **19** in 7 steps. Deprotection of the TBS group and Dess-Martin oxidation afforded enynal **28**. The acetylene was converted to the corresponding dicobalthexacarbonyl complex **29** in 97% yield.

The cobalt complex **29** was subjected to various Lewis acidic conditions for cyclization in dichloromethane (Table 1). Treatment with TMSOTf provided a mixture of β-hydroxylated **30** and α-hydroxylated **31** as a 2:1 mixture in 49% yield (entry 1). Treatment with tin tetrachloride at 0 °C yielded **30** selectively in 56% yield (entry 2). Several aluminum Lewis acids also promoted exclusively the cyclization to generate the β-hydroxylated isomer **30** (entries 3−6). In particular, treatment of **29** with ethyldichloroaluminum afforded **30** in 93% yield. All of the products had the trisubstituted double bond in ring C, i.e. an exo double bond with respect to the seven-membered ring.

However, the cyclization promoted by titanium tetrachloride generated solely **32** bearing not only the requisite β-hydroxyl group but also a tetrasubstituted double bond, endo with respect to the cycloheptanoid ring, with the best yield being 54% (Table 1, entry 8). Addition of molecular sieves to decrease the acidity and prevent the decomposition of the starting material was helpful to increase the cyclization yield (entries 9−12). The stereochemistry at C-9 was always of an *S*-configuration when these metal-based Lewis acids were used.

Table 1. Seven-Membered Ring Cyclization Induced by Lewis Acid

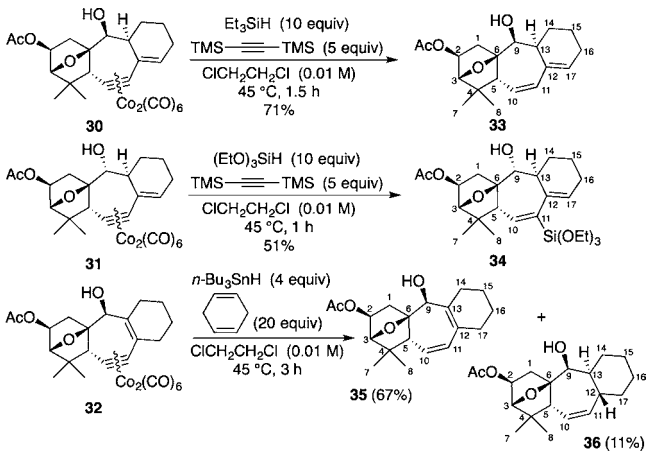


entry[a]	Lewis acid	concn (mM) of Lewis acid	base[g]	temp (°C)	products (yields)
1[b]	TMSOTf	10	—	0	**30** (33%), **31**(16%)
2[b]	$SnCl_4$	40	—	0	**30** (56%)
3[b]	Et_2AlCl	100	—	0	**30** (60%)
4[b]	Me_2AlCl	40	—	0	**30** (78%)
5[b]	$EtAlCl_2$	20	—	0	**30** (74%)
6[c]	$EtAlCl_2$	30	—	−10	**30** (93%)
7[c]	$TiCl_4$[d]	8	—	−70	**32** (37%)
8[c,f]	$TiCl_4$[d]	5	—	−70	**32** (54%)
9[c,f]	$TiCl_4$[e]	3	—	−70	**29** (27%), **32** (23%)
10[c,f]	$TiCl_4$[e]	3	0.5 equiv	−70	**29** (27%), **32** (30%)
11[c,f]	$TiCl_4$[e]	12	1.0 equiv	−70	**29** (28%), **32** (46%)
12[c,f]	$TiCl_4$[e]	16	0.8 equiv	−70	**29** (trace), **32** (42%)

[a]The substrate concentration is 10 mM. [b]The reaction time is 0.5 h. [c]The reaction time is 1 h. [d]1.0 M $TiCl_4$ in toluene. [e]1.0 M TiC_4 in CH_2Cl_2. [f]Molecular sieve 4 Å was added. [g]The base is 2,6-di-*tert*-butyl-4-methylpyridine.

Because of the effect of the paramagnetic cobalt atom, the resolution of the NMR spectra of cyclized **30**−**32** was low. The structures were finally determined after the removal of the cobalt (Scheme 3). The dicobalt moieties of **30** and **32** were

Scheme 3. Reductive Removal of Dicobalthexacarbonyl by Hydrosilylation or Tributylstannane Reduction



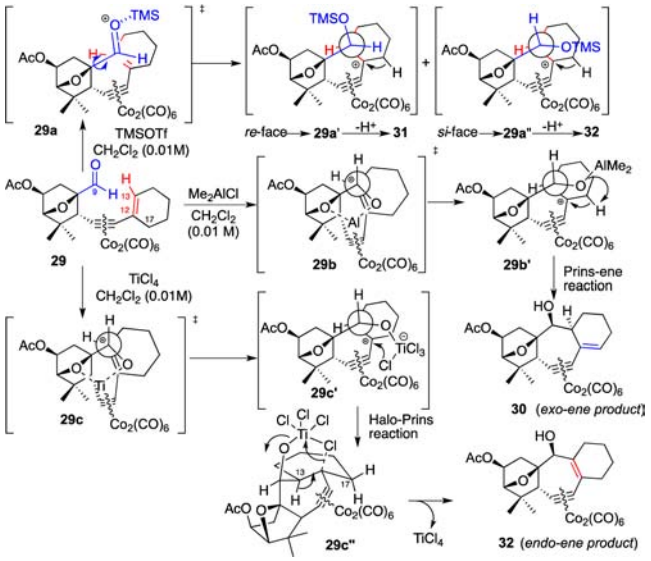
removed by hydrosilylation[12] using triethylsilane, to give diene **33** in 71% yield. The minor isomer **31** was treated with triethoxysilane to afford dienyl silane **34** in 51% yield. The dicobalt moiety of **32** was removed by tributyltin hydride to afford diene **35** and over-reduced alkene **36** in 67% and 11% yield, respectively.

A postulated mechanism for explaining the outcomes of seven-membered ring cyclization under the influence of

dx.doi.org/10.1021/ol5029755 | *Org. Lett.* 2014, 16, 5948−5951

different Lewis acids is shown in Scheme 4. The acetylene-dicobalthexacarbonyl moiety in **29** is positioned below the

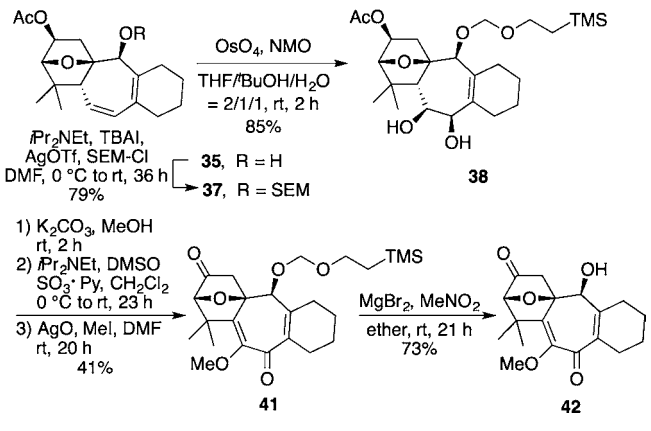
Scheme 4. Postulated Mechanism of the Nicholas–Prins–Ene Cyclization



oxabicyclic ring, and thus it is the *si*-face of the cyclohexene that would react with the aldehyde carbonyl group. TMSOTf activates the aldehyde to form **29a′** and **29a″** that exposes the *re*- and *si*-face of the carbonyl respectively for attack. This leads to the formation of Nicholas cations **29a′** and **29a″**, and subsequent deprotonation yields **31** and **30** respectively. The aluminum Lewis acids could form a complex **29b** that chelates both the aldehyde and oxygen bridge, leading to the formation of the Nicholas cation **29b′**. The deprotonation of H-17 rather than H-13 to give **30** could be due to the assistance provided by the aluminum alkoxide.[13] In the presence of $TiCl_4$ as a Lewis acid, a chelated transition state **29c** along with **29b** is also proposed, yielding Nicholas cation **29c′**. However, the nucleophilic chloride could react in a halo-Prins[14] reaction to form **29c″**. Due to the angle twist and reactivity of the tertiary chloride, a concerted elimination of H-13 and chloride aided by titanium affords **32**.[15]

With diene **35** in hand, we tried to concisely achieve the refunctionalizations to complete rings **ABC** of **1** in Scheme 5. The synthetic route was modified from Hiemstra's strategy,[2a,b]

Scheme 5. Completion of Rings ABC of Solanoeclepin A



because of the different stereochemistry of **35** compared with Hiemstra's intermediate.[2a,b] First, the hydroxyl group of **35** was protected with the SEM group to give **37**, a compound which proved to be helpful to confirm the stereochemistry of the seven-membered ring through NOE experiments. Due to the bulkiness around C12–C13, only the double bond at C11–C12 in **37** was dihydroxylated to generate diol **38** using catalytic osmium tetraoxide with NMO,[16] to afford 2-*β*, 10-*β* diol **38** in 85% yield. Compound **38** was deacylated and oxidized under Parikh–Doering conditions to afford a triketone, as its enol tautomer **40**. The enol in **40** was methylated to afford **41** in 41% yield over three steps. The SEM group was finally removed by treatment with $MgBr_2$[17] to obtain alcohol **42**, which was identical spectroscopically to that in Hiemstra's report (see an NMR comparison table on pp S-29–S-30 in the Supporting Information (SI)).[2a,b]

In conclusion, we have accomplished the central seven-membered ring cyclization through a Nicholas–Prins reaction to give **32** and the Prins–ene reaction to yield **30**, respectively, featuring three important concepts leading to stereochemical control: (i) choice of an appropriate Lewis acid for the initiation of the Prins reaction, (ii) Nicholas cation formation and stabilization, and (iii) ene reaction for the synthesis of **30** or thermodynamic stepwise deprotonation to give the desired **32**. Further functional group transformations provided **42** having rings ABC of solanoeclepin A. This stereoselective synthetic strategy will be combined with our previous work to accomplish the asymmetric total synthesis of solanoeclepin A.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: minoru@mx.nthu.edu.tw.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the National Science Council and National Tsing Hua Univ., Taiwan for the financial support.

■ REFERENCES

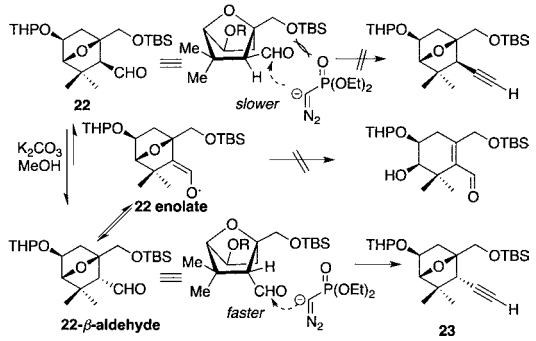
(1) Schenk, H.; Driessen, R. A. J.; de Gelder, R.; Goubitz, K.; Nieboer, H.; Brüggemann-Rotgans, I. E. M.; Diepenhorst, P. *Croat. Chem. Acta* **1999**, *72*, 593–606.

(2) (a) Benningshof, J. C. J.; Blaauw, R. H.; van Ginkel, A. E.; Rutjes, F. P. J. T.; Fraanje, J.; Goubitz, K.; Schenk, H.; Hiemstra, H. *Chem. Commun.* **2000**, 1465–1466. (b) Benningshof, J. C. J.; Blaauw, R. H.; van Ginkel, A. E.; Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1693–1700. (c) Benningshof, J. C. J.; Ijsselstiijn, M.; Walner, S. R.; Koster, A. L.; Blaauw, R. H.; van Ginkel, A. E.; Briere, J.-F.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, *1*, 1701–1713.

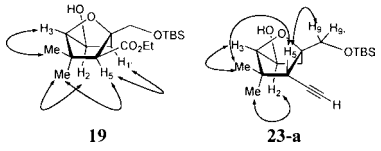
(3) (a) Brière, J.-F.; Blaauw, R. H.; Benningshof, J. C. J.; van Ginkel, A. E.; Hiemstra, H. *Eur. J. Org. Chem.* **2001**, 2371–2377. (b) Hue, B. T. B.; Dijkink, J.; Kuiper, S.; van Schaik, S.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2006**, 127–137. (c) Lutteke, G.; Kleinnijenhuis, R. A.; Jacobs, I.; Wrigstedt, P. J.; Correia, A. C. A.;

dx.doi.org/10.1021/ol5029755 | *Org. Lett.* 2014, 16, 5948–5951

Nieuwenhuizen, R.; Buu, H. B. T.; Goubitz, K.; Peschar, R.; van Maareseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2011**, 3146−3155.
(4) Tanino, K.; Takahashi, M.; Tomata, Y.; Tokura, H.; Uehara, T.; Miyashita, M. *Nat. Chem.* **2011**, *3*, 484−488.
(5) Komada, T.; Adachi, M.; Nishikawa, T. *Chem. Lett.* **2012**, *41*, 287−289.
(6) (a) Tojo, S.; Isobe, M. *Synthesis* **2005**, 1237−1244. (b) Adachi, M.; Yamauchi, E.; Komada, T.; Isobe, M. *Synlett.* **2009**, 1157−1161. (c) Tsao, K.-W.; Isobe, M. *Org. Lett.* **2010**, *12*, 5338−5341. (d) Isobe, M.; Niyomchon, S.; Cheng, C.-Y.; Hasakunpaisarn, A. *Tetrahedron Lett.* **2011**, *52*, 1847−1850.
(7) (a) Tsao, K.-W.; Cheng, C.-Y.; Isobe, M. *Org. Lett.* **2012**, *14*, 5274−5277. (b) Chuan, H.-Y.; Isobe, M. *Org. Lett.* **2014**, *16*, 4166−4169.
(8) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, *19*, 1689−1692.
(9) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29−32.
(10) The addition of the diazophosphonate anion to the β-aldehyde **22** is rationalized to be slower due to steric hindrance conferred by the gem-dimethyl group and O-TBS, while the epimerized α-aldehyde is less hindered and reacted more readily, giving rise to only the α-acetylene **23**.



(11) No β-acetylene isomer was found. The stereochemistry of **23-a** was deduced by NOESY experiments on the alcohol obtained from **23** by deprotection of the THP ether (see note in SI), compared with NOESY experiments on ester **19**, confirming the epimerization at the C-5.



(12) Isobe, M.; Nishizawa, R.; Nishikawa, T.; Yoza, K. *Tetrahedron Lett.* **1999**, *40*, 6927−6932. (b) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485−6492.
(13) Miles, R. B.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493−1501.
(14) Nagasawa, T.; Kitamura, M.; Suzuki, K. *Synlett* **1995**, *11*, 1183−1186.
(15) Aubert, C.; Begue, J. P. *Chem. Lett.* **1989**, 1835−1838.
(16) Rouse, M. B.; Winkler, J.-D. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728.
(17) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1447−145.

dx.doi.org/10.1021/ol5029755 | *Org. Lett.* 2014, 16, 5948−5951