Total Synthesis

International Edition: DOI: 10.1002/anie.201600055
German Edition: DOI: 10.1002/ange.201600055

The Total Synthesis of (±)-Naupliolide: A Tetracyclic Sesquiterpene Lactone

*Hideki Abe, Tomoyuki Morishita, Toshihiro Yoshie, Kérya Long, Toyoharu Kobayashi, and Hisanaka Ito**

Abstract: *The first total synthesis of (±)-naupliolide has been achieved. The synthetic method includes a Simmons–Smith cyclopropanation of an allyl alcohol, diastereoselective cleavage of a benzylidene acetal group, radical cyclization of an aldehyde with a cyclopropane ring, and construction of an eight-membered ring by ring-closing metathesis.*

Naupliolide (**1**), isolated from the aerial parts of *Nauplius graveolens* subsp. *oborus* (Schousb) *Wikl.* in 2006 by Barrero et al., is a sesquiterpene lactone possessing a three-membered ring, a five-membered ring, an eight-membered ring, and a γ-lactone.[1] The structure of naupliolide (**1**), assigned based on 1D NOE and 2D NMR spectra (specifically HSQC, HMBC, and ^{1}H–^{1}H COSY), is depicted in Figure 1. This compound was isolated along with 6,7,9,10-tetradehydroasteriscanolide (**2**)[2] and asteriscunolides A–D (**3a**–**3d**),[3] and a biosynthetic pathway towards **1** and **2** was proposed that included an acid-induced cyclization of asteriscunolide C (**3c**). Biological activities of novel sesquiterpene lactones **1** and **2** have not been reported yet, but those of asteriscunolides A–D (**3a**–**3d**) have been investigated. In particular, asteriscunolide D (**3d**) exhibits moderate cytotoxic activities (IC_{50} = 1–4 μM) against neoplastic cell lines, including the human cancer cells A-549, HT-20, and MEL-28.[4]

Although many examples of the total synthesis of related sesquiterpene lactones 6,7,9,10-tetradehydroasteriscanolide (**2**),[5] asteriscunolides A–D (**3a**–**3d**),[6] asteriscanolide (**4**),[7] and aquatolide (**5**)[8] have been reported, to our knowledge no publication has reported the total synthesis of naupliolide (**1**). There has been only one reported attempt to synthesize naupliolide (**1**), specifically by Li et al. in 2014 through an acid-mediated cyclization of asteriscunolide,[5] but this effort was unsuccessful. The structural features of **1** provided the motivation for this synthesis study of tetracyclic sesquiterpene lactones. Herein, we report the first total synthesis of (±)-naupliolide employing radical cyclization as the key step.

Our retrosynthetic analysis for the total synthesis of **1** is shown in Figure 2. The final compound would be obtained from diene derivative **6** by a ring-closing metathesis step. The diene derivative **6** would be derived from tricyclic lactone **7**. The stereoselective construction of tricyclic lactone **7** would be achieved by radical cyclization of aldehyde **8**, which has an unsaturated ester and a cyclopropane ring, using SmI_2 as the reagent. Aldehyde **8** would be prepared from the known alcohol **10** through a *Z*-selected Horner–Wadsworth–Emmons reaction and a Simmons–Smith cyclopropanation.

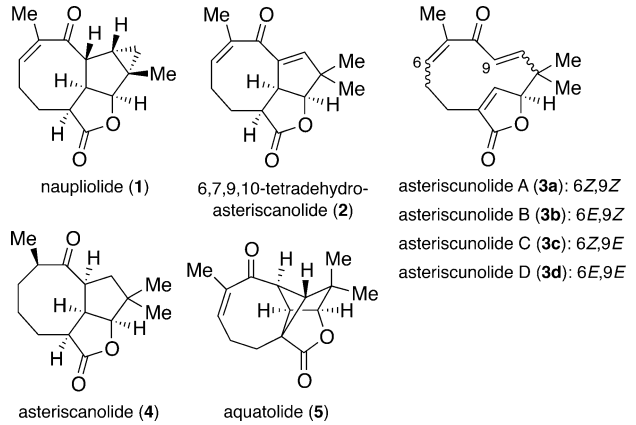


Figure 1. Structures of naupliolide (**1**) and related sesquiterpenes **2**–**5**.

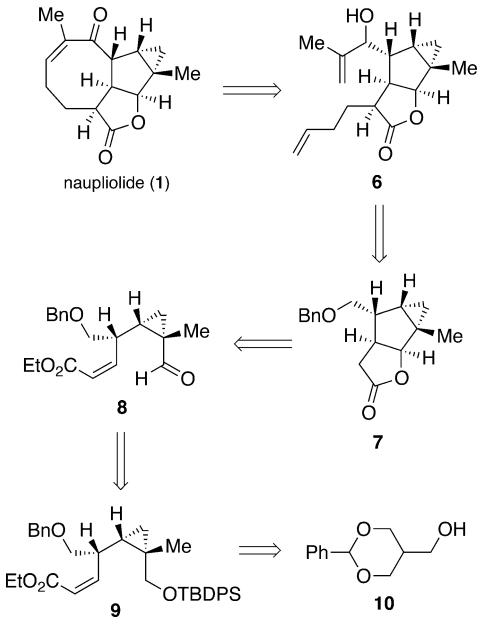
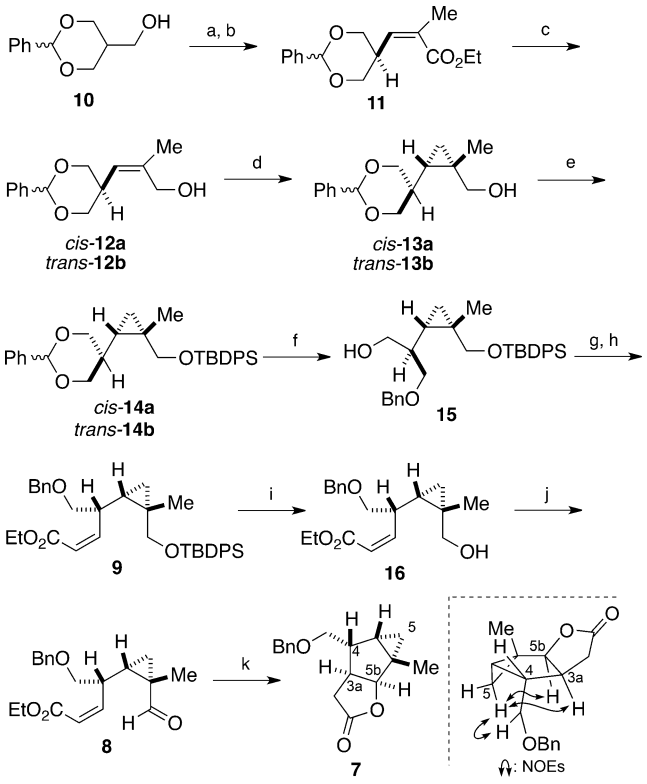


Figure 2. Retrosynthetic analysis for the total synthesis of naupliolide (**1**). Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl.

[*] Dr. H. Abe, T. Morishita, T. Yoshie, K. Long, Dr. T. Kobayashi, Prof. H. Ito
School of Life Sciences
Tokyo University of Pharmacy and Life Sciences
1432-1 Horinouchi, Hachioji, Tokyo 192-0392 (Japan)
E-mail: itohisa@toyaku.ac.jp

Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201600055.

Stereoselective construction of the tricyclic lactone was the first aim of this synthetic project. The synthesis began from the known cyclic acetal **10**,[9] as shown in Scheme 1. Oxidation of **10** with Dess–Martin periodinane,[10] followed by *Z*-selective Horner–Wadsworth–Emmons olefination[11] of the resulting aldehyde, gave the unsaturated ester **11** as an inseparable mixture of *cis* and *trans* isomers at the phenyl group on the benzylidene acetal. This mixture could be separated after reduction of ethyl ester **11** with DIBALH, affording *cis* isomer **12a** and *trans* isomer **12b** in 43% and 42% yields, respectively.[12] The Simmons–Smith cyclopropanation[13] of *cis*-**12a** tethering the *Z*-olefin afforded *cis*-**13a** and *trans*-**13b** in 18% and 54% yields, respectively. Under these cyclopropanation reaction conditions, epimerization of the phenyl group at the C2 position in the 1,3-dioxolane to the thermodynamically more stable *trans* isomer occurred. Cyclopropanation of *trans*-**12b** gave the same result to afford *cis*-**13a** and *trans*-**13b** in 18% and 79% yields, respectively. Protection of the hydroxy group of **13a** and **13b** with a TBDPS group gave **14a** and **14b**, respectively. Diastereoselective ring opening at the benzylidene acetal of **14a** and **14b** was achieved by reduction with DIBALH to afford **15** in 82 and 92% yield, respectively.[14] Two-step operations including Swern oxidation of **15**, followed by *Z*-selective olefination of the resulting aldehyde, produced the unsaturated ester **9** in 74% yield as a single isomer. Cleavage of the TBDPS group in **9** using hydrogen fluoride, and oxidation of the resulting alcohol **16** by Swern oxidation gave the radical-cyclization precursor **8** in excellent yield. The construction of the perhydrocyclopropa[4,5]cyclopenta[1,2-*b*]furan-2-one framework was achieved by radical cyclization of **8** using SmI_2[15] and *t*-BuOH as a proton source, affording tricyclic lactone **7** as a single isomer in 61% yield. The relative configuration of the resulting tricyclic compound **7** was confirmed by extensive spectroscopic analysis including NOESY experiments. Selected NOESY correlations of **7** are presented in Scheme 1. Clear NOE interactions between the α-hydrogen (H5α) at the C5 position and both H3a and H5b protons were detected. In addition, a NOE interaction between H5α and the methylene of the C4 side-chain was also detected. These results indicate that the stereochemical relationship between the bridgehead protons at the C5b position and the methyl group at C5a was *anti*, and that the relationship between the proton at C4 and the proton at the C4a position was *syn*.



Scheme 1. Synthesis of the tricyclic lactone **7**. a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0°C, 1 h, 65%; b) $(PhO)_2P(O)CH(Me)CO_2Et$, NaH, THF, −50°C, 2 h, 91%; c) DIBALH, Et_2O, −78°C, 2 h, 43% for *cis*-**12a** and 42% for *trans*-**12b**; d) Et_2Zn, CH_2I_2, CH_2Cl_2, RT, 1 h, 18% for *cis*-**13a** and 54% for *trans*-**13b** from *cis*-**12a**, 18% for *cis*-**13a** and 79% for *trans*-**13b** from *trans*-**12b**; e) TBDPSCl, imidazole, DMF, RT, 2 h, 94% for **14a** from **13a**, and 92% for **14b** from **13b**; f) DIBALH, CH_2Cl_2, −78°C then −20°C, 24 h, 82% [+8% diastereoisomer] from **14a**, and 92% [+5% diastereoisomer] from **14b**; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C then RT, 1 h; h) $(PhO)_2P(O)CH_2CO_2Et$, NaH, THF, −50°C, 2 h, 74% over 2 steps; i) HF-pyridine, pyridine, RT, 18 h, 92%; j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C then RT, 1 h, 85%; k) SmI_2, *t*-BuOH, THF, 0°C, 1 h, 61%. DIBALH = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

The stereoselectivity of the radical cyclization of **8** was explained by chelation control as depicted in Figure 3. After the single-electron reduction of the aldehyde group of **8** with SmI_2, a seven-membered cyclic transition state was formed with the oxygen atom at the aldehyde group and the oxygen atom at the ester carbonyl group tethering the Sm atom. Transition state (TS) **A** was more stable than TS **B**, in which steric hindrance existed between the benzyloxymethyl group and the ethyl ester unit of the *Z*-unsaturated ester group.

Having obtained the desired tricyclic compound **7**, our interest turned to the synthesis of target molecule **1**. After the

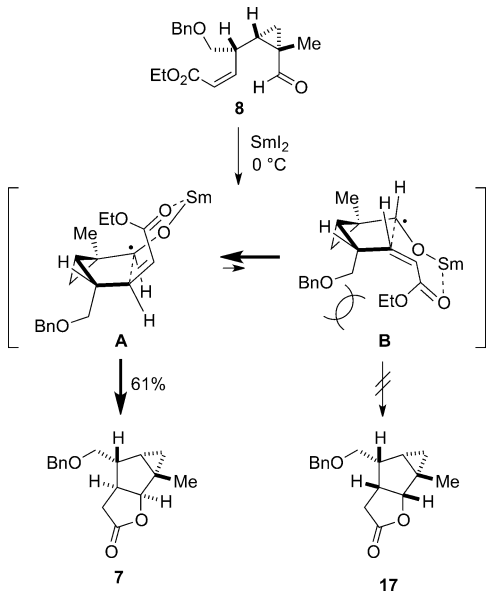
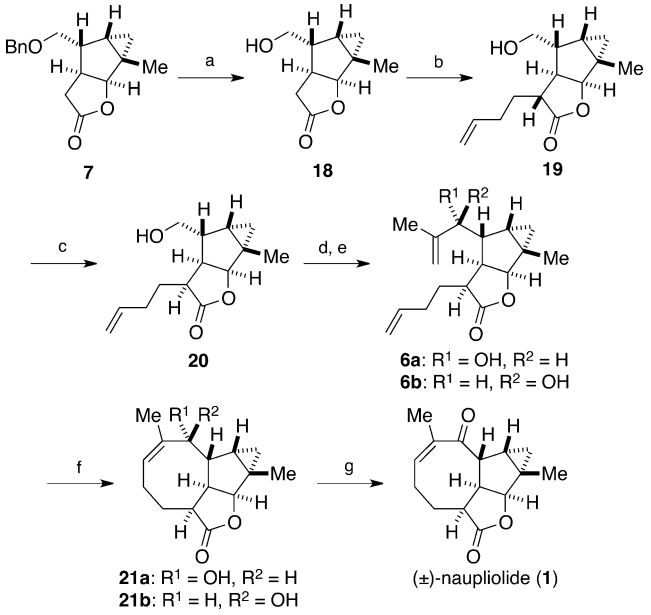


Figure 3. Stereoselectivity of the radical cyclization of **8**.

benzyl group of **7** was removed, butenylation at the α position to the carbonyl group of the resulting alcohol **18** gave alcohol **19** (d.r. = 19:1) in 56% yield. The obtained configuration at the C3 position in **19** was not desired, therefore many different sets of conditions (LDA and a proton source, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *t*-BuOK) for epimerization of the C3 position to the desired configuration were examined. Finally, combining the formation of the enolate with LDA and protonation with solid silica gel gave the best result, forming desired **20** and the undesired **19** in a 5:1 ratio. After the resulting mixture was separated by HPLC, Swern oxidation of **20**, followed by Grignard reaction of the resulting aldehyde with isopropenylmagnesium bromide, gave two separable diastereoisomers **6a**[16] and **6b**[17] (ratio of 2:1) at the secondary hydroxy group in 58% total yield over two steps. Ring-closing metathesis[18] of the mixture of **6a** and **6b** using Grubbs second-generation reagent achieved construction of the 8-membered ring and the *Z*-olefin moiety, affording the tetracyclic compounds **21a** and **21b** in 50% yield in a 2:1 ratio. Finally, Swern oxidation of **21** resulted in the formation of (±)-naupliolide (**1**) in 76% yield. Spectroscopic data (^{1}H and ^{13}C NMR spectra, IR, and mass spectra) of synthetic naupliolide were identical with those of the reported natural product.[1] Additionally, the stereochemistry of (±)-**1** was confirmed using X-ray crystallographic analysis (stereochemistry of (±)-**1** shown in Scheme 2).[19]

In conclusion, the first total synthesis of racemic (±)-naupliolide (**1**) was accomplished from the known alcohol **10** in a total of 18 steps. The synthetic method involved the following features: a) Simmons–Smith cyclopropanation of an allyl alcohol; b) diastereoselective cleavage of a benzylidene acetal group; c) construction of the tricyclic core of **1** by radical cyclization by using the reagent SmI_2; and d) ring-closing metathesis of diene compound **6** yielding tetracyclic compound **21** having an 8-membered ring and *Z*-olefin moieties. This synthetic strategy will be applicable to the synthesis of (+)-naupliolide, the natural enantiomer, which is now in progress in our laboratory.



Scheme 2. Total synthesis of naupliolide **1**. a) H_2, $Pd(OH)_2$/C, MeOH, RT, 1 h, 83%; b) LDA, 4-iodo-1-butene, THF, −78 °C then −10 °C, 6 h, 56%, d.r. = 19:1; c) LDA, THF, −78 °C, 1 h, then silica gel, −78 °C, 0.5 h, 90%, d.r. = 5:1 for **20**:**19**; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C then RT, 1 h; e) isopropenylmagnesium bromide, THF, −78 °C, 2 h, 40% for **6a** and 18% for **6b**, over 2 steps; f) Grubbs 2nd generation catalyst, toluene, 60 °C, 16 h, 50% yield, 2:1 mixture of **21a** and **21b**; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C then RT, 1 h, 76%. LDA = lithium diisopropylamide.

Acknowledgements

This work was supported by the Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Keywords: cyclopropanation · lactones · radicals · ring-closing metathesis · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3795–3798
Angew. Chem. **2016**, *128*, 3859–3862

[1] M. Akssira, F. Mellouki, A. Salhi, H. Alilou, A. Saouf, F. El Hanbali, J. F. Arteaga, A. F. Barrero, *Tetrahedron Lett.* **2006**, *47*, 6719–6721.
[2] S. El Dahmy, J. Jakupovic, F. Bohlmann, T. M. Sarg, *Tetrahedron* **1985**, *41*, 309–316.
[3] a) A. San Feliciano, A. F. Barrero, M. Medarde, J. M. Miguel del Corral, A. A. Aizpiri, F. Sánche-Ferrando, *Tetrahedron* **1984**, *40*, 873–878; b) A. San Feliciano, A. F. Barrero, M. Medarde, J. M. Miguel del Corral, E. Ledesma, F. Sánche-Ferrando, *Tetrahedron Lett.* **1982**, *23*, 3097–3100.
[4] A. P. Rauter, I. Branco, J. Bermejo, A. G. González, M. D. García-Grávalos, A. San Feliciano, *Phytochemistry* **2001**, *56*, 167–171.
[5] a) J.-C. Han, C. -C, Li, *Synlett* **2015**, *26*, 1289–1304; b) J.-C. Han, F. Li, C. -C, Li, *J. Am. Chem. Soc.* **2014**, *136*, 13610–13613.
[6] a) B. M. Trost, A. C. Burns, M. J. Bartlett, T. Tautz, A. Weiss, *J. Am. Chem. Soc.* **2012**, *134*, 1474–1477; b) R. A. Fernandes, V. P. Chavan, *Chem. Commun.* **2013**, *49*, 3354–3356; c) See Ref. [5].
[7] a) P. A. Wender, N. C. Ihle, C. R. D. Correia, *J. Am. Chem. Soc.* **1988**, *110*, 5904–5906; b) L. A. Paquette, J. Tae, M. P. Arrington, A. H. Sadoun, *J. Am. Chem. Soc.* **2000**, *122*, 2742–2748; c) J. Limanto, M. L. Snapper, *J. Am. Chem. Soc.* **2000**, *122*, 8071–8072; d) M. E. Krafft, Y.-Y. Cheung, C. A. Juliano-Capucao, *Synthesis* **2000**, 1020–1026; e) M. E. Krafft, Y. Y. Cheung, K. A. Abboud, *J. Org. Chem.* **2001**, *66*, 7443–7448; f) Y. Liang, X. Jiang, Z.-X. Yu, *Chem. Commun.* **2011**, *47*, 6659–6661; g) Y. Liang, X. Jiang, X.-F. Fu, S. Ye, T. Wang, J. Yuan, Y. Wang, Z.-X. Yu, *Chem. Asian J.* **2012**, *7*, 593–604; h) See Ref. [5].
[8] J. M. Saya, K. Vos, R. A. Kleinnijenhuis, J. H. van Maarseveen, S. Ingemann, H. Hiemstra, *Org. Lett.* **2015**, *17*, 3892–3894.
[9] a) A. Toda, T. Matsuya, H. Mizuno, H. Matsuda, K. Murano, D. Barrett, T. Ogino, K. Matsuda, PTC Int. Appl., 2001060846; b) E. Juaristi, F. Díaz, G. Cuéllar, H. A. Jiménez-Vázquez, *J. Org. Chem.* **1997**, *62*, 4029–4035; c) E. Bosies, D. B. J. Herrmann, U. Bicker, R. Gall, W. Pahlke, *Lipids* **1987**, *22*, 947–951.
[10] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.
[11] K. Ando, *J. Org. Chem.* **1997**, *62*, 1934–1939.
[12] The configuration of 2-phenyl-5-substituted-1,3-dioxane derivatives was presumed from the comparison of chemical shifts at the C2 and C5 positions in the ^{1}H NMR spectrum: see Ref. [9b].

[13] For a review, see: H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050.
[14] The presumed diastereoselectivity of the ring opening at the benzylidene acetal of **14** is described in the Supporting Information.
[15] For reviews, see: a) T. Nakata, *Chem. Soc. Rev.* **2010**, *39*, 1955 – 1972; b) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307 – 338.
[16] CCDC 1439959 contains the supplemental crystallographic data for compound **6a**. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
[17] CCDC 1439960 contains the supplemental crystallographic data for compound **6b**..
[18] For reviews, see: a) A. Gradillas, J. Pérez-Castells, *Angew. Chem. Int. Ed.* **2006**, *45*, 6086 – 6101; *Angew. Chem.* **2006**, *118*, 6232 – 6247; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490 – 4527; *Angew. Chem.* **2005**, *117*, 4564 – 4601; c) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199 – 2238.
[19] CCDC 1439961 contains the supplemental crystallographic data for compound **1**.

Received: January 4, 2016
Published online: February 10, 2016

