Total Synthesis

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Organocatalytic, Asymmetric Total Synthesis of (−)-Haliclonin A

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In memory of Yu-Lin Li

Abstract: *The first total synthesis of the alkaloid (−)-haliclonin A is reported. The asymmetric synthesis relied on a novel organocatalytic asymmetric conjugate addition of nitromethane with 3-alkenyl cyclohex-2-enone to set the stereochemistry of the all-carbon quaternary stereogenic center. The synthesis also features a Pd-promoted cyclization to form the 3-azabicyclo[3,3,1]nonane core, a SmI_2-mediated intermolecular reductive coupling of enone with aldehyde to form the requisite secondary chiral alcohol, ring-closing alkene and alkyne metathesis reactions to build the two aza-macrocyclic ring systems, and an unprecedented direct transformation of enol into enone.*

The macrocyclic alkaloid (−)-haliclonin A (**1**, Figure 1) was isolated in 2009 from a marine sponge *Haliclona* sp. collected from Korean waters by Shin and co-workers.[1] The structure of **1** was determined using 2D NMR spectroscopy and mass spectrometry techniques. The absolute configuration of this compound remained confusing because it was partially assigned as 1*E*,3*S*,4*R*,6*S*,11*S* by Shin and co-workers on the basis of spectral and chemical analyses, but presented the enantiomer shown in Figure 1.[1] (−)-Haliclonin A (**1**) contains two aza-macrocycles and is structurally related to sarains A–C,[2] but possesses an unprecedented 3-azabicyclononane framework. Preliminary bioassays showed that this unique natural product exhibits moderate antibacterial activity against several microbial strains, and cytotoxicity against the K562 leukemia cell line. Despite its intriguing structure, no total synthesis of (−)-haliclonin A (**1**) has been reported to date.

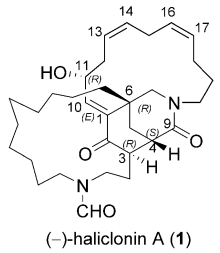

Figure 1. Structure of (−)-haliclonin A (**1**).

In connection with our interest in the total synthesis of alkaloids,[3] we recently disclosed a racemic synthesis of a tricyclic core of (−)-haliclonin A (**2**, Figure 2).[4] We have developed an asymmetric strategy for this skeleton and report herein the first total synthesis of (−)-haliclonin A (**1**).

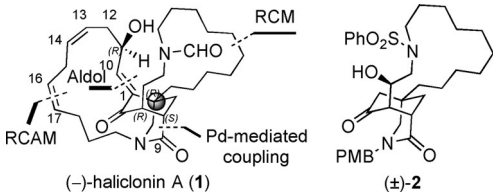

Figure 2. Key disconnections of (−)-haliclonin A (**1**) and a tricyclic core.

To achieve asymmetric synthesis of (−)-haliclonin A, we needed to build the all-carbon quaternary stereogenic center[5] at C6 with high enantioselectivity. According to our retrosynthetic analysis (refer to **1** in Figure 2 and Ref. [4]), enantioselective addition of nitromethane to 3-(hex-5-enyl)-cyclohex-2-enone (**4**) was envisioned. A survey of relevant literature showed that very few examples of such highly enantioselective addition reactions have been reported.[6–9] In light of these precedents, and after extensive experimentation, we found[10] that the cheap and readily available thiourea **5**[11] is an excellent catalyst for our purposes. Treatment of enone **4** with thiourea **5** (0.20 equiv) in neat nitromethane at 45 °C for 5 days afforded the desired adduct **6** in 80 % yield with 97 % *ee*[12] (Scheme 1). The *R*-configuration of the newly-formed quaternary stereogenic center was determined by single-crystal X-ray diffraction analysis of the bromotetrahydrocarbazole derivative[13] **7**.[14]

With a reliable route to (*R*)-**6** in hand, we proceeded to construct the aza-bicyclic compound **13**. A more efficient and scalable seven-step approach to (−)-**13** was developed on the basis of our eight-step approach[4] (Scheme 2). Specifically, regioselective silyl enol etheration of ketone **6** followed by modification of Nicolaou's IBX-oxidation[15] using pyridine-*N*-oxide (PNO) as the ligand instead of the expensive 4-methoxypyridine-*N*-oxide (MPO), produced enone **8** in 79 % yield. Subsequent Luche reduction[16] of the carbonyl group and conversion of the nitro group into an amine (using Zn, HCl, and MeOH) in one pot, produced aminol **9** as a diastereomeric mixture. The amino group was protected

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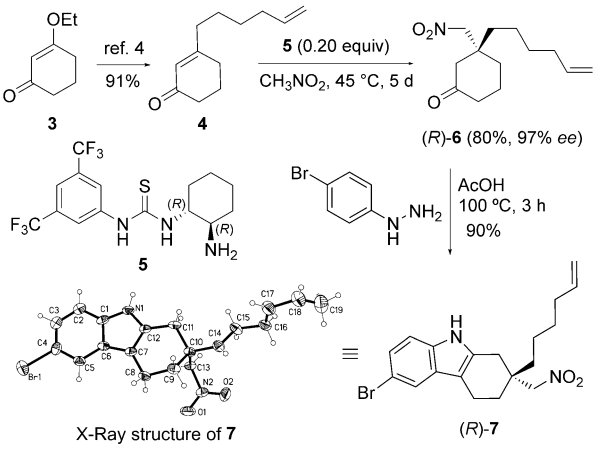
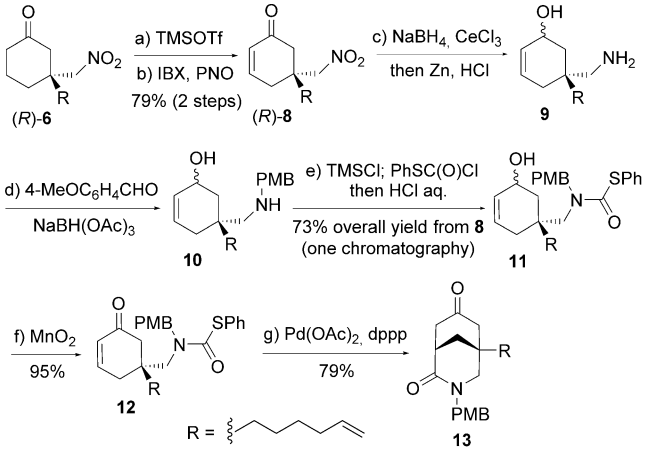


Scheme 1. Organocatalytic, asymmetric conjugate addition of nitromethane to 3-(hex-5-enyl)cyclohex-2-enone (**4**) and determination of the absolute configuration of the adduct.

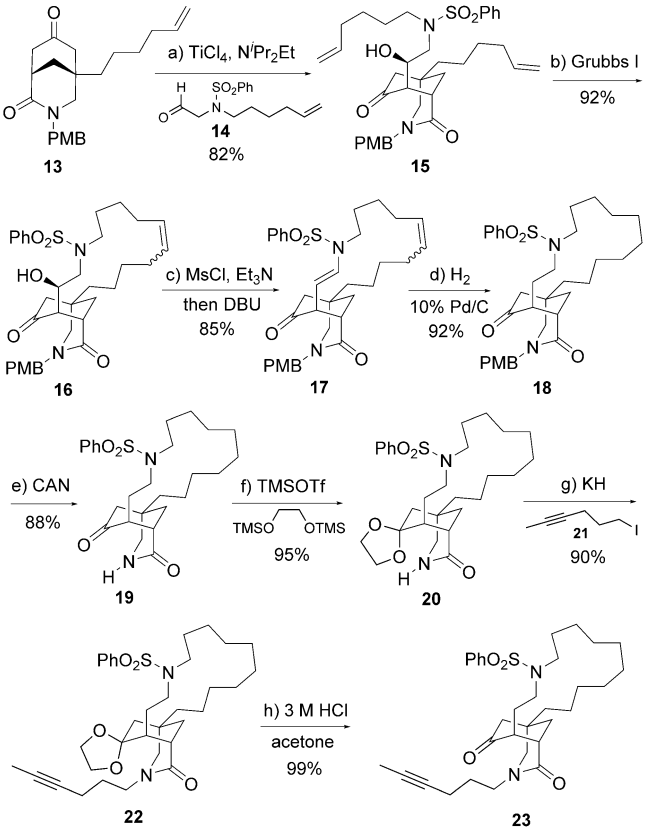


Scheme 2. Construction of the bicyclic ketolactam **13**. Reagents and conditions: a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; b) IBX, pyridine-*N*-oxide (PNO), DMSO, 50 °C; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C→RT; Zn, 4 M HCl; d) 4-$MeOC_6H_4CHO$, $NaBH(OAc)_3$, CH_2Cl_2, 0 °C→RT; e) TMSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C→RT; PhSC(O)Cl; 3 M HCl; f) MnO_2, CH_2Cl_2; g) $Pd(OAc)_2$, dppp, CH_3CN, 120 °C, sealed tube. TMSOTf = trimethylsilyl trifluoromethanesulfonate, IBX = 2-iodoxybenzoic acid, PMB = *p*-methoxybenzyl, DMSO = dimethylsulfoxide, TMSCl = trimethylsilyl chloride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, dppp = 1,3-bis(diphenylphosphino)propane.

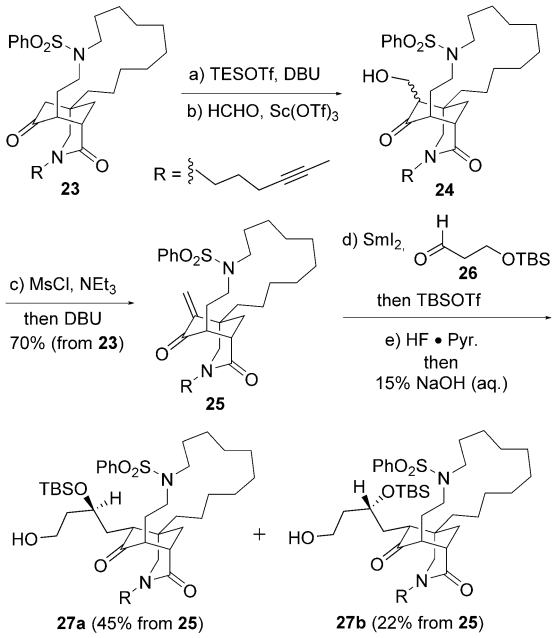
as an N-PMB amine and converted in one pot into phenylthiocarbamate **11** by sequential in situ protection of the free alcohol with a TMS group, reaction with phenyl chlorothioformate, and chemoselective removal of the silyl group. Note that only one chromatographic purification was needed from compound **8** to **11** (a 73% overall yield of compound **8** was obtained). Oxidation of **11** with MnO_2 afforded enone **12** (95% yield), which was cyclized to give the key bicyclic ketolactam **13** in 79% yield by employing our previously reported Pd-catalysis conditions.[4]

$TiCl_4$/Hünig base-mediated aldol addition[17] of **13** with aldehyde **14**[4] yielded diene **15** in 82% yield as a single regio- and diastereomer, with previously confirmed stereochemistry[4] (Scheme 3). The ring-closing methathesis (RCM) reaction[18] of **15**, using Grubbs' first-generation catalyst,[19] produced **16** as a geometric mixture in 92% yield. The hydroxy group was then removed by mesylation and elimination. Catalytic hydrogenation of the resulting diene **17** yielded compound **18** with the desired aza-macrocycle in place. To install an alkynyl group on the amide nitrogen, the PMB group was removed and the ketone was protected as an acetal to give compound **20**. Alkylation using the alkynyl iodide **21** (90% yield) and subsequent acidic hydrolysis of the acetal group afforded the alkyne **23** (99% yield).

Subsequently, we turned our attention to α-functionalization of ketone **23**. After unsuccessful trials that targeted a direct aldol reaction of **23** with *n*-butanal (a model aldehyde),[20] an indirect approach was pursued. Thus, ketone **23** was successively treated with TESOTf/DBU and formalin/$Sc(OTf)_3$[21] to yield the presumed α-hydroxymethylation product **24** (Scheme 4). We were unable to isolate **24** in a pure form because partial epimerization and elimination of **24** into **25** occurred during purification by column chromatography. The diastereomeric mixture **24** was subjected to



Scheme 3. Construction of the diazatricyclic ketolactam **23**. Reagents and conditions: a) $TiCl_4$, N^iPr_2Et, **14**, CH_2Cl_2, −78 °C; b) Grubbs I (0.10 equiv), CH_2Cl_2 (1.8 mM), 40 °C; c) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C→RT; DBU; d) H_2, 10% Pd/C, THF; e) CAN, CH_3CN/H_2O (10:1), 0 °C→RT; f) $TMSOCH_2CH_2OTMS$, ethylene glycol, TMSOTf, CH_2Cl_2, 0 °C→RT; g) KH, **21**, THF; h) 3 M HCl, acetone. MsCl = methanesulfonyl chloride, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran, CAN = ceric ammonium nitrate.

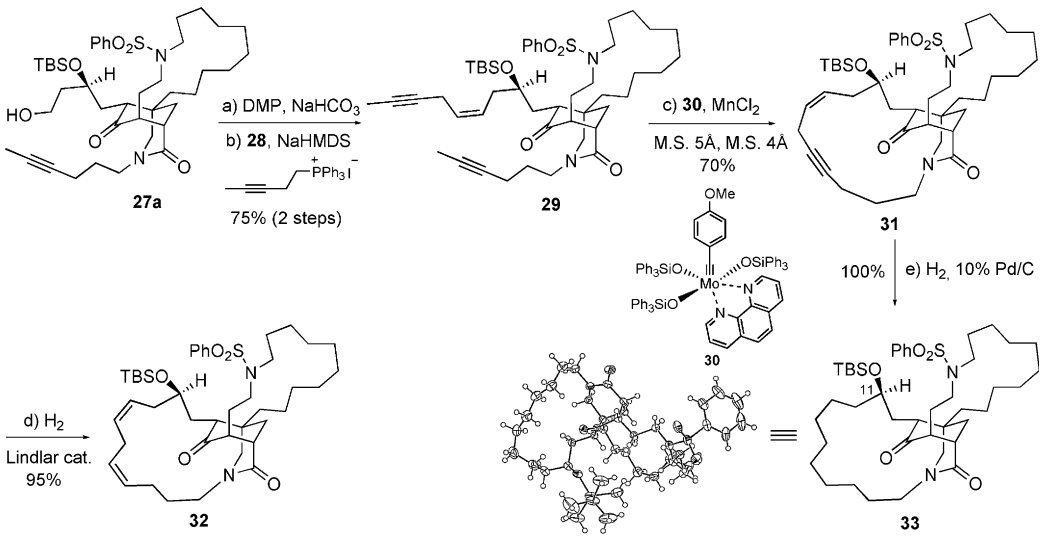


Scheme 4. α-Functionalization of ketone **23** to prepare **27a**. Reagents and conditions: a) TESOTf, DBU, CH_2Cl_2, 0°C→RT; b) $Sc(OTf)_3$, 37% aqueous HCHO, THF; c) MsCl, DMAP, Et_3N, CH_2Cl_2, 0°C→RT; DBU; d) SmI_2, **26**, THF, −78°C; TBSOTf, Et_3N, −78°C→RT; e) HF·Pyr., Pyr., THF, 0°C→RT; 15% aqueous NaOH, 0°C→RT. TESOTf = triethylsilyl trifluoromethanesulfonate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, Pyr. = pyridine.

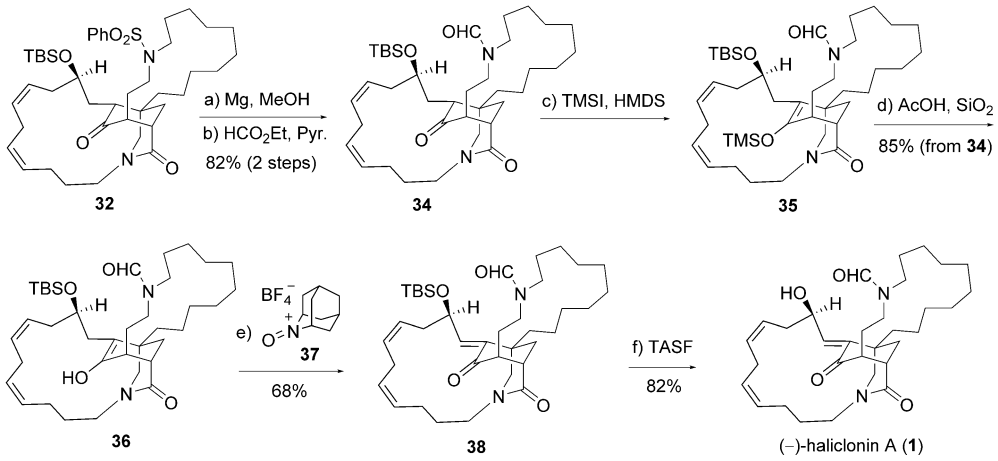
mesylation and elimination with DBU to produce enone **25** (70% yield from **23**). Enone **25** and aldehyde **26** were reductively coupled using SmI_2 (Kagan reagent),[22] followed by *O*-silylation with TBSOTf, monodesilylation with hydrogen fluoride/pyridine in THF, and basic work-up. In this manner, two separable diastereomers **27a** and **27b** were obtained from **25** in 45% and 22% overall yield, respectively. It is noteworthy that although intramolecular reductive coupling of enones[22c] with aldehydes is known, the intermolecular version of this reaction is unprecedented. The stereochemistries of the two newly formed stereogenic centers were not determined at this stage, but deduced from compound **33** at a later stage (see below). The major diastereomer **27a** was employed in the subsequent total synthesis.

To introduce the enyne moiety required for the key ring-closing alkyne metathesis (RCAM)[23,24] reaction, diastereomer **27a** was subjected to Dess–Martin oxidation and Wittig reaction with **28**[25] to afford enediyne **29** in 75% yield over two steps (Scheme 5). Compound **29** cyclized smoothly to give enyne **31** in 70% yield using Fürstner's catalyst (**30**) and alkyne metathesis conditions.[26,27] Compound **31** was hydrogenated to give **33**, allowing confirmation of its structure by single crystal X-ray diffraction analysis. Controlled hydrogenation of the alkynyl group in **31** using Lindlar catalyst afforded tetracyclic diene (13*Z*,16*Z*)-**32** in 95% yield.

To complete the total synthesis, compound **32** was desulfonylated by reaction with Mg in methanol under ultrasonic irradiation,[28] and the resulting crude amine formylated with ethyl formate/pyridine to give diamide **34** in 82% yield over two steps (Scheme 6). Transformation of ketone **34** into enone **38** was quite challenging. After extensive experimentation, a three-pot procedure was developed. Thus, ketone **34** was converted into isolable enol **36** by silyl enol ether formation using TMSI-HMDS in refluxing acetonitrile,[29] followed by desilylation with AcOH/silica gel. Predominant formation of the enol tautomer[30] **36** might result from formation of a H-bond with lactam in this special tetracyclic ring system. Although the attempted oxidation of silyl ether **35** with oxoammonium salt ($AZADO^+BF_4^-$)[31] **37** failed to give the desired enone, oxidation of enol **36** produced enone **38** in 68% yield. The geometry of **38** was not determined at this stage, but deduced from the final product **1**. To the best of our knowledge, this represents the first example of direct conversion of an enol into an enone. Finally, desilylation of **38** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[32] afforded (−)-haliclonin A (**1**) in 82% yield. The sense of optical rotation and spectral data of our synthetic compound (^1H and ^{13}C NMR spectroscopy reveals that the ratio of rotamers is 3:2) fully matched those reported for the natural (−)-haliclonin A (**1**), but



Scheme 5. Construction of the tetracyclic core of (−)-haliclonin A. Reagents and conditions: a) DMP, $NaHCO_3$, CH_2Cl_2; b) NaHMDS, **28**, THF, −78°C→RT; c) Fürstner's catalyst **30**, $MnCl_2$, M.S. 5 Å, M.S. 4 Å, toluene; d) H_2, Lindlar catalyst, 1-hexene, EtOAc; e) H_2, 10% Pd/C, THF. DMP = Dess–Martin periodinane, NaHMDS = sodium hexamethyldisilazane.



Scheme 6. Completion of the total synthesis of (−)-haliclonin A (**1**). Reagents and conditions: a) Mg, MeOH, ultrasonic irradiation; b) HCO_2Et, Pyr., reflux; c) TMSI, HMDS, CH_3CN, reflux; d) AcOH, SiO_2, CH_2Cl_2; e) **37**, CH_2Cl_2, −20–0 °C; f) TASF, H_2O, DMF. Pyr. = pyridine, TMSI = trimethylsilyl iodide, HMDS = hexamethyldisilazane, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, DMF = *N*,*N*-dimethylformamide.

a difference was observed in the values of specific rotation (synthetic **1**: $[\alpha]_D^{20}$ −42.1 (*c* 1.0, MeOH); natural **1**: $[\alpha]_D^{20}$ −23.6 (*c* 0.14, MeOH)[1]). The fact that the synthetic compound displayed the same sign of optical rotation as that of the natural product implies that the absolute configuration of natural (−)-haliclonin A (**1**) is 3*R*,4*S*,6*R*,11*R*, which is in agreement with the structure displayed in Figure 1 of Ref. [1] (see Figure 1), but different from that suggested in the text of Ref. [1] (3*S*,4*R*,6*S*,11*S*).[1]

In summary, we have accomplished the first total synthesis of (−)-haliclonin A (**1**). Through this enantioselective total synthesis, the structure of natural (−)-haliclonin A (**1**) has been confirmed, and its absolute configuration clarified as 1*E*,3*R*,4*S*,6*R*,11*R*,13*Z*,16*Z*. During the course of this work, new chemistry has been developed, which includes the thiourea **5**-catalyzed asymmetric conjugate addition of nitromethane and 3-substituted cyclohex-2-enone, SmI_2-mediated bimolecular reductive coupling of enone with aldehyde, and direct transformation of enol into enone.

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