CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201203203

Toward the Total Synthesis of Haliclonin A: Construction of a Tricyclic Substructure

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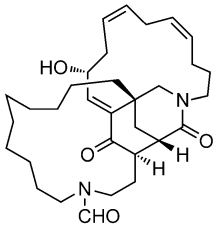
In memory of Wei-Shan Zhou

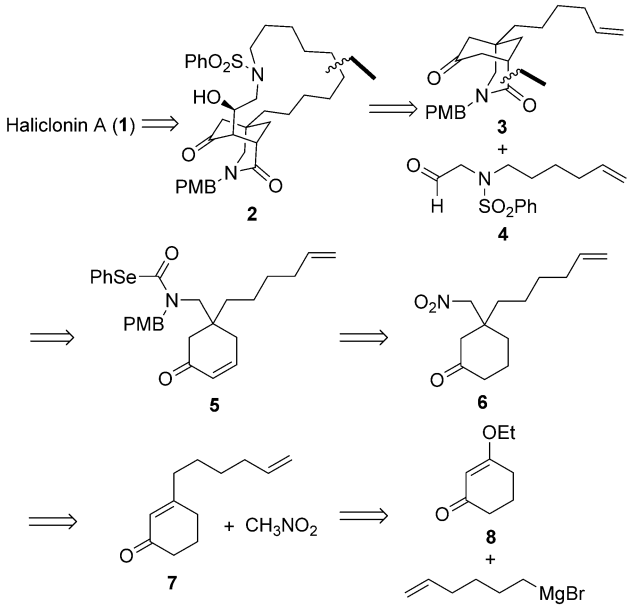


Haliclonin A (**1**)

Haliclonin A (**1**) is a macrocyclic natural product isolated in 2009 from a marine sponge, *Haliclona* sp., collected from Korean waters.[1] The isolated compound was shown to be a mixture of two rotamers. The structure of the major rotamer was determined, only partially, on the basis of mass-spectrometric, spectroscopic, and chemical analyses. The absolute configuration of that portion was assigned as 1*E*,3*S*,4*R*,6*S*,11*S*. Preliminary bioassays showed that this compound exhibits moderate antibacterial activity against several microbial strains, and cytotoxicity against the K562 leukemia cell line with an IC_{50} value of 15.9 μg mL^{-1}. However, to date, no synthetic study towards haliclonin A (**1**) has been reported.

In continuation of our longstanding interest in the total synthesis of natural products,[2] we have recently reported a concise synthesis of the diazatricyclic core of sarain A.[3] In connection with this, we have undertaken a study aimed at the total synthesis of haliclonin A (**1**). Preliminary results, involving the construction of compound **2**, a tricyclic core of haliclonin A (**1**), are reported herein.

Structurally, haliclonin A (**1**) is a tetracyclic compound containing two macrocyclic rings and an azabicyclic core. The tricyclic core is similar to that found in sarain A,[4] although the 3-azabicyclo[3.3.3]nonane system in the form of a keto amide is unprecedented. Our retrosynthetic analysis of haliclonin A (**1**) is outlined in Scheme 1, and features



Scheme 1. Retrosynthetic analysis of haliclonin A (**1**). PMB = *para*-methoxybenzyl.

construction of the trienic macrocycle as the final step. Thus, tricyclic substructure **2** was selected as a target en route to the final compound. For the synthesis of this molecule, construction of the macrocycle was planned through a ring-closing metathesis (RCM) reaction.[5,6] The bicyclic compound **3** was envisioned to be accessible from phenylselenocarbamate **5** through an intramolecular radical reaction[7] or a transition-metal-mediated reaction.[8]

The synthesis of **2** started from commercially available 3-ethoxycyclohex-2-enone (**8**; Scheme 2). Addition of a Grignard reagent gave, upon workup, the desired β-substituted enone **7** in 84% yield.[9] The Michael addition of nitromethane to enone **7** was achieved by the Hanessian method,[10] with a minor modification. In the event, treatment of enone **7** with nitromethane, racemic proline (0.4 equiv) and *meso*-*N*,*N*-dimethyl-2,4-piperazine (1.5 equiv) in chloroform at 50 °C for 7 d produced the desired addition product (**6**) in 81% yield (98% BRSM). For the transformation of the cyclohexanone derivative **6** into

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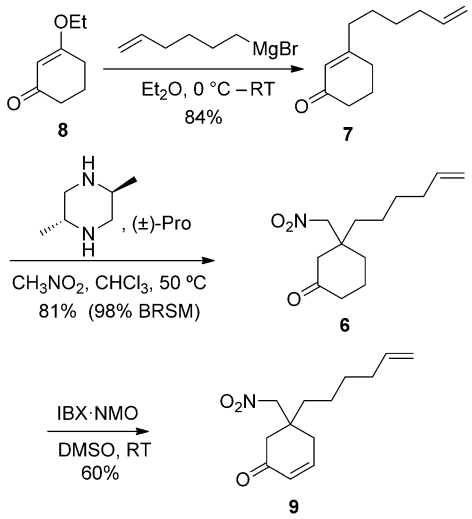
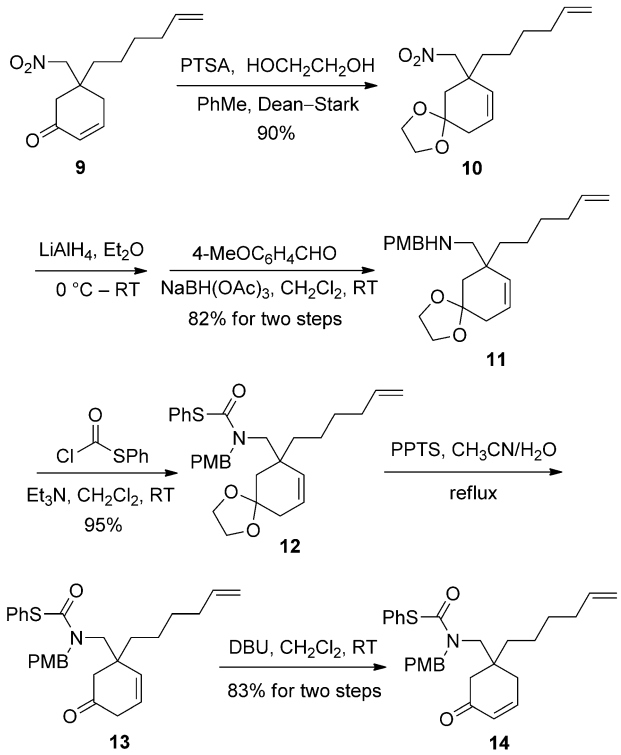
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203203.



Scheme 2. Synthesis of compound **9**. Pro = proline; BRSM = based on recovered starting material; IBX·NMO = 2-iodoxybenzoic acid *N*-methylmorpholine *N*-oxide complex; DMSO = dimethyl sulfoxide.



Scheme 3. Synthesis of the key intermediate enone **14**. PTSA = *para*-toluenesulfonic acid; PPTS = pyridinium *para*-toluenesulfonate; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

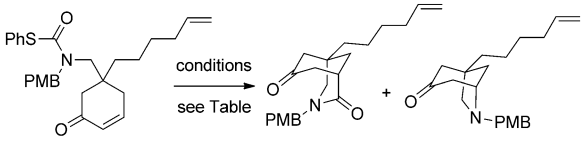
α,β-enone **9**, the Saegusa oxidation[11] was attempted, but without success. Furthermore, oxidation with 2-iodoxybenzoic acid (IBX) in DMSO[12] gave only a low yield. However, oxidation with a complex formed from IBX and *N*-methylmorpholine *N*-oxide (NMO) in DMSO[13] at room temperature for 3 d produced the desired racemic enone **9** in a one-pot process in 60% yield.

Protection of the ketone **9** was undertaken by PTSA-catalyzed acetalization with ethylene glycol in toluene at reflux for 24 h,[14] which gave the double-bond-migration product **10** in 90% yield (Scheme 3). Reduction of the nitro group with $LiAlH_4$,[15] followed by reductive alkylation[16] of the crude amine with anisaldehyde and $NaBH(OAc)_3$ in CH_2Cl_2 at room temperature for 4 h furnished the desired PMB-protected product **11** in 82% yield over the two steps from **10**.

Our next task was the synthesis of phenylselenocarbamate **5**, a precursor for cyclization.[17] After many unsuccessful attempts, we modified our plan by selecting phenylthiocarbamate **14** as an alternative to compound **5**. Thus, compound **12** was synthesized by acylation with (*S*)-phenyl carbonochloridothioate.[18] Deacetalization of compound **12** by PPTS-catalyzed hydrolysis in MeCN/H_2O, gave ketone **13**, which afforded, upon treatment with DBU (1.0 equiv) in CH_2Cl_2 for 4 h at room temperature, the reconjugated[19] enone **14** in 83% yield.

With the enone precursor (**14**) for the cyclization reaction in hand, we first attempted the intramolecular radical cyclization reaction.[7] Unfortunately, if the $(Me_3Si)_3SiH$/AIBN combination was used,[7e,20] the starting material remained intact (Table 1, entry 1), whereas, if the Bu_3SnH/AIBN combination[7e,21] was used, a complex mixture of products was obtained (Table 1, entry 2). We thereupon turned to the investigation of the transition-metal-mediated cyclization reactions.[8,22] After several unsuccessful attempts (see Table 1, entries 3 and 4), we found that treatment of compound **14** with a catalytic amount of $[Pd(Ph_3P)_4]$ in toluene at 110 °C for 12 h could give the desired cyclization product **3** in 12% yield, along with a 4% yield of the decar-

Table 1. Pd-mediated cyclization of enone **14**.



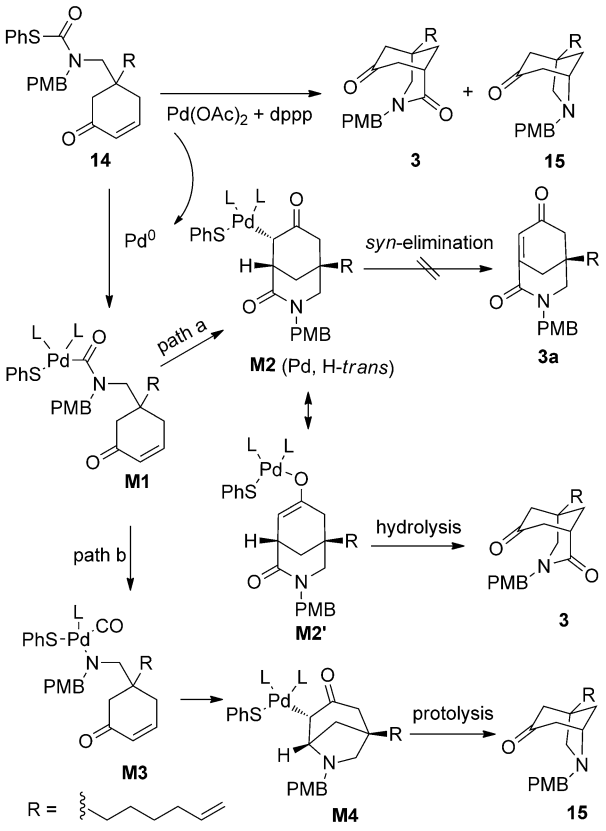
Entry	Conditions ([equiv])	Product (yield [%])[a]
1	$(Me_3Si)_3SiH$ (1.2), AIBN (0.20), PhMe, 110 °C	N.R.[b]
2	Bu_3SnH (1.2), AIBN (0.20), PhMe, 110 °C	Complex mixture
3	$Pd(OAc)_2$ (0.20), Bu_4NCl, $HCOONH_4$, DMF, 120 °C	N.R.
4	$[Pd(dppb)Cl_2]$ (0.20), PhMe, dppb, 110 °C	N.R.
5	$[Pd(Ph_3P)_4]$ (0.20), PhMe, 110 °C	**3** (12), **15** (4), **14** (70)
6	$[Pd(Ph_3P)_4]$ (0.20), Et_3N or $HCOONH_4$, PhMe, 100 °C	Low yield
7	$[Pd(Ph_3P)_4]$ (0.50), PhMe, 110 °C	**3** (28), **15** (10), **14** (45)
8	$[Pd(Ph_3P)_4]$ (1.0), PhMe, 110 °C	**3** (50), **15** (28)
9	$[Pd(Ph_3P)_4]$ (1.0), PhMe, dppp (1.0), 110 °C	**3** (58), **15** (15)
10	$Pd(OAc)_2$ (1.0), dppp (1.5), CH_3CN, RT–90 °C	N.R.
11	$Pd(OAc)_2$ (1.0), dppp (1.5), CH_3CN, 100 °C	**3** (75), **15** (5)
12	$Pd(OAc)_2$ (1.0), dppp (2.0), CH_3CN, 100 °C	**3** (79), **15** (trace)

[a] Yield of the isolated product. [b] No reaction. AIBN = azobisisobutyronitrile; DMF = *N*,*N*-dimethylformamide; dppb = 1,4-bis(diphenylphosphino)butane; dppp = 1,3-bis(diphenylphosphino)propane.

bonylative cyclization side product **15** and a 70% yield of the recovered starting material (Table 1, entry 5). Triethylamine and ammonium formate were then tested as additives; however, neither led to any improvement (Table 1, entry 6). On the other hand, the yield of the desired product could be improved by increasing the catalyst loading; however, an increased amount of the decarbonylative side product **15** was obtained (Table 1, entries 5, 7, and 8).

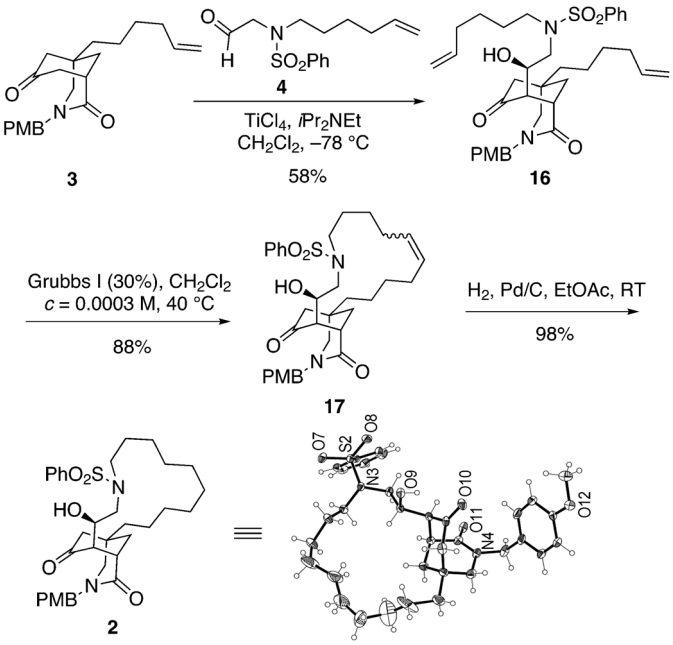
These results indicated that a catalytic cycle was not formed during the reaction.[22i] The decarbonylative side product **15** might be produced as a result of the oxidative addition of Pd^0 to phenylthiocarbamate **14**, followed by a decarbonylation and intramolecular insertion reaction.[22g,23] On the basis of this consideration, the addition of a chelating diphosphine ligand was envisioned to be able to inhibit this side reaction. Indeed, in the presence of 1.0 equivalent of dppp, the ratio of **3**/**15** was slightly improved (Table 1, entry 9). Further optimization showed that when a combination of 1.0 equivalent of $Pd(OAc)_2$ and 2.0 equivalents of dppp was used as the source of Pd^0, along with MeCN as a chelating solvent, the reaction proceeded smoothly at 100 °C to yield the desired product **3** in 79% yield, with only a trace amount of side product **15** observed (Table 1, entry 12).

A plausible mechanism for this unprecedented Pd-mediated cyclization reaction is depicted in Scheme 4. Oxidative addition of compound **14** with Pd^0 gives Pd complex **M1**, from which two pathways are possible. The first, path a, involves an intramolecular insertion reaction, leading to Pd complex **M2**, the *syn*-β-elimination[22g] of which (leading to the bridgehead enone **3a**)[24] is not possible. However, hydrolysis of Pd complex **M2** via its tautomer **M2′** gives the major product **3**.[22i,j] In the second, path b, Pd complex **M1** undergoes a decarbonylation reaction to give Pd complex **M3**,[22g,23] which goes through an intramolecular insertion reaction to give **M4**. Protolysis of Pd complex **M4** produces the side product **15**. Use of the bidentate dppp ligand and MeCN as a chelating solvent inhibits the decarbonylation of Pd complex **M1** to give Pd complex **M3**, thus preventing the formation of the side product **15**.



Scheme 4. Proposed mechanism of the Pd-mediated cyclization.

For the aldol reaction of ketone **3** with aldehyde **4**, prepared in three steps from 6-bromohex-1-ene,[25] several methods were attempted. It was found that treatment of **3** and **4** with $TiCl_4$/iPr$_2$NEt[26] gave the optimal result (58% yield, Scheme 5), providing aldol **16** as the only observable



Scheme 5. Construction of the racemic tricyclic substructure **2**.

isomer in the ^{1}H NMR spectrum. The high regio- and diastereomeric selectivity of this reaction was surprising because several regio- and diastereomers were possible. Since no isomers were observed in either the ^{1}H or ^{13}C NMR spectra, in order to check the purity of the product the crude aldol product was subjected to LC-MS analysis. Indeed, only a trace of an isomer was found, in a ratio of **16**/isomer as high as 56.5:1 (see the Supporting Information for the LC-MS diagram). Thus, the high regio- and diastereomeric selectivity of this reaction was confirmed.

As displayed in the retrosynthetic analysis (Scheme 1), the formation of the macrocycle was planned to be accomplished by an RCM reaction. For this purpose, diene **16** was subjected to the RCM reaction by using the Grubbs first-

generation catalyst and a high-dilution technique ($0.0003\ mol\ L^{-1}$ in CH_2Cl_2, 40 °C, 24 h)[27,28] to give the cyclized product **17** as an inseparable mixture of geometric isomers in a ratio of approximately 5.2:1 (as determined by ^1H NMR spectroscopy) in 88 % yield.[29] Without separation, the isomeric mixture was hydrogenated in the presence of 10 % Pd/C as the catalyst[27] to give the desired product **2**[30] in 98 % yield. The structure of compound **2** was confirmed by single-crystal X-ray diffraction analysis (Scheme 5).

In summary, we have developed a concise method for the construction of a tricyclic substructure (**2**) of haliclonin A (**1**). In this synthesis, a new, Pd-mediated chemoselective carbonyl–enone coupling reaction was developed for the key cyclization step in the construction of the bridged bicyclic system. In addition, this synthesis also features an organocatalytic reaction and a RCM reaction for the construction of the macrocyclic ring. Work towards the total synthesis of haliclonin A (**1**) is in progress.

Acknowledgements

The authors are grateful to the NSF of China (20832005, 21072160) and the National Basic Research Program (973 Program) of China (Grant No. 2010CB833200) for financial support.

Keywords: alkaloids · haliclonin A · palladium · ring-closing metathesis · total synthesis · transition metals

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[29] The stereochemistry of the isomers was not determined. However, many macrocycles formed by use of the Grubbs first-generation catalyst were reported to give (*E*)-olefins as the major diastereomers. See ref. [20] for details.
[30] Data for Compound **2**: white solid; m.p. 96–98 °C (EtOAc); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.82$–7.78 (m, 2H; Ar-*H*), 7.66–7.52 (m, 3H; Ar-*H*), 7.07–7.03 (m, 2H; Ar-*H*), 6.86–6.82 (m, 2H; Ar-*H*), 4.59 (d, $J = 14.4$ Hz, 1H; PhCH_2), 4.34–4.27 (m, 1H; C*H*OH), 4.26 (d, $J = 14.4$ Hz, 1H; PhCH_2), 3.78 (s, 3H; CH_3), 3.35 (d, $J = 2.2$ Hz, 1H; O*H*), 3.19–2.99 (m, 4H; CH_2NS), 2.94 (d, $J =$

12.2 Hz, 1H; CH_2NCO), 2.90–2.78 (m, 3H; CH_2NCO, COCH_2, NCOC*H*), 2.67–2.59 (m, 1H; CCH_2CH), 2.52 (d, J=6.3 Hz, 1H; OCHC*H*C=O), 1.97 (d, J=15.4 Hz, 1H; NCOCHCH_2), 1.66–1.59 (m, 1H; CCH_2CH), 1.56–1.18 ppm (m, 18H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=208.0, 170.3, 159.1, 137.2, 133.1, 129.6 (2C), 129.3 (2C), 128.3, 127.4 (2C), 114.0 (2C), 70.3, 59.8, 55.6. 55.2, 54.1, 52.7, 49.4 (2C), 42.7, 37.5, 29.7, 28.7 (2C), 28.6, 28.3, 27.6, 27.4, 27.2, 26.0, 22.4 ppm; IR (film): $\tilde{\nu}_{max}$=3433, 2930, 2855, 1717, 1644, 1624, 1513, 1446, 1336, 1264, 1160, 746 cm^{-1}; MS (ESI): m/z (%): 633 (100) $[M+Na]^+$; HRMS (ESI): m/z calcd for $[C_{34}H_{46}N_2O_6S+Na]^+$: 633.2974; found: 633.2975.

Received: September 8, 2012
Revised: November 12, 2012
Published online: December 5, 2012

