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Total Synthesis of Shishijimicin A

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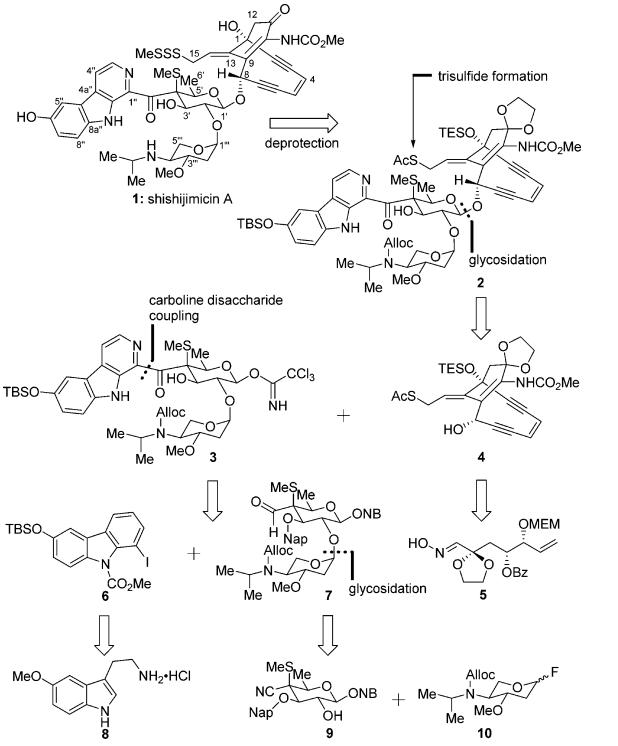
Supporting Information

ABSTRACT: The total synthesis of the rare but extremely potent antitumor agent shishijimicin A has been achieved via a convergent strategy involving carboline disaccharide **3** and hydroxy enediyne thioacetate **4**.

Naturally occurring substances provided the first medications to treat disease and continue to be a rich source and inspiration for drug discovery and development.[1,2] Among them are cytotoxic compounds, some of which are used to treat cancer.[1] Unfortunately, most cytotoxic compounds, including those with the highest potencies, fail to make it to the clinic because of severe side effects. The advent of antibody−drug conjugates (ADCs) ushered in by Mylotarg, the first ADC to be approved by the FDA and equipped with the highly potent natural product calicheamicin γ_1^I,[3,4] led to a new paradigm whereby previously failed potent cytotoxic agents became highly desirable as payloads for conjugation to antibodies as potential targeted drugs against cancer.[5,6] Shishijimicin A (**1**) (Scheme 1)[7] is a rare marine natural product endowed with extremely potent antitumor properties (IC_{50} = 0.48 pM against P388 leukemia cells).[7] In view of its phenomenal biological activity and the new paradigm for targeted cancer chemotherapy, shishijimicin A constitutes a highly desirable payload for ADCs, an attractive possibility thus far hindered by its scarcity. In this Communication, we report the first total synthesis of shishijimicin A, rendering the molecule readily available for further biological investigations and opening the way for the construction of designed analogues of this valuable but rare molecule.

The similarities between **1**[7] and calicheamicin γ_1^I[3,4] extend from their common enediyne moiety to their Bergman cycloaromatization-based mechanism of action involving double-stranded DNA cleavage.[8] Their structures, however, differ substantially with regard to the constitution of their pentacyclic DNA binding domains, which include a carboline system for shishijimicin A and a fully substituted iodophenyl ring for calicheamicin γ_1^I, both of which are known DNA-binding structural motifs.[9,10] The synthetic roadmap toward **1** was designed on the basis of the retrosynthetic analysis shown in Scheme 1. Thus, protection of the phenolic (TBS), amino (Alloc), and tertiary hydroxyl (TES) groups and transformation of the methyl trisulfide of the target molecule to a thioacetate moiety in the retrosynthetic sense led to its protected enediyne thioacetate **2** as a potential precursor. Disconnection of the glycoside bond linking the enediyne domain of **2** with its pentacyclic appendage revealed enediyne fragment **4** and trichloroacetimidate **3** as potential advanced intermediates for coupling in the synthetic direction. Enediyne **4** was traced back to the readily available key building block **5**, which was previously

Scheme 1. Structure and Retrosynthetic Analysis of 1[a]



[a]Abbreviations: TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; Ac = acetyl; Alloc = allyloxycarbonyl; Bz = benzoyl; MEM = (2-methoxyethoxy)methyl; Nap =2-naphthylmethyl; NB = *o*-nitrobenzyl.

employed in the total synthesis[11−14] of calicheamicin γ_1^I.[15] The pentacyclic advanced intermediate **3** was further disconnected at the indicated carbon−carbon bond bridging the carboline structural motif to the disaccharide domain, furnishing iodocarboline **6** and disaccharide aldehyde **7** [upon modification of the trichloroacetimidate group to the photolabile *o*-nitrobenzyl (NB) ether protecting group] as potential precursors. Finally, **6** was traced back to tryptamine derivative **8**, while **7** was disconnected into its obvious monosaccharide units **9** (acceptor) and **10** (donor) as key building blocks.[16]

The synthesis of the required enediyne thioacetate precursor **4** from key building block **5**[13] proceeded as shown in Scheme 2. This route represents a streamlined and significantly improved version of the original synthesis of the benzoate counterpart of **4** employed in the total synthesis of calicheamicin γ_1^I (19 steps,

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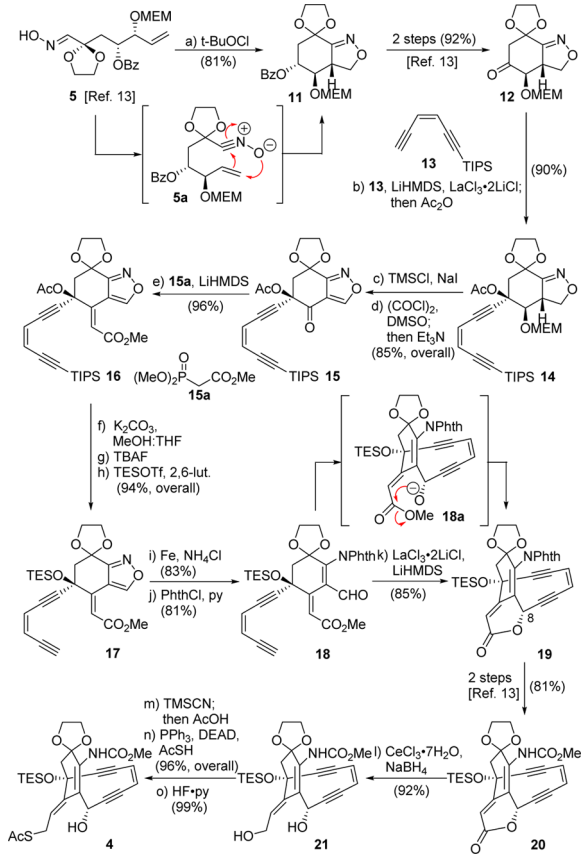
Scheme 2. Synthesis of 4[a]



[a]Reagents and conditions: (a) *t*-BuOCl (3.0 equiv), benzene, 25 °C, 30 min, 81%; (b) **13** (3.0 equiv), LiHMDS (2.8 equiv), $LaCl_3$·2LiCl (5.0 equiv), THF, −78 °C, 30 min, then **12**, −78 °C, 30 min, then Ac_2O (10.0 equiv), −78 to 25 °C, 2 h, 90%; (c) TMSCl (4.0 equiv), NaI (2.0 equiv), MeCN, 0 to 25 °C, 30 min; (d) $(COCl)_2$ (4.0 equiv), DMSO (8.0 equiv), CH_2Cl_2, −78 °C, 30 min, then Et_3N (10.0 equiv), −78 to 25 °C, 1.5 h, 85% for the two steps; (e) **15a** (2.0 equiv), LiHMDS (1.5 equiv), THF, −78 to 25 °C, 1.5 h, 96%; (f) K_2CO_3 (1.0 equiv), MeOH/THF (1:1), 0 to 25 °C, 3 h; (g) TBAF (1.0 equiv), THF, 0 °C, 10 min; (h) TESOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 to 25 °C, 2 h, 94% for the three steps; (i) Fe (25 equiv), NH_4Cl (50 equiv), EtOH/H_2O (1:1), 60 °C, 8 h, 83%; (j) PhthCl (1.5 equiv), py (4.0 equiv), $MeNO_2$, 0 °C, 30 min, 81%; (k) LiHMDS (2.0 equiv), $LaCl_3$·2LiCl (3.0 equiv), THF, −78 °C, 1 h, 85%; (l) $NaBH_4$ (2.0 equiv), $CeCl_3$·$7H_2O$ (3.0 equiv), MeOH, 25 °C, 2 h, 92%; (m) TMSCN (neat), 25 °C, 30 min, then remove excess TMSCN, then dissolve in THF/H_2O (5:1), AcOH (5.0 equiv), 0 °C, 30 min; (n) PPh_3 (5.0 equiv), DEAD (5.0 equiv), AcSH (5.0 equiv), THF, 0 °C, 5 min, 96% for the two steps; (o) HF·py/THF (1:20), 0 °C, 30 min, 99%. LiHMDS = lithium bis(trimethylsilyl)amide; TMS = trimethylsilyl; DMSO = dimethyl sulfoxide; TBAF = tetra-*n*-butyl ammonium fluoride; Phth = phthaloyl; py = pyridine; DEAD = diethyl azodicarboxylate.

21% overall yield from **5** vs 21 steps, 1.7% overall yield from **5**).[11−14] It should also be noted that thioacetate **4** is a more advanced precursor for the methyl trisulfide unit required for both shishijimicin A and calicheamicin γ_1^I, thereby saving steps in the postcoupling sequence to the final target. Thus, as shown in Scheme 2, oxidation of oxime **5** to the corresponding nitrile oxide (**5a**) with the improved conditions involving *t*-BuOCl followed by spontaneous [3 + 2] dipolar cycloaddition of the latter intermediate (see **5a** in Scheme 2) led to **11** in 81% overall yield with ≥10:1 dr (compared with 51% yield and ca. 4:1 dr in the previous route).[13] Conversion of the latter compound to ketone **12** (deprotection/oxidation) proceeded smoothly as previously reported (two steps, 92% overall yield).[13] The subsequent coupling of **12** with enediyne fragment **13**,[17] however, was significantly improved by using LiHMDS in the presence of $LaCl_3$·2LiCl,[18] affording, after in situ acetylation, the desired enediyne **14** in 90% overall yield (compared with 69% yield under the originally employed conditions).[13] Removal of the MEM group from **14** followed by Swern oxidation of the resulting secondary alcohol and concomitant oxidation of the isoxazoline to the isoxazole moiety furnished keto−isoxazole **15** (85% overall yield for the two steps). The latter intermediate served admirably as a substrate for the exclusively *E*-selective Horner−Wadsworth−Emmons olefination that followed [$(MeO)_2P(O)CH_2CO_2Me$ (**15a**), LiHMDS], leading to *E*-α,β-unsaturated methyl ester **16** in 96% yield. Acetate **16** was then transformed to terminal acetylene TES ether **17** in 94% overall yield through a sequence involving removal of the acetate group (K_2CO_3), cleavage of the TIPS moiety (TBAF), and silylation (TESOTf). Rupture of the isoxazole moiety in **17** was then achieved more conveniently and efficiently than before[13] through the use of Fe in EtOH/H_2O (83%), and the resulting amino aldehyde was captured by phthaloyl chloride (PhthCl) in the presence of pyridine to afford *N*-phthalide aldehyde **18** (81%). The direct and stereoselective cyclization of **18** to give cyclic enediyne **19** (via intermediate **18a**; see Scheme 2) using LiHMDS−$LaCl_3$·2LiCl[18] in THF in 85% yield represents a major improvement over the previously used three-step sequence requiring inversion of the opposite configuration at C8 obtained from the same substrate (i.e., **18**) through the use of KHMDS in toluene.[13] The observed stereoselectivity is presumed to be due to complexation of La^{3+} to the aldehyde and ester oxygens, which fixes the conformation of the aldehyde moiety in the proper orientation. The *N*-phthalide moiety of **19** was then converted to the desired methyl carbamate group by reaction with $MeNHNH_2$ followed by exposure of the resulting amine to triphosgene in the presence of pyridine and MeOH as previously reported,[13] affording enediyne lactone **20** in 81% overall yield. Reduction of the lactone moiety in **20** was achieved in one step and 92% yield using $NaBH_4$−$CeCl_3$·$7H_2O$ (as opposed to two steps and 84% overall yield in the original route),[13] providing a further improvement in the overall sequence to enediyne diol **21**. Finally, conversion of **21** to the targeted enediyne thioacetate fragment **4** was accomplished efficiently by sequential treatment with excess TMSCN (bis-silylation), AcOH (selective primary TMS cleavage), Ph_3P-DEAD-AcSH (Mitsunobu reaction, thioacetate formation), and HF·py (secondary TMS cleavage) in 95% overall yield.

To construct iodocarboline **6** (Scheme 3a), carboline **22** [prepared in 52% overall yield from commercially available 5-methoxytryptamine (**8**) through a known three-step sequence[19]] was silylated (TBSOTf, Et_3N, 97% yield) to afford **23**, which was converted to carbamate **24** (KHMDS, $ClCO_2Me$, 98% yield). The latter compound was reacted with 2,2,6,6-tetramethylpiperidinylmagnesium chloride·lithium chloride complex (TMPMgCl·LiCl)[20] and I_2, furnishing the desired iodocarboline **6** in 83% yield.

The required disaccharide **7** was synthesized from the readily available glucal **25**[21] and glycosyl fluoride **10**[16,22] as depicted in Scheme 3b. Benzoylation of the free hydroxyl group of **25** (BzCl, Et_3N, 97% yield) followed by sequential treatment of the resulting benzoate glucal **26** with in situ-generated DMDO and *o*-nitrobenzyl alcohol (*o*-NBOH) furnished hydroxy-*o*-nitro-

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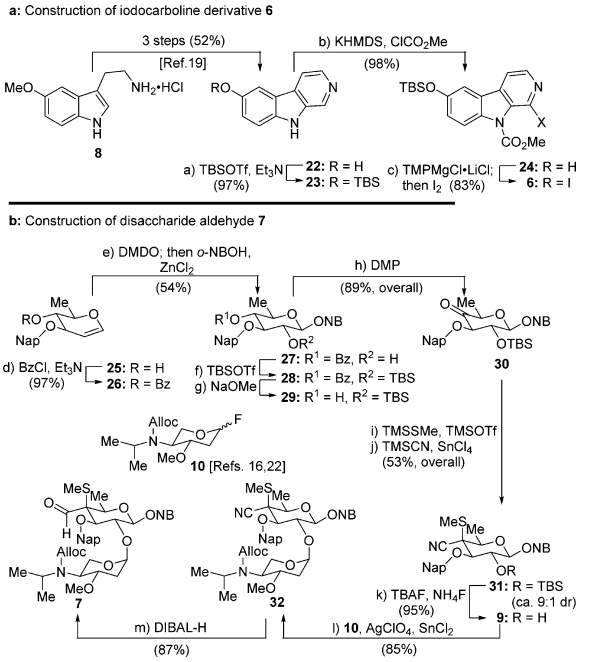
Scheme 3. Syntheses of 6 and 7[a]

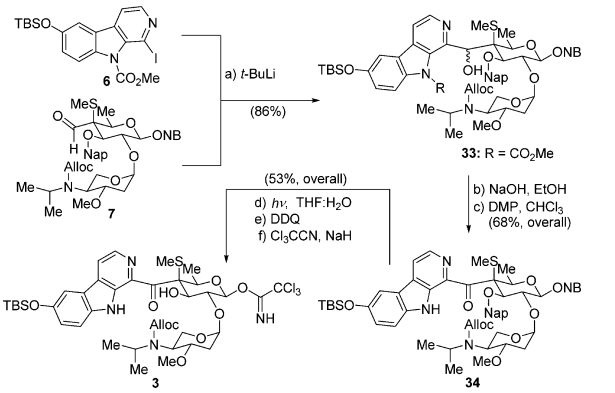


[a]Reagents and conditions: (a) TBSOTf (1.05 equiv), Et_3N (3.0 equiv), DMF, 0 °C, 30 min, 97%; (b) $ClCO_2Me$ (1.1 equiv), KHMDS (1.05 equiv), THF, 0 °C, 30 min, 98%; (c) TMPMgCl·LiCl (4.0 equiv), THF, −78 to 25 °C, 4 h, then I_2 (5.0 equiv), THF, −78 to 0 °C, 30 min, 83%; (d) BzCl (1.05 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C, 30 min, 97%; (e) Oxone (5.0 equiv), $NaHCO_3$ (25 equiv), acetone/H_2O/CH_2Cl_2 (1:3:4), 25 °C, 4 h, then *o*-NBOH (3.0 equiv), $ZnCl_2$ (1.5 equiv), 4 Å MS, THF, −78 to 25 °C, 4 h, 54%; (f) TBSOTf (1.05 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C, 30 min; (g) NaOMe (10.0 equiv), MeOH, 40 °C, 24 h; (h) DMP (1.2 equiv), CH_2Cl_2, 0 to 25 °C, 1 h, 89% for the three steps; (i) TMSSMe (2.5 equiv), TMSOTf (1.5 equiv), toluene, −20 to 0 °C, 30 min, 61%; (j) TMSCN (3.5 equiv), $SnCl_4$ (1.5 equiv), CH_2Cl_2, 0 °C, 3 h, 87% (ca. 9:1 dr); (k) TBAF (5.0 equiv), NH_4F (10.0 equiv), THF, 0 °C, 1 h, 95%; (l) **10** (2.2 equiv), $AgClO_4$ (2.5 equiv), $SnCl_2$ (2.5 equiv), 4 Å MS, THF, −78 to 25 °C, 12 h, 85%; (m) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 45 min, 87%. KHMDS = potassium bis(trimethylsilyl)amide; TMP = 2,2,6,6-tetramethylpiperidinyl; DMDO = dimethyldioxirane; *o*-NBOH = *o*-nitrobenzyl alcohol; DMP = Dess–Martin periodinane; DIBAL-H = diisobutylaluminum hydride.

benzyl ether **27** in 54% overall yield via the corresponding epoxide intermediate.[23] The newly generated hydroxyl group of **27** was converted to its TBS ether (TBSOTf, Et_3N) to afford **28**, from which the benzoate moiety was cleaved (NaOMe) to give alcohol **29**. DMP oxidation of **29** led to ketone **30** in 89% overall yield for the three steps from **27**. Reaction of **30** with TMSSMe in the presence of TMSOTf furnished the corresponding methylthioketal,[16,24] which underwent stereoselective cyanation[25] upon exposure to TMSCN and $SnCl_4$ to afford nitriles **31** and 4-*epi*-**31** (ca. 9:1 dr, 53% yield for the two steps). Removal of the TBS group from **31** (TBAF, NH_4F)[26] gave carbohydrate acceptor **9** (95% yield), whose coupling with carbohydrate donor **10**[16,22] proceeded smoothly in the presence of $AgClO_4$ and $SnCl_2$ to afford the desired α-glycoside **32** stereoselectively in 85% yield. Finally, DIBAL-H reduction of the nitrile group in **32** led to the targeted aldehyde **7** in 87% yield.

The coupling of iodocarboline **6** and disaccharide aldehyde **7** proceeded through the lithio derivative of the former (generated with *t*-BuLi at −78 °C) to give alcohol **33** (86% yield, ca. 1:1 dr, inconsequential), as shown in Scheme 4. Treatment of carboline carbamate **33** with NaOH in EtOH led to the corresponding free amine, whose oxidation with DMP gave ketone **34** in 68% yield over the two steps. Photolytic cleavage[14] of the *o*-nitrobenzyl ether moiety from the latter compound followed by sequential treatment with DDQ (removal of naphthyl group) and Cl_3CCN–NaH (trichloroacetimidate formation) resulted in the stereoselective formation of the coveted trichloroacetimidate **3** (53% overall yield, β-anomer exclusively).

Scheme 4. Coupling of 6 and 7 and Elaboration To Give 3[a]



[a]Reagents and conditions: (a) **6** (3.0 equiv), *t*-BuLi (6.0 equiv), THF, −78 °C, 30 min, then **7** (1.0 equiv), −78 to −35 °C, 40 min, 86% (ca. 1:1 dr) based on **7**; (b) NaOH (3.0 equiv), EtOH, 0 to 25 °C, 2.5 h; (c) DMP (1.1 equiv), $CHCl_3$, 0 to 35 °C, 10 min, 68% for the two steps; (d) $h\nu$, THF/H_2O (10:1), 4.5 h; (e) DDQ (2.5 equiv), CH_2Cl_2/H_2O (10:1), 30 °C, 1.5 h; (f) NaH (2.0 equiv), Cl_3CCN/CH_2Cl_2 (1:2), 25 °C, 5 min, 53% for the three steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Having assembled the two advanced intermediates, trichloroacetimidate **3** and hydroxy enediyne **4**, the next objective became their coupling and elaboration of the resulting product to give shishijimicin A (**1**). Scheme 5 depicts how this challenging task was accomplished. Indeed, it was after considerable experimentation that the two fragments (i.e., **3** and **4**) were joined through the action of BF_3·Et_2O to afford β-glycoside **2** selectively in 26% yield. It should be noted that the corresponding naphthyl ether trichloroacetimidate proved resistant to glycosidation, presumably because of severe steric hindrance, an effect also assumed to be responsible for the rather low yield observed for the reaction between **3** and **4**. Improvement of this coupling reaction ought to be possible, and studies toward this goal are currently in progress. Enediyne thioacetate **2** was transformed to the protected form of shishijimicin A, precursor **36**, through sequential treatment with KOH in MeOH (acetate cleavage) and *N*-methyldithiophthalimide (PhthNSSMe)[27] in 50% overall yield via thiol derivative **35**. Desilylation of **36** with HF·py furnished advanced intermediate **37** (80% yield), from which the Alloc protecting group was removed by exposure to catalytic $Pd(PPh_3)_4$, leading to the shishijimicin A penultimate precursor ketal **38** (91% yield). Finally, cleavage of the ketal moiety from precursor **38** gave the targeted natural product, shishijimicin A (**1**), in 73% yield. The physical data for synthetic **1** matched those reported for the natural substance.[7]

In conclusion, we have developed a convergent and modular strategy for the total synthesis of the rare and precious marine natural product shishijimicin A (**1**). The reported synthesis

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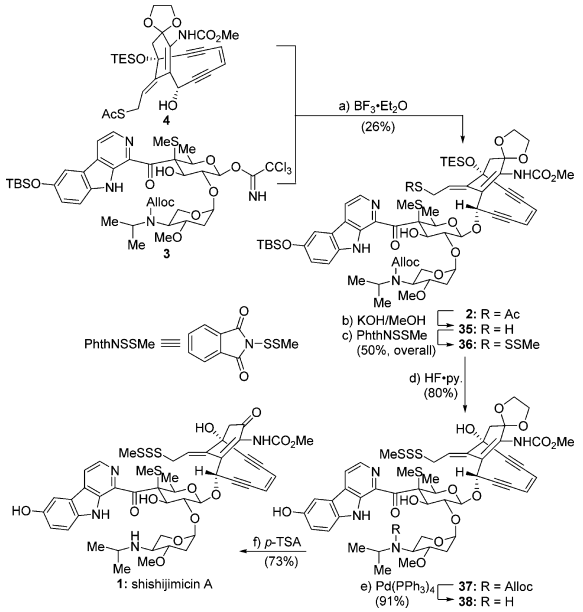
Scheme 5. Coupling of 3 and 4 and Total Synthesis of 1[a]



[a]Reagents and conditions: (a) **3** (1.0 equiv), **4** (1.6 equiv), $BF_3{\cdot}OEt_2$ (3.5 equiv), 4 Å MS, CH_2Cl_2, −78 to −40 °C, 1 h, 26% based on **3**; (b) KOH (10.0 equiv), MeOH, −5 °C, 1.5 h, then AcOH (10.0 equiv); (c) PhthNSSMe (6.0 equiv), CH_2Cl_2, 0 °C, 15 min, 50% for the two steps; (d) HF·py/THF (1:20), 0 to 25 °C, 4 h, 80%; (e) $Pd(PPh_3)_4$ (0.5 equiv), morpholine (15 equiv), THF, 0 °C, 45 min, 91%; (f) *p*-TSA (3.0 equiv), THF/acetone/H_2O (20:20:1), 25 °C, 48 h, 73%. *p*-TSA = *p*-toluenesulfonic acid.

makes this potent antitumor agent available for further biological investigations and potential medical applications, including the design and synthesis of ADCs and other conjugate assemblies for which shishijimicin A may serve as a uniquely powerful payload. Improvements and applications of the described chemistry could now be envisioned for the synthesis of congeners[7,28] and analogues of **1** as potentially useful molecular entities for incorporation into these types of targeted and personalized cancer chemotherapeutic agents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05575.

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Notes

The authors declare no competing financial interest.

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