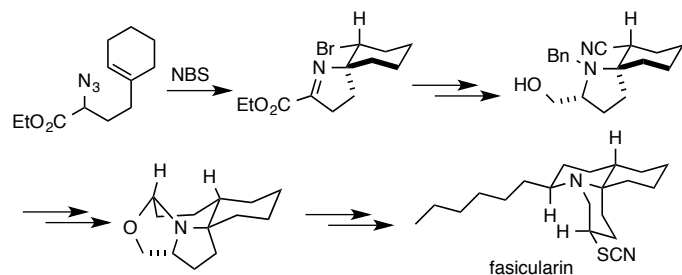


Synthesis of Fascicularin

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Supporting Information Placeholder



ABSTRACT: The synthesis of a tricyclic marine alkaloid, fascicularin was accomplished. Stereoselective synthesis of the azaspirocyclic BC ring precursor and ensuing construction of the A-ring with stereo-controlled installation of the C2 hexyl group feature prominently in the synthesis.

Fascicularin (**1**) is a marine tricyclic alkaloid isolated from ascidian *Nephteis fascicularis*¹ and exhibits cytotoxicity through alkylation of the cellular DNA (Figure 1).² The structure of fascicularin (**1**) is based on the *trans*-1-azadecalin AB ring of chair-chair conformation, that is connected with the piperidine C ring having a thiocyanate unit. There is another class of marine tricyclic alkaloids, lepadiformines (**2**),³ which contain the twist boat-chair *trans*-1-azadecalin AB ring fused with the hydroxymethyl pyrrolidine C ring. The difference of the AB ring conformation between fascicularin (**1**) and lepadiformines (**2**) is attributed to the stereochemistry of C2 with the alkyl chain; fascicularin (**1**) bears a β -hexyl group, while the C2-alkyl group of lepadiformines (**2**) is oriented α . Their unique chemical structures and biological activities have stimulated many groups to be engaged in synthetic studies of these classes of alkaloids.^{4,6} Our group has been independently engaged in synthetic studies of them. We herein report a new approach for stereoselective synthesis of fascicularin (**1**) that takes advantage of the characteristic structure of the spirocyclic BC ring precursor.

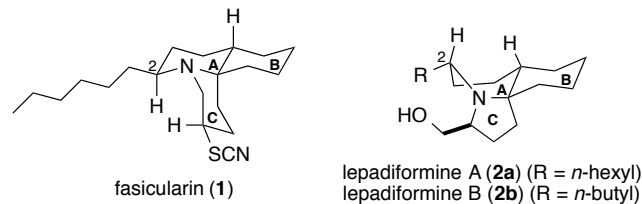
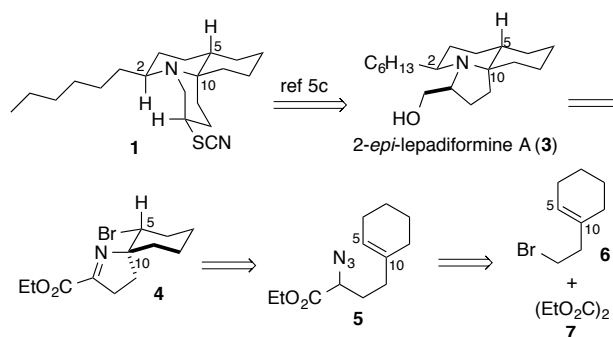


Figure 1. Fascicularin and lepadiformines

Our retrosynthetic analysis is illustrated in Scheme 1. It was reported by Kibayashi that fascicularin (**1**) could be ap-

proached from *C2-epi*-lepadiformine A (**3**).^{5c} It is envisaged that *C2-epi*-lepadiformine A (**3**) would be derived from the spirocyclic iminoester **4** having a bromo substituent at C5 *trans* to the C10-N bond through A-ring construction. Azaspirocyclic **4** would be constructed by aminobromination of α -azido ester **5**, that could be synthesized from 1-(2-bromoethyl)cyclohexene (**6**)⁷ and diethyl oxalate (**7**).

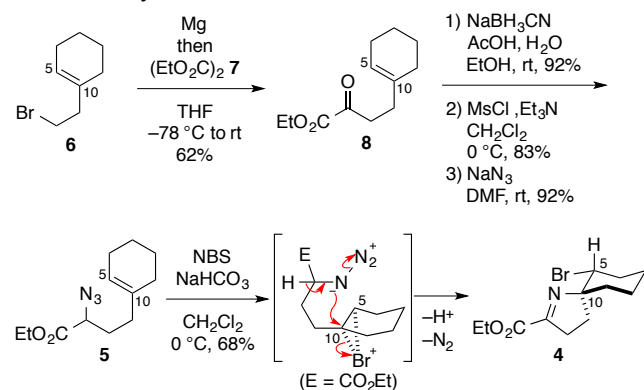
Scheme 1. Retrosynthesis



Our synthesis commenced with the reaction of the Grignard reagent prepared from bromide **6** with diethyl oxalate (**7**) to afford α -keto ester **8**, which was subsequently converted into α -azido ester **5** in a three-step sequence involving reduction of the keto carbonyl group by NaBH_3CN , mesylation of the resulting hydroxyl group, and azidation through nucleophilic substitution with NaN_3 (Scheme 2). Treatment of α -azido ester **5** with NBS in the presence of NaHCO_3 could induce denitrogenative spirocyclization through *trans*-

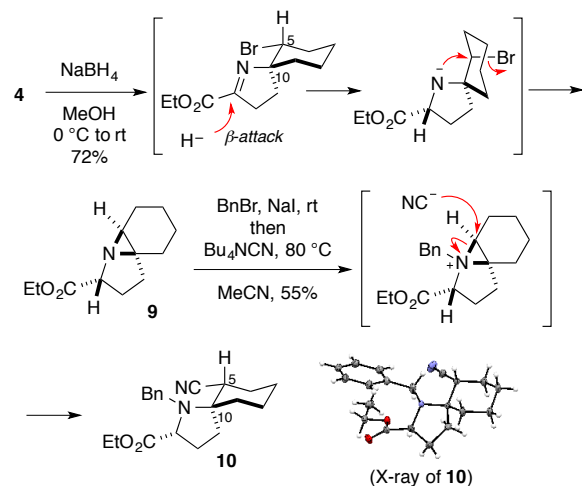
aminobromination of alkene, forming desired spirocyclic iminoester **4** in good yield.

Scheme 2. Synthesis of **4**



We next focused on introduction of carbon functionality at C5 for construction of the A-ring. Reduction of the C=N bond of **4** by NaBH₄ resulted in formation of tricyclic aziridine **9** in diastereoselective fashion.⁸ In this process, the hydride reduction occurred from the sterically less hindered β-face, that was followed by intramolecular nucleophilic substitution reaction at C5 to form the aziridine ring. Treatment of aziridine **9** with benzyl iodide (prepared *in situ* from BnBr and NaI) followed by addition of Bu₄NCN to the resulting N-benzyl aziridinium ion successfully opened the aziridine ring with installation of a cyano group at C5 in regio- and stereoselective manner, affording azaspirocyclic **10**.⁹

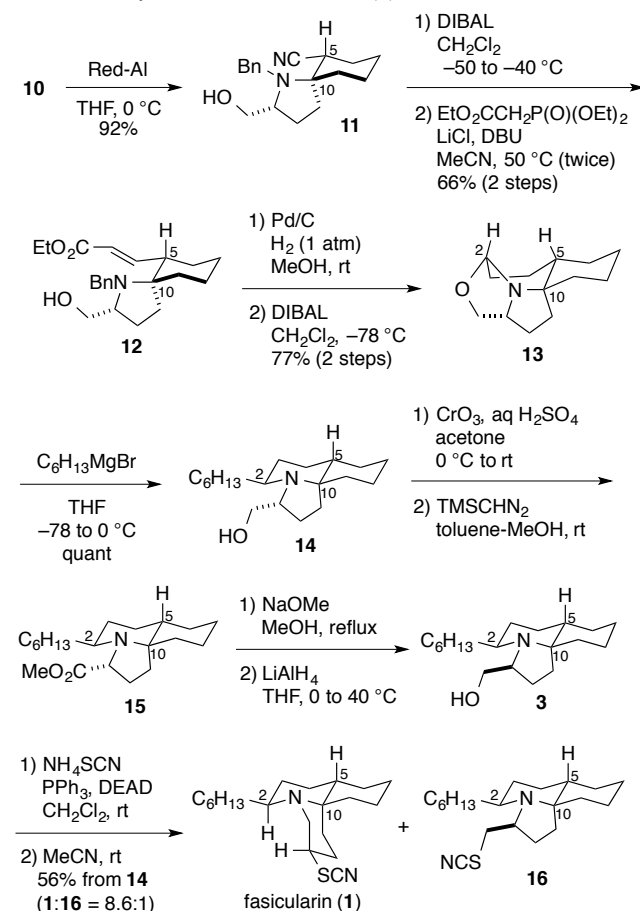
Scheme 3. Synthesis of **10**



Chemoselective reduction of ethoxy carbonyl group of **10** by Red-Al provided alcohol **11**.^{10,11} Without protection of the hydroxyl group of **11**, the cyano group was reduced with DIBAL to form the corresponding aldehyde, which was subsequently converted into α,β-unsaturated ester **12** by the reaction with triethyl phosphonoacetate under the Masamune-Roush protocol.¹² Hydrogenation to reduce the C=C bond and remove N-benzyl protection followed by DIBAL reduction of the ethoxy carbonyl group produced tetracyclic *N,O*-acetal **13**. The reaction of **13** with hexylmagnesium bromide enabled

stereoselective ring-opening of the *N,O*-acetal with inversion of the configuration to afford alcohol **14** having a β-hexyl group at C2.¹³ Alcohol **14** was converted into methyl ester **15** through Jones oxidation followed by esterification of the resulting carboxylic acid with trimethylsilyl diazomethane. Subsequent treatment of ester **15** with NaOMe enabled epimerization of C13 and ensuing LiAlH₄ reduction delivered C2-*epi*-lepadiformine (**3**). Finally, installation of the thiocyanate unit and ring-expansion of **3** was conducted according to the Kibayashi's method to complete the synthesis of fascicularin (**1**), which was obtained as a mixture with its structural isomer **16**. The synthetic sample was identical to the natural product by comparison with the reported spectroscopic data (¹H and ¹³C NMR, MS).^{5c}

Scheme 4. Synthesis of fascicularin (**1**)



In summary, we have achieved a synthesis of fascicularin (**1**). The characteristic feature of the synthesis includes construction of the azaspirocyclic BC-ring intermediate through spirocyclizing aminobromination of α-azido ester and stereoselective installation of the cyano group at C5 via ring-opening of aziridine ring as well as A-ring construction with stereocontrolled installation of the β-hexyl group.¹⁴

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic data for compound **10** (CIF)
Crystallographic data for compound **19** (CIF)
Experimental procedures, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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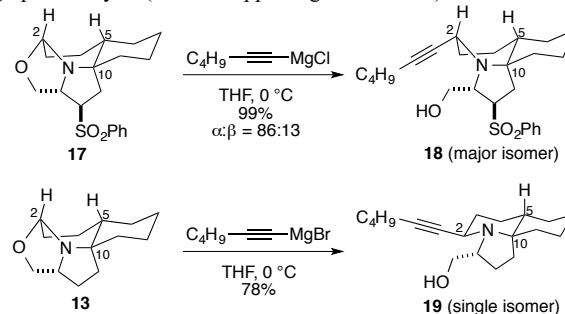
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(11) The attempt to reduce both ethoxy carbonyl and cyano groups of **10** by DIBAL (4.5 equiv), followed by conversion of the resulting aldehyde into α,β -unsaturated ester, afforded **12** in only 20% yield. Thus, we adopted the stepwise reduction through **11**.

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(13) Craig demonstrated in the synthesis of lepadiformine that ring-opening of hemiaminal **17** having sulfonyl group at C12 with hexynyl Grignard reagent occurs majorly in retention of the configuration to afford α -alkynyl **18** (see, ref 6i). In sharp contrast, interestingly, the reaction of hemiaminal **13** with hexynyl Grignard reagent resulted in inversion of the configuration to form β -alkynyl **19** as a single isomer, the stereochemistry of which was confirmed by X-ray single crystallographic analysis (see the Supporting Information).



(14) The key feature in stereoselective construction of C2 stereocenter of fascicularin (**1**) is the use of the α -hydroxy methyl unit at C13 as the anchimeric handle for construction of the tetracyclic hemiaminal **13** and ensuing installation of the hexyl group in inversion of the configuration (Scheme 4). In turn, we also investigated the possibility of constructing the A-ring having α -hexyl group at C2 toward synthesis of lepadiformine A (**2a**). For this purpose, we envisioned using the α -oxymethyl tether of the BC-ring derived from intermediate **11** as the steric handle for the desired stereo-control (see below). Thus, **11** was converted into amino ketone **20**, the thermal treatment of which in the presence of PPTS at 170°C in xylene under sealed conditions allowed for the formation of highly strained cyclic enamine **21**. We assumed that the bulky silyloxy methyl group at C13 makes the α -face of the cyclic enamine **21** sterically hindered, that might induce selective β -hydride attack. However, subsequent treatment of cyclic enamine **21** with NaBH_3CN occurred exclusively from the sterically more hindered α -face to afford **14** after deprotection of the TBS group. This unexpected stereochemical outcome might be attributed to less torsional strain in the β -hydride attack. See the Supporting Information for the detailed synthetic scheme and procedures.

