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Synthesis of Fasicularin

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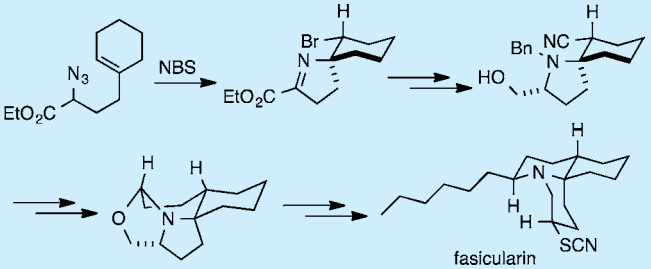
Supporting Information

ABSTRACT: The synthesis of a tricyclic marine alkaloid, fasicularin, was accomplished. Stereoselective synthesis of the aza-spirocyclic BC-ring precursor and ensuing construction of the A-ring with stereocontrolled installation of the C2 hexyl group feature prominently in the synthesis.



Fasicularin (**1**) is a marine tricyclic alkaloid isolated from ascidian *Nephteis fasicularis*[1] and exhibits cytotoxicity through alkylation of the cellular DNA (Figure 1).[2] The

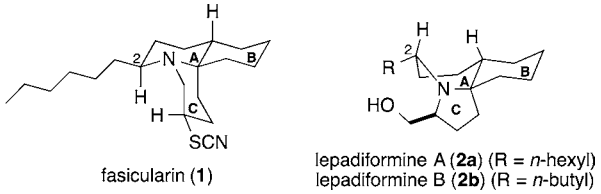
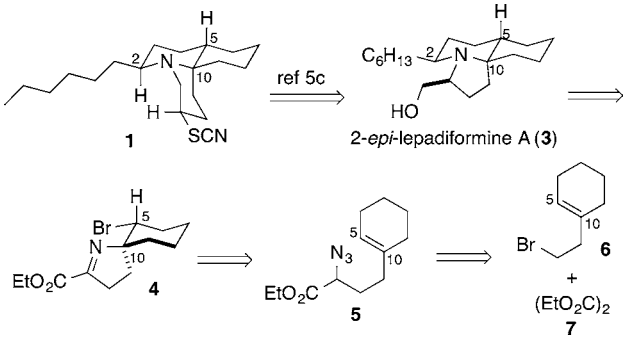


Figure 1. Fasicularin and lepadiformines.

structure of fasicularin (**1**) is based on the *trans*-1-azadecalin AB-ring of chair−chair conformation, which 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 fasicularin (**1**) and lepadiformines (**2**) is attributed to the stereochemistry of C2 with the alkyl chain; fasicularin (**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 the stereoselective synthesis of fasicularin (**1**) that takes advantage of the characteristic structure of the spirocyclic BC-ring precursor.

Our retrosynthetic analysis is illustrated in Scheme 1. It was reported by Kibayashi that fasicularin (**1**) could be approached 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. Azaspirocycle **4** would be constructed by aminobromination of α-azido ester **5**,

Scheme 1. Retrosynthesis



which could be synthesized from 1-(2-bromoethyl)cyclohexene (**6**)[7] and diethyl oxalate (**7**).

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.

We next focused on the introduction of carbon functionality at C5 for construction of the A-ring. Reduction of the C═N bond of **4** by $NaBH_4$ resulted in formation of tricyclic aziridine **9** in a diastereoselective fashion (Scheme 3).[8] In this process, the hydride reduction occurred from the sterically less hindered β-face, which was followed by an intramolecular nucleophilic substitution reaction at C5 to form the aziridine ring. Treatment of aziridine **9** with benzyl iodide (prepared *in situ*

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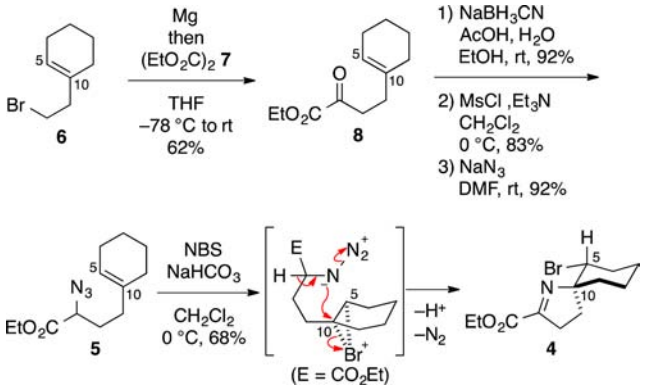
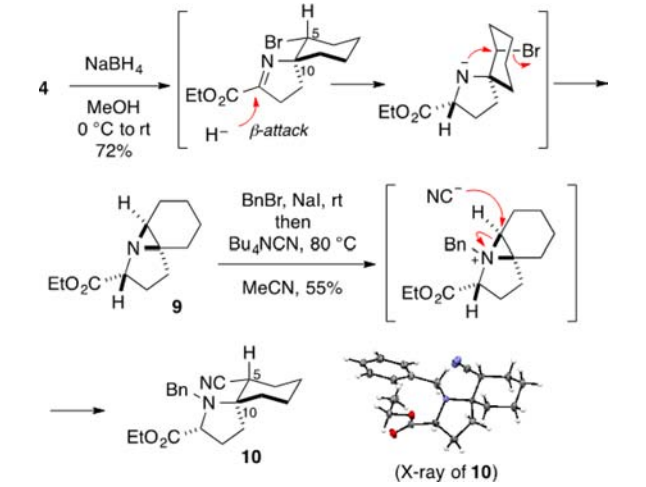
Scheme 2. Synthesis of 4



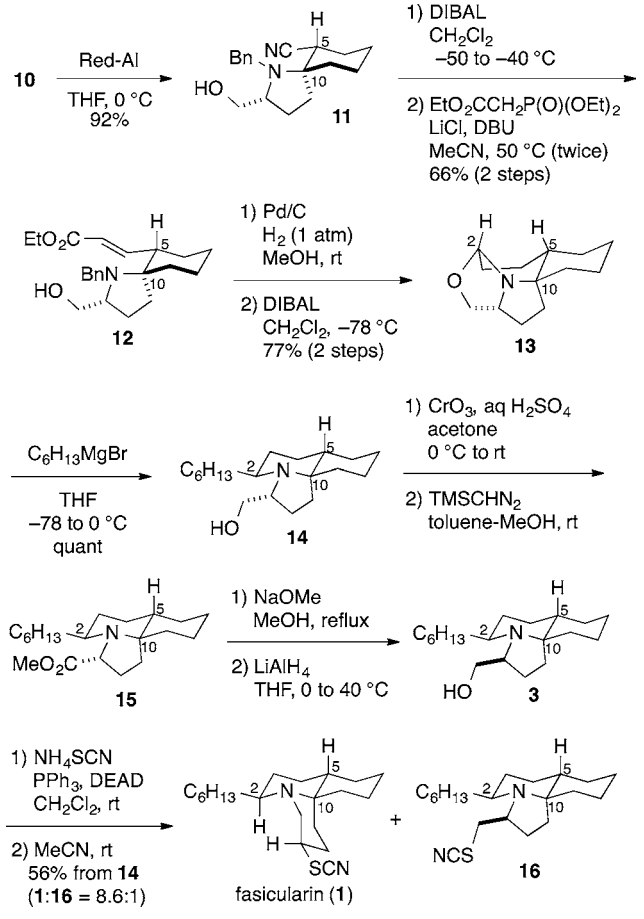
Scheme 3. Synthesis of 10



from BnBr and NaI) followed by addition of Bu_4NCN to the resulting *N*-benzyl aziridinium ion successfully opened the aziridine ring with installation of a cyano group at C5 in a regio- and stereoselective manner, affording azaspirocycle **10**.[9]

Chemoselective reduction of the ethoxy carbonyl group of **10** by Red-Al provided alcohol **11** (Scheme 4).[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 $LiAlH_4$ reduction delivered C2-*epi*-lepadiformine A (**3**). Finally, installation of the thiocyanate unit and ring expansion of **3** were conducted according to the Kobayashi's method to complete the synthesis of fasicularin (**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 ^{13}C NMR, MS).[5c]

Scheme 4. Synthesis of Fasicularin (1)



In summary, we have achieved the synthesis of fasicularin (**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 the 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 at DOI: 10.1021/acs.orglett.6b01669.

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

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Notes

The authors declare no competing financial interest.

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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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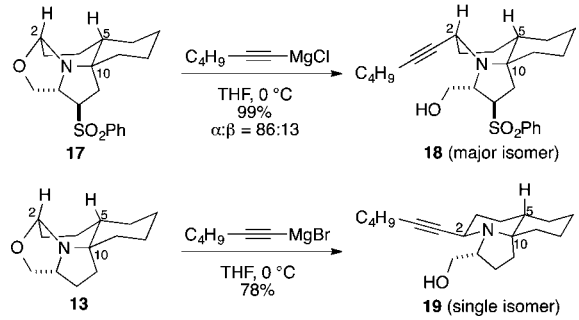
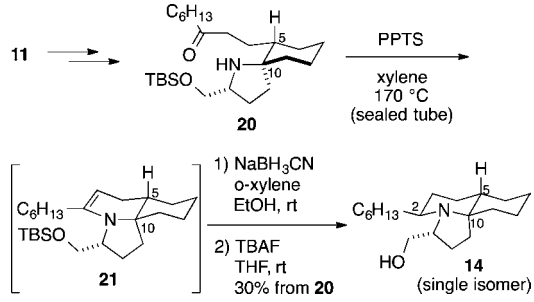
(13) Craig demonstrated in the synthesis of lepadiformine A that ring opening of hemiaminal **17** having a sulfonyl group at C12 with a hexynyl Grignard reagent occurs majorly in retention of the configuration to afford α-alkynyl **18** (see, ref 6i). In sharp contrast, interestingly, the reaction of hemiaminal **13** with the 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 the C2 stereogenic center of fasicularin (**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 an α-hexyl group at C2 toward the 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 stereocontrol (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, which 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 α-hydride attack. See the Supporting Information for the detailed synthetic scheme and procedures.



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