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# An approach to total synthesis of the cylindricine B pyridoquinoline subclass of tricyclic marine ascidian alkaloids

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**Abstract**—Employing an intramolecular *N*-acylketiminium ion/olefin hetero Diels–Alder reaction, and a ring closing metathesis of a vinyl chloride as pivotal steps, it is possible to directly access the pyridoquinoline tricyclic ring system of the marine alkaloids cylindrines B and J.


In the 1990s, Blackman et al. described a small family of structurally related tricyclic alkaloids isolated from the ascidian *Clavelina cylindrica*, which was collected off the east coast of Tasmania.[1] The major components of the alkaloidal extract are cylindricines A (**1**) and B (**7**), whose structures were secured by spectral analysis, and X-ray crystallography of the corresponding picrates (Fig. 1). Cylindricine A possesses a pyrrolo-[2,1-*j*]quinoline tricyclic framework, whereas cylindricine B contains a C-ring-expanded pyrido-[2,1-*j*]quinoline system. It was found that upon standing for several days in solution, these compounds produce the same 3:2 equilibrium mixture of **1** and **7**. Since this equilibration occurs only with the free bases of the two alkaloids, it was proposed that the interconversion occurs via an aziridinium intermediate **6**.[1a]

Subsequent work by the Blackman group led to the elucidation of some congeneric minor compounds having cylindricine A pyrroloquinoline framework and

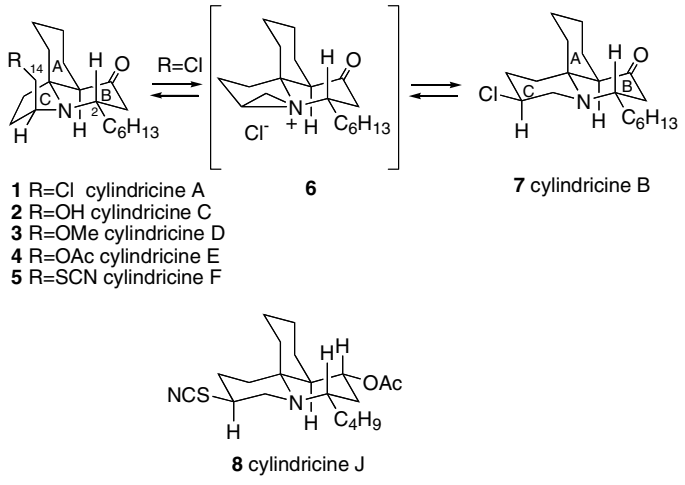


**Figure 1.**

*Keywords*: Alkaloids; Ring closing metathesis; Hetero Diels–Alder reaction; *N*-Acyliminium ion; Nitrogen heterocycles; Cycloaddition.
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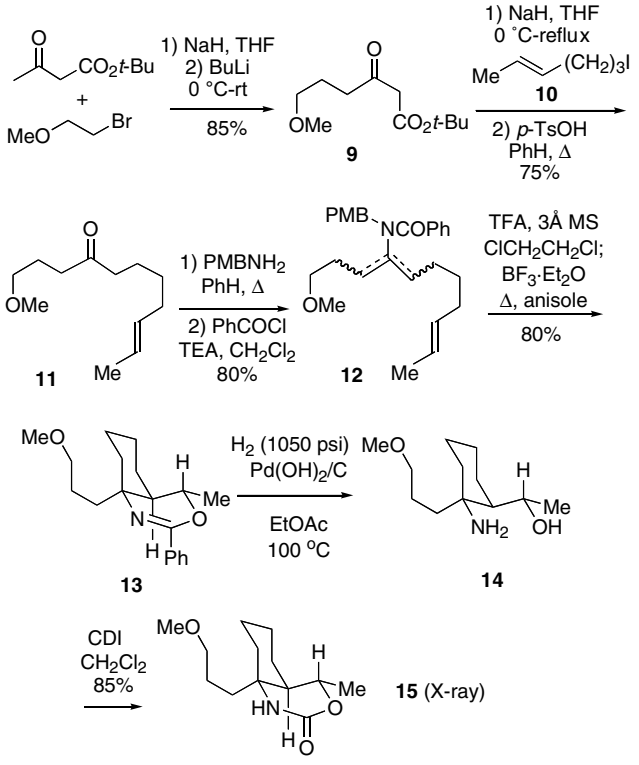
stereochemistry, but differing in the functionality at C(14). Examples of alkaloids in this series include cylindricines C (**2**), D (**3**), E (**4**) and F (**5**). Moreover, a few cylindricine A-type alkaloids were found, which possess a butyl group at C(2) rather than a hexyl chain. A second compound was isolated, which falls in the cylindricine B pyridoquinoline subclass, but has a C(2) butyl appendage, and was named cylindricine J (**8**). All of the cylindricine alkaloids possess a cis-fused perhydroquinoline A/B-ring system and also exist in the conformations indicated, supported by X-ray crystal structure and NMR data, along with molecular mechanics calculations.[1c] The absolute configurations of these alkaloids are unknown at present.

A substantial amount of synthetic work has appeared to date on the cylindricines.[2] However, all of these studies have been specifically directed towards the cylindricine A pyrroloquinoline series of alkaloids. In this letter, we describe a new strategy for accessing the pyridoquinoline framework of the cylindricine B subgroup of metabolites.[3] Our approach makes use of some synthetic methodology, which we expressly developed for this project, namely intramolecular *N*-acylketiminium ion hetero Diels–Alder cycloadditions[4] and vinyl chloride ring closing metathesis chemistry.[5]

In order to prepare the precursor required for the key hetero Diels–Alder step, we began with *tert*-butyl acetoacetate, which was converted to the Weiler dianion and alkylated with bromoethyl methyl ether to afford **9** in good yield (Scheme 1)[6]. This β-ketoester was deprotonated with sodium hydride and the enolate was alkylated with (*E*)-1-iodo-4-hexene (**10**).[7] The reaction



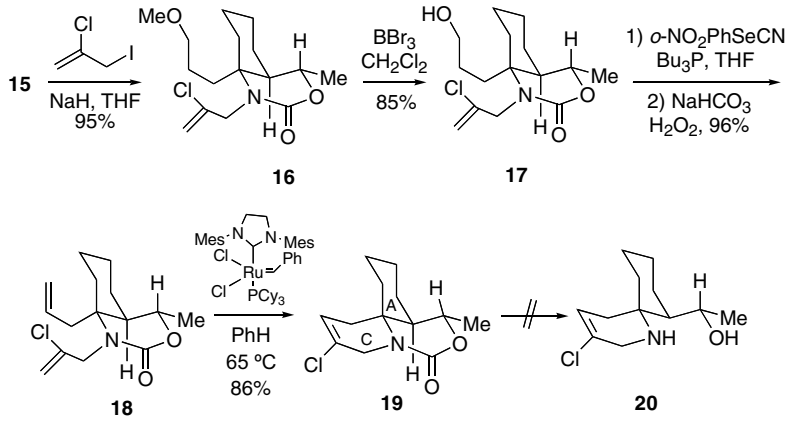

**Scheme 1.**

product was then decarboxylated[8] by refluxing in benzene with a catalytic amount of *p*-toluenesulfonic acid to afford ketone **11** in 75% yield for the two steps. Ketone **11** was first transformed into the corresponding imine with *p*-methoxybenzylamine, and this imine was subsequently N-acylated with benzoyl chloride to provide a regioisomeric mixture of enamides **12**. The [4+2]-cycloaddition was effected with intermediate **12**, using the experimental procedure, which we have previously described.[4] Thus, treatment of enamide **12** with TFA in dichloroethane at room temperature overnight, followed by heating with boron trifluoride etherate and anisole, led to the expected 3,5-dihydrooxazine cycloaddition product **13** as a single diastereoisomer in good yield. As we had found earlier in analogous systems, the dihydrooxazine ring in cycloadduct **13** is resistant to acid or base hydrolysis. However, hydrogenolysis[9] of adduct **13** using Pearlman's catalyst gave the desired amino alcohol **14**, which was converted to the crystalline cyclic carbamate **15** in high overall yield for the two steps, using carbonyldiimidazole. The stereostructure and solid state conformation of this carbamate was firmly established to be as shown by X-ray analysis.[10]

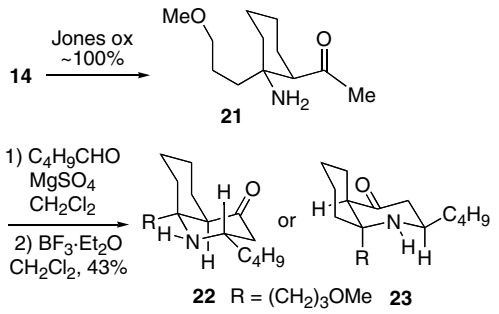
At this stage, we decided to explore the annulation of the six-membered C-ring of the alkaloids using our vinyl chloride RCM methodology.[5] To this end, carbamate **15** was N-alkylated with 3-iodo-2-chloropropene to give **16** in excellent yield (Scheme 2). The methyl ether protecting group of **16** could then be removed with boron tribromide to yield alcohol **17**. Dehydration of this compound could be effected cleanly using the Grieco protocol to generate the requisite diene **18**.[11] We were gratified to find that exposure of this diene to the second generation Grubbs catalyst smoothly promoted ring closing metathesis to give the desired tricyclic vinyl chloride **19** in high yield. In order to construct the final B-ring of the alkaloids, it was necessary at this point to cleave the carbamate functionality of tricycle **19** to produce amino alcohol **20**. Unfortunately, this functionality appears to be quite hindered and all hydrolysis attempts failed.

Since we could not proceed any further with intermediate **19**, we were consequently forced to investigate some alternative sequences. One sequence, which was explored involved initial Jones oxidation of amino alcohol **14** to amino ketone **21** (Scheme 3). Compound **21** could then be condensed with valeraldehyde in a Mannich reaction to afford a single stereoisomeric bicyclic product in 43% unoptimized yield.[12] Although it was possible to determine from $^1$H NMR coupling constants that the butyl substituent in the product occupies an equatorial position, we could not distinguish between the desired bicycle **22** and its epimer **23**. However, since this amine could not be N-alkylated with 3-iodo-2-chloropropene, as was necessary in order to set the stage for the RCM process, the sequence was not pursued any further.

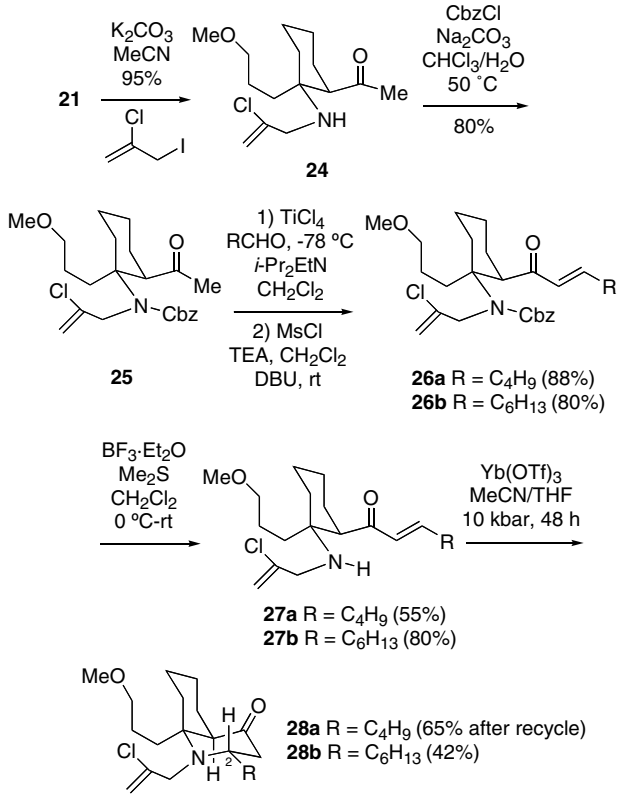
In another more promising approach, amino ketone **21** was first N-alkylated with 3-iodo-2-chloropropene to produce chloroalkene **24** in high yield (Scheme 4). Unlike compound **21**, this amino ketone unfortunately



Scheme 2.



Scheme 3.



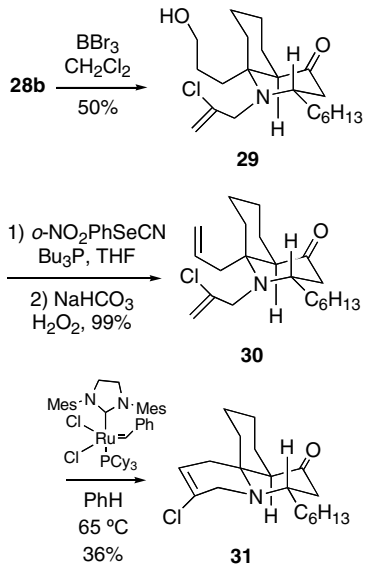
Scheme 4.

showed no tendency to undergo Mannich reactions, and an alternative route for constructing the B-ring was required. Therefore, amine **24** was first protected as the Cbz derivative **25**, and the methyl ketone was combined with valeraldehyde in an aldol condensation/dehydration process to afford enone **26a** needed for cylindricine J (**8**).[13] Similarly, for entry to cylindricine B (**7**), ketone **25** could also be condensed with heptanal to produce the corresponding enone **26b**.

The Cbz protecting groups of intermediates **26a** and **26b** could be removed with boron trifluoride/dimethyl sulfide to afford amines **27a** and **27b**, respectively. Much to our surprise, these amino enones are resistant to cyclization via acid, base, or thermally promoted intramolecular conjugate addition, depite the fact that similar processes are widely documented in cylindricine syntheses.[2,14] After some experimentation with amino enone **27b**, it was discovered that the desired aza-Michael cyclization can be effected at high pressure (10 kbar) using ytterbium triflate as a catalyst in 2:1 acetonitrile/THF, giving a single diastereoisomeric product in 42% isolated yield along with unreacted starting amino enone. Although we hope that this product has the desired stereostructure of **28b**, to date we have been unable to firmly establish the configuration at C(2). Using other catalysts (e.g., $Bi(OTf)_3$, $Cu(OAc)_2$, $FeCl_3$, etc.) or additives, such as triethylamine, led to lower product yields, complex mixtures, or no reaction at all. Under the same optimized cyclization conditions, enone **27a** also produced a single adduct, hoped to be stereoisomer **28a**, in similar yield. In this case the recovered starting material was recycled, leading to a total product yield of 65%.

With these cyclization products in hand, we explored the feasibility of effecting the final C-ring closure. Thus, bicyclic compound **28b** was demethylated to form alcohol **29**, which could be dehydrated to afford diene **30** (Scheme 5). Finally, exposure of this diene to the second generation Grubbs ruthenium catalyst led to RCM product **31** in 36% unoptimized yield.

In conclusion, we have successfully tested a strategy for the construction of the tricyclic pyridoquinoline




**Scheme 5.**

framework of cylindricines B (**7**) and J (**8**) using our hetero Diels–Alder[4] and vinyl chloride RCM methodology.[5] We now plan to determine the C(2) stereochemistry of the key bicyclic intermediates **28a** and **28b**. If the configuration is correct for the cylindricines, we will then explore conversion of these compounds into the natural products via appropriate functional group manipulations.

## Acknowledgements

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