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Studies toward the synthesis of pinnatoxins: the spiroimine fragment

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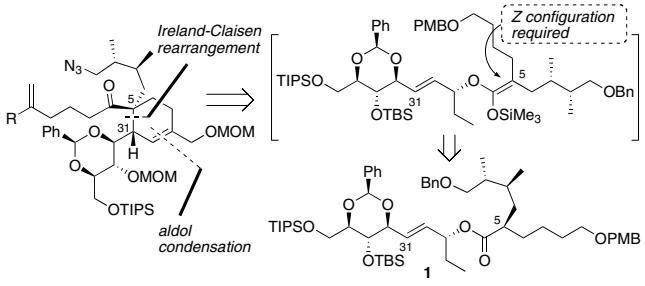
Abstract—An enantioselective approach to the spiroimine fragment of pinnatoxins is described. The strategy is based on a recently developed diastereoselective Ireland–Claisen rearrangement to establish the challenging congested quaternary and tertiary stereocenters within the cyclohexene ring.

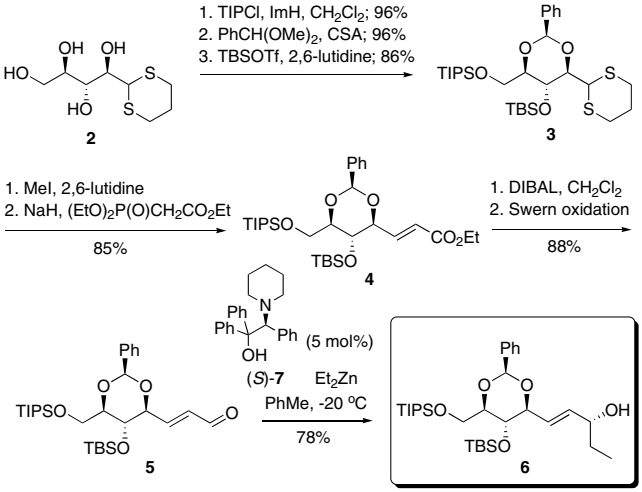
Pinnatoxins are 'fast-acting' marine toxins commonly found in the bivalve *Pinna pectinata (muricata)*.[1] Pinnatoxin A was isolated and structurally characterized by the Uemura group in 1995.[2] The fascinating chemical structure of pinnatoxins, featuring an unusual spiroimine, presents a compelling challenge for organic synthesis.[3] Our first approach to construction of the spiroimine fragment was based on a tandem Claisen–Mislow–Evans rearrangement that introduced the quaternary chiral center at the core of the ring system.[4] Because we were unable to introduce an appropriately functionalized side-chain at C31 by allylic substitution with required stereo- or regiocontrol, we developed a different strategy that allowed a successful incorporation of the side-chain, which we report in this Letter.

According to the new plan, the sterically congested stereocenters at C5 and C31 will be stereoselectively introduced by a single carbon–carbon bond-forming reaction (Scheme 1). The sigmatropic rearrangement of silyl ketene acetal generated from allylic ester **1** was expected to fulfill this goal, provided that ketene acetal could be generated stereoselectively. The enolate geometry in the critical enolization step will be controlled by a method recently developed in our laboratory.[5] Subsequently, the cyclohexene ring will be formed by an intramolecular aldol condensation.[6] This analysis allows for a highly convergent disconnection of **1** to the corresponding allylic alcohol and carboxylic acid.



Scheme 1.

The synthesis of the allylic alcohol began with dithiane **2**, readily available from D-ribose in one step (Scheme 2).[7] Initial protecting group manipulations involved installation of silyl ethers at C3 and C5 and the



Scheme 2.

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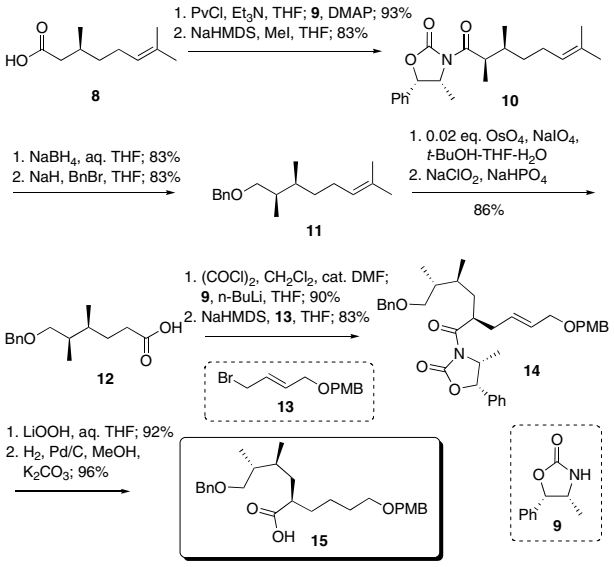
benzylidene group at the C2 and C4 of ribose. Hydrolysis of dithioacetal by treatment with iodomethane in aqueous acetone[8] followed by the Horner–Wadsworth–Emmons olefination gave ester **4** in 85% overall yield. Reduction of the ester with DIBAL and oxidation[9] afforded aldehyde **5**, which was subjected to diastereoselective diethylzinc addition catalyzed by chiral amino-alcohol (*S*)-**7**.[10] The requisite secondary allyic alcohol **6** was obtained in 78% yield along with its diastereomer (10%). In this strategic step, the chirality of the alcohol established by the catalytic asymmetric diethylzinc addition will be ultimately translated into the C5 and C31 stereocenters of the spiroimine fragment.

The synthesis of carboxylic acid **15** started with the condensation of (*S*)-citronellic acid[11] with 4*R*-methyl-5*S*-phenyl-2-oxazolidinone (**9**) to the corresponding Evans imide (Scheme 3).[12] Methylation of sodium enolate generated from imide afforded **10** in 83% yield. Reduction with sodium borohydride, benzylation, and oxidative cleavage of the double bond delivered acid **12**. At this stage, chiral oxazolidinone **9** recovered in the sodium borohydride reduction step was reattached, and subsequent allylation with bromide **13** afforded imide **14** in good yield. The concluding operations involved peroxide-assisted hydrolytic removal of the chiral auxiliary and the chemoselective hydrogenation of the double bond, giving acid **15** in ten steps from (*S*)-citronellic acid.



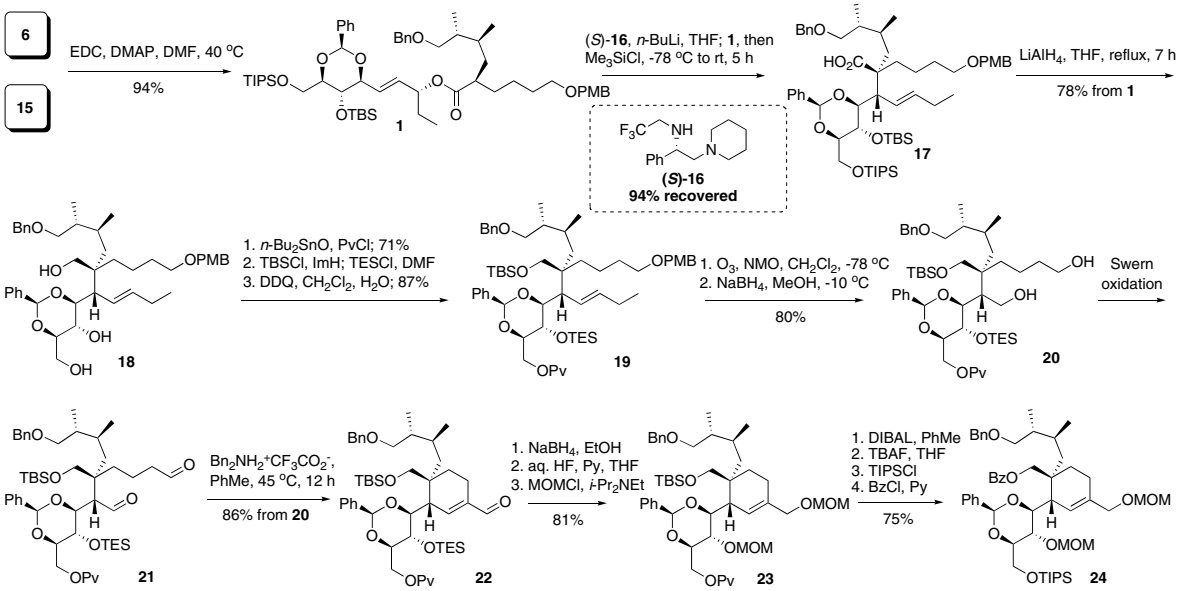
Scheme 3.

The fragment union by esterification of **6** with **12** in the presence of EDC and DMAP took place smoothly (Scheme 4). The crucial diastereoselective Ireland–Claisen rearrangement was accomplished using amine (*S*)-**16**.

This ensured high selectivity in the formation of the *Z*-enolate, which was trapped as the trimethylsilyl ketene acetal that underwent a [3,3]-sigmatropic transposition at room temperature to furnish acid **17** after aqueous work-up (Fig. 1, **A**→**B**).

The chiral amine was recovered in high yield by extraction with aqueous hydrochloric acid. The crude rearrangement product (**17**) was reduced with lithium aluminum hydride to triol **18** in 78% yield from ester **1**.

To our surprise, all silyl protecting groups were cleaved during the reduction with lithium aluminum hydride, possibly due to intramolecular hydride delivery from an intermediate aluminate such as **C** and proceeding to the end of the chain bearing the silyl protecting groups (Fig. 1).[13] After selective mono-pivaloation of the triol, the remaining hydroxyl groups were silylated, and the product was converted to diol **20** by removal of the PMB group, ozonolysis,[14] and reduction. Double oxidation of **20** to dialdehyde **21** set the stage for the pivotal intramolecular aldol condensation. We found that in the presence of piperidinium acetate[15] the desired cyclization was slow, however, upon treatment with



Scheme 4.

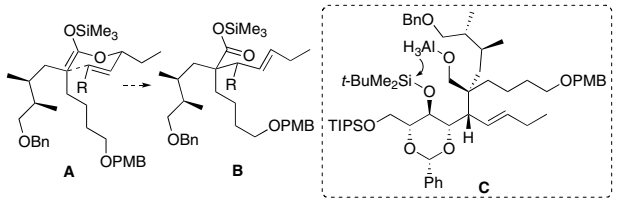
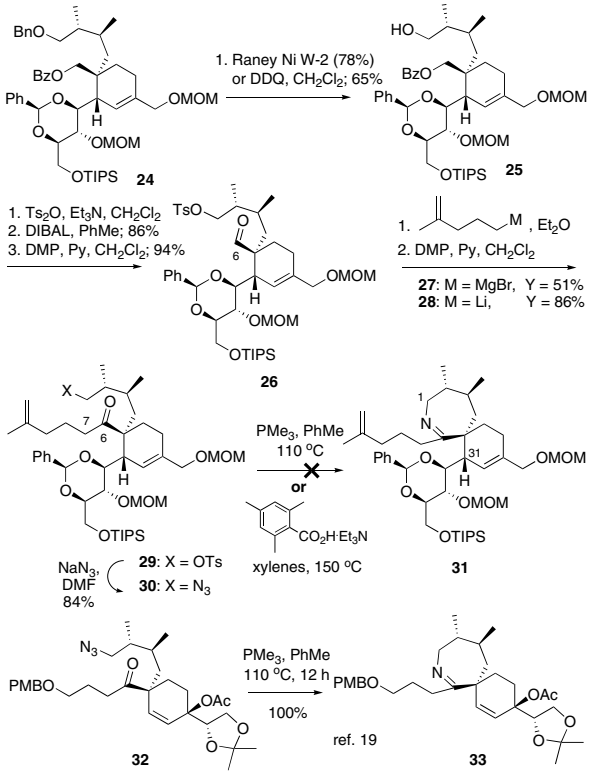


Figure 1.

dibenzylammonium trifluoroacetate[16] at 45 °C for 12 h the dialdehyde cyclized to cyclohexene **22** in excellent yield (86% over two steps). When the cyclization was attempted at higher temperatures ($\geqslant$80 °C), partial epimerization at C31 was observed.

The goal of subsequent transformations was to explore chemistry that might be involved in fragment coupling en route to the total synthesis of pinnatoxins. After reduction of the aldehyde and protection of the allylic alcohol as the methoxymethyl ether (96%), we found that the primary TBS ether could not be removed selectively. Instead, the secondary TES was cleaved with aqueous HF while the TBS ether remained intact. Our experiments revealed that the initially adopted protecting group strategy is less than optimal and will have to be reevaluated in future work. For the purpose of present study, we introduced the MOM group in place of TES, and replaced the pivaloate ester with TIPS ether and the TBS with benzoyl group.

Removal of the benzyl group could be carried out reductively with Raney Ni W-2 or oxidatively with DDQ (Scheme 5).[17,18] Subsequent tosylation followed by treatment with DIBAL gave primary alcohol **25**. Its oxidation with Dess–Martin periodinane[19] delivered the corresponding aldehyde, which we envision as the key functional group in the projected fragment coupling. We carried out a model study to investigate the C6–C7 bond formation. Addition of Grignard reagent **27** was accompanied by reduction to a significant extent, affording, after oxidation of the crude mixture of alcohols, ketone **29** (51%) along with starting aldehyde **26** (37%). On the other hand, the addition of alkyllithium reagent **28** occurred cleanly at −78 °C within 10 min, delivering ketone **29** in 86% yield after oxidation.



Scheme 5.

Substitution of the tosyl group with azide (**29**→**30**) installed the requisite nitrogen at C1 and provided an opportunity to study the spiroimine formation with this substrate. Previously, we observed facile imine formation under Staudinger reduction[20]/aza-Wittig cyclization reaction conditions with azido ketone **32** lacking a side-chain at C31.[21] With azide **30**, only clean reduction to the intermediate iminophosphorane was noted followed by decomposition under forcing reaction conditions.[22] Similar results were obtained when modified conditions developed by Kishi were used with the amine generated upon the Staudinger reduction of azide **30**.[3j] These observations indicate that imine-group formation and possibly its stability are highly sensitive to the nature of the substituent at C31.

In summary, the described study validated the new strategy for the synthesis of the spiroimine of pinnatoxins. The key elements of the strategy are the diastereoselective Ireland–Claisen rearrangement that builds the critical C5–C31 stereocenters and the aldol cyclodehydration forming the cyclohexene ring. At the same time, we found that an improved protecting group strategy is desirable. The study also revealed that organolithium addition to aldehyde at C6 holds a strong potential for fragment coupling in the total synthesis endeavor.

Acknowledgments

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Supplementary data

Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra, and other Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.182.

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