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Toward the Synthesis of (+)-Peloruside A via an Intramolecular Vinylogous Aldol Reaction

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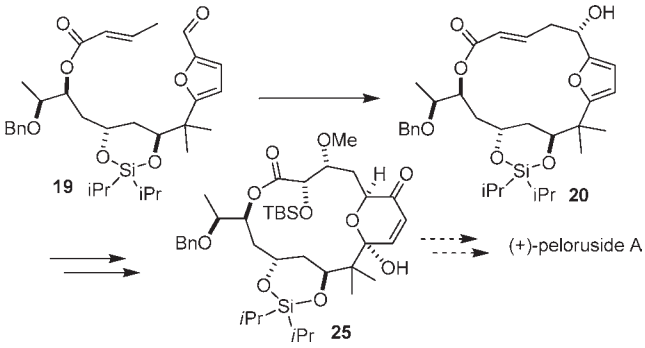
ABSTRACT



The use of the intramolecular vinylogous aldol reaction for the preparation of an advanced intermediate for the synthesis of peloruside A is described. The reaction was applied to compound 19 and proceeds in high yield and good levels of diastereoselectivity. Application of the Achmatowicz reaction to this intermediate provided the corresponding pyranone, a late stage intermediate well positioned for conversion to the natural product.

Peloruside A is a polyoxygenated 16-membered macrolide isolated from the marine sponge *Mycale hentscheli* by Northcote and co-workers (Figure 1).[1] It displays potent antimitotic activity, arresting cells at the G2-M boundary with low nanomolar activity against several cancer cell lines.[2] Its combination of potent biological activity and complex structure has led to intense interest by the synthetic organic community with six total syntheses reported to date.[3] We describe herein our progress toward the synthesis of peloruside A using the intramolecular vinylogous aldol[4] reaction in a novel approach to the construction of the macrocycle.

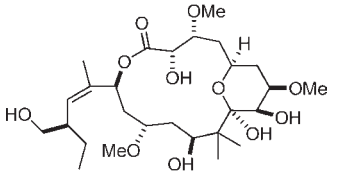


Figure 1. (+)-Peloruside A.

One of the challenges associated with the synthesis of peloruside A is the construction of the macrocycle, and all previous total syntheses have utilized a macrolactonization

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for this purpose. While macrolactonization has become a reliable method for the synthesis of medium- to large-membered rings, it can at times provide modest yields, and there can be strategic advantages to other methods of macrocycle formation. We have recently described the application of the Yamamoto vinylogous aldol reaction[5] for the synthesis of medium-membered rings using non-enolizable aldehydes.[6] These reactions proceed in good to excellent yields and with high levels of remote stereocontrol, and we wished to demonstrate the utility of this method in the context of natural products synthesis. The vinylogous aldol reaction produces an α,β-unsaturated ester, the alkene of which can be subjected to functionalization, and we targeted peloruside A for synthesis as this compound contains functionality that can be installed from the product of an intramolecuar vinylogous aldol reaction. Our retrosynthesis is shown in Figure 2.

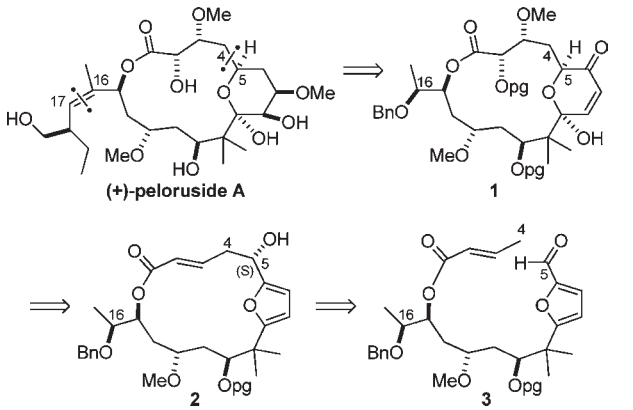
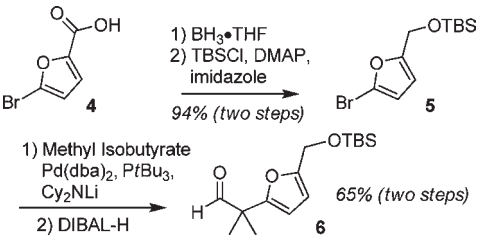


Figure 2. Retrosynthetic analysis.

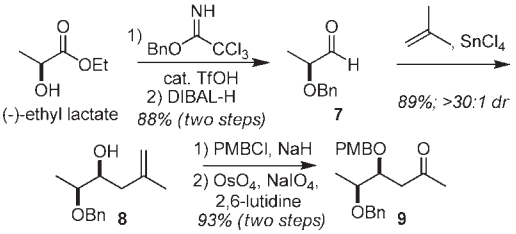
The most straightforward disconnection utilizing the intramolecular vinylogous aldol reaction involves the use of an enolizable aldehyde to make the C4–C5 bond; however, this reaction is currently limited to nonenolizable aldehydes. We therefore chose to utilize a nonenolizable furfural derivative (**3**) lacking the C16–C17 alkene and which upon cyclization would provide a furyl alcohol (**2**) that could be subjected to the Achmatowicz oxidative rearrangement[7] to provide a pyranone (**1**) with a handle to install the requisite functionality in the natural product (Figure 2).

Scheme 1. Synthesis of Aldehyde **6**



The preparation of cyclization precursor **3** began with the synthesis of aldehyde **6** as follows. 5-Bromo-2-furoic acid (**4**) was reduced with BH_3•THF to provide the corresponding alcohol which was protected as the TBS ether to provide bromofuran **5** in 94% yield over two steps (Scheme 1). Methyl isobutyrate was then subjected to α-arylation with bromofuran **5** under Hartwig's conditions[8] ($Pd(dba)_2$, $P(t\text{-}Bu)_3$, and Cy_2NLi) and then reduced with DIBAL-H to provide aldehyde **6**. This aldehyde was then coupled to ketone **9** using a 1,5-*anti*-aldol reaction,[9] as shown in Scheme 3.

Scheme 2. Synthesis of Ketone **9**



Ketone **9** was prepared from (−)-ethyl lactate by protection as the benzyl ether (benzyltrichloroacetimidate, catalytic TfOH) and reduction (DIBAL-H) to provide aldehyde **7** (Scheme 2). Subjection of this aldehyde to a chelation-controlled ene-reaction using 2-methyl propene as described by Mikami[10] selectively provided alcohol **8** (> 30:1 dr). Protection as the PMB ether (NaH, PMBCl) and oxidative cleavage (OsO_4, $NaIO_4$, 2,6-lutidine)[11] provided methyl ketone **9** ready for coupling with aldehyde **6**.

The coupling of aldehyde **6** and methyl ketone **9** was accomplished using Evans' conditions[12] ($n\text{-}Bu_2BOTf$,$i\text{-}Pr_2NEt$) to provide **10** in 87% yield and 7:1 diastereoselectivity (Scheme 3). Anti-selective hydroxyl-directed reduction

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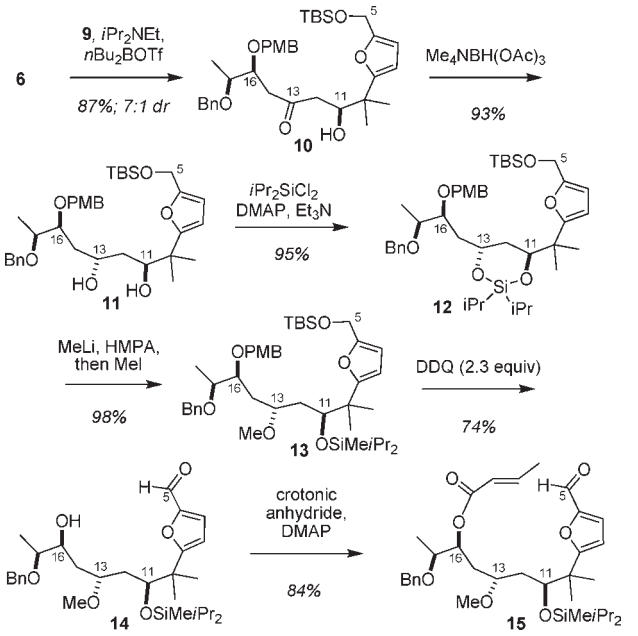
(13) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

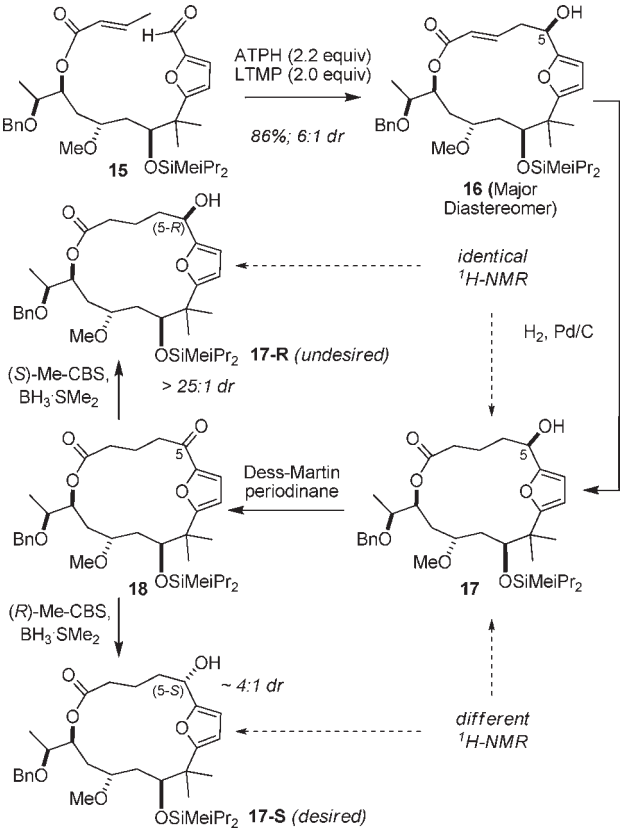
Scheme 3. Synthesis of Cyclization Precursor **15**



$(Me_4NBH(OAc)_3)$[13] of **10** provided diol **11** which was protected as the diisopropyl silylene (**12**). Compound **12** was then treated with methyl lithium in the presence of HMPA followed by methyl iodide to provide **13** bearing a methyl ether at C-13 and a diisopropyl methyl silyl ether at C-11 as a single constitutional isomer to the limits of ^{1}H NMR detection.[14] Deprotection of the C-16 PMB group (DDQ) resulted in simultaneous oxidation of the TBS ether at C-5 to provide hydroxy aldehyde **14**. This fortuitous result is likely the result of oxidation of the electron-rich furan by a mechanism similar to that of DDQ oxidation of a PMB ether to provide a silyl oxocarbenium ion which upon attack by water would provide the aldehyde.[15] Acylation with crotonic anhydride provided cyclization precursor **15** ready for the key intramolecular C–C bond forming reaction.

We were pleased to find that subjection of compound **15** to our standard intramolecular vinylogous aldol reaction conditions (lithium 2,2,6,6-tetramethyl-piperidine (LTMP), 2.0 equiv; aluminum tris(2,6-diphenylphenoxide) (ATPH), 2.2 equiv; toluene/THF, −48 °C) provided the cyclized product in 86% yield as a 6:1 diastereomeric mixture (Scheme 4). In order to determine the stereochemistry at C-5 of this material, the alkene was reduced (H_2, Pd/C, **17**) and the alcohol oxidized to provide ketone **18**. Reduction of the C-5-ketone with the (*S*)-CBS catalyst[16] provided the C-5 *R*-alcohol (**17-R**) in greater than 25:1 diastereoselectivity while reduction with the (*R*)-CBS catalyst provided the C-5 *S*-alcohol (**17-S**) in 4:1 diastereoselectivity. The spectral data of **17-R** were identical to those of **17**, indicating that the product of the intramolecular vinylogous aldol reaction (**16**) bears the undesired configuration at C-5. While it is feasible that the stereochemistry at C-5 in compound **16** can be inverted, we instead studied a different cyclization precursor in order to directly obtain the desired stereochemical outcome as described below.

Scheme 4. Intramolecular Vinylogous Aldol Reaction and Proof of Stereochemistry



We reasoned that the stereochemistry of the cyclization could be dictated by the conformation of the forming macrocycle and that a different conformation could provide the desired stereochemical outcome. We therefore studied cyclization of silylene **19**, which was prepared from silylene **12** by subjection to DDQ (Scheme 5). Again, this resulted in the simultaneous deprotection of the PMB ether and oxidation at C-5 to provide the corresponding hydroxy aldehyde as observed on compound **13**. Acylation with crotonic anhydride then provided cyclization precursor **19**. Subjection of compound **19** to our intramolecular vinylogous aldol reaction conditions provided macrolide **20** in 84% yield, again as a 6:1 diastereomeric mixture . The stereochemistry of the C-5 alcohol in **20** was determined by chemical correlation as described for macrolide **16** in Scheme 4 and was found to have the desired *S*-configuration (see Supporting Information).

(14) (a) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y-i.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem.—Eur. J.* **1999**, *5*, 121. (b) Van den Bossche, J.; Shin, J.; Thompson, D. H. *J. Org. Chem.* **2007**, *72*, 5005.

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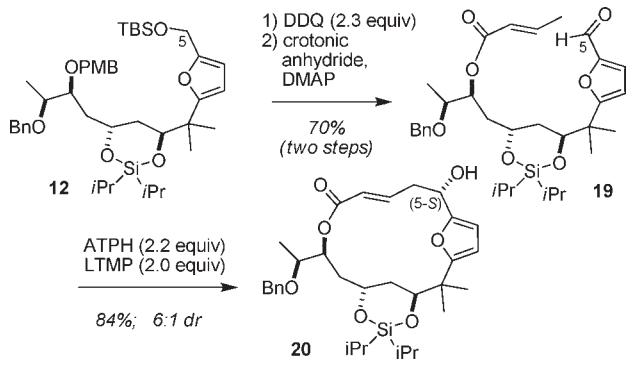
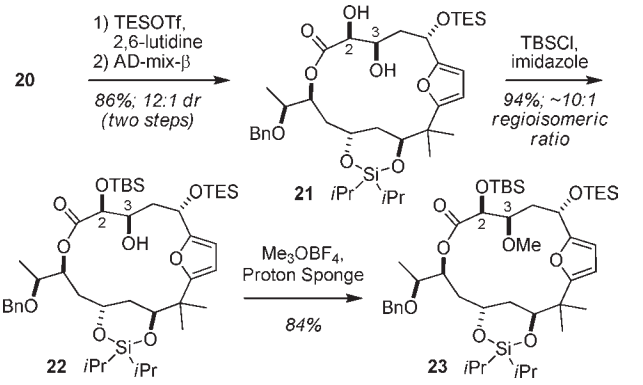
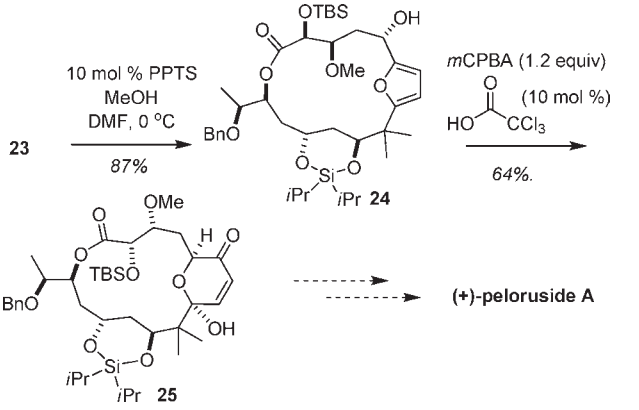
Scheme 5. Intramolecular Vinylogous Aldol Reaction of Aldehyde **19**



Scheme 6. Synthesis of Achmatowicz Precursor **23**



Scheme 7. Achmatowicz Reaction of Furan **24**



The hydroxyl group at C-5 was protected as a TES ether, and the alkene was subjected to dihydroxylation using AD-mix-β[17] to provide the diol bearing the natural stereochemistry in a 12:1 diastereomeric ratio (Scheme 6). The stereochemistry of the product was established by subjection of compound **20** to dihydroxylation using the Upjohn conditions,[18] which provided a 3:1 mixture of diastereomers, and usage of AD-mix-α, which proved to be the mismatched case and provided the product in a 1.4:1 diastereomeric ratio. This indicates that intrinsic peripheral attack provides the desired stereochemistry, which can be enhanced using AD-mix-β. The C-2 hydroxyl group was then selectively protected as the TBS ether (TBSCl, imidazole), and the C-3 alcohol was methylated (trimethyloxonium tetrafluoroborate, proton sponge).

With the installation of the protected diol complete, we turned our attention to the Achmatowicz reaction. We found that subjection of compound **23** to a mild acid (PPTS, MeOH/DMF) selectively removed the TES group in preference to the silylene (Scheme 7).[19] Subjection of this material to Achmatowicz reaction conditions[7] (*m*-CPBA in the presence of trichloroacetic acid) induced the oxidative rearrangement and provided the desired pyranone in 64% yield which is in a good position for conversion to the natural product.

This synthesis illustrates the utility of the intramolecular vinylogous aldol reaction for the synthesis of medium-membered rings. The key reaction is efficient and stereoselective and enables rapid entry into the cyclic core structure of peloruside A. Further, application of the Achmatowicz reaction allows the use of a furfural derivative that is nonenolizable and provides the pyran ring of the natural product with handles for the installation of the required functional groups. Other highlights of this synthesis include the selective conversion of a silylene to a differentially protected 1,3-diol and the oxidation of a furfuryl ether to the corresponding aldehyde using DDQ. Completion of the synthesis of peloruside A is currently under investigation.

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Supporting Information Available. Experimental procedures for the synthesis of compounds **5**–**12** and **19**–**25** and full characterization. The material is available free of charge via the Internet at http://pubs.acs.org.

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(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

(19) Selective removal of the silylene in preference to the TES ether could be accomplished using HF•pyridine in 75% yield.