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# Stereoselective Synthesis of a Monocyclic Peloruside A Analogue

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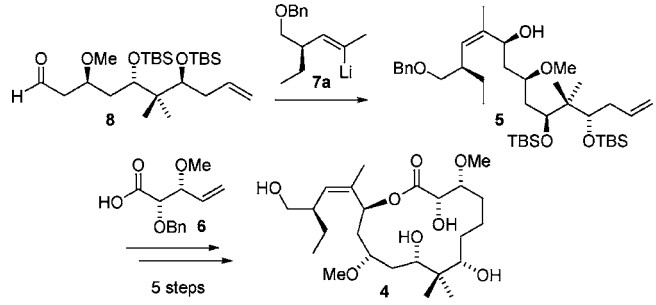
## ABSTRACT




**The stereoselective synthesis of the monocyclic peloruside A analogue 4 has been achieved, following a new efficient approach for the introduction of the side chain, involving a late-stage addition of vinyl lithium species 7a to aldehyde 8. Further key steps are a highly diastereoselective allyltitanation reaction and a RCM-based macrocyclization.**

Pelorusides A (**1**)[1] and B (**2**)[2] (Figure 1) are 16-membered macrolides that have been isolated from the marine sponge *Mycale hentscheli* by Northcote and co-workers. Both **1** and **2** are microtubule-stabilizing agents[2,3] and as a result exhibit potent growth-inhibitory and apoptosis-inducing activity in human cancer cells.[2−4] Interestingly, however, peloruside A does not bind to the taxol site on $\beta$-tubulin,[5] and it has been suggested, on the basis of computational[6] and spectroscopic[7] work, that the microtubule binding site of peloruside A could in fact be located on α- rather than on $\beta$-tubulin. This hypothesis has been questioned, however, in more recent work.[8]

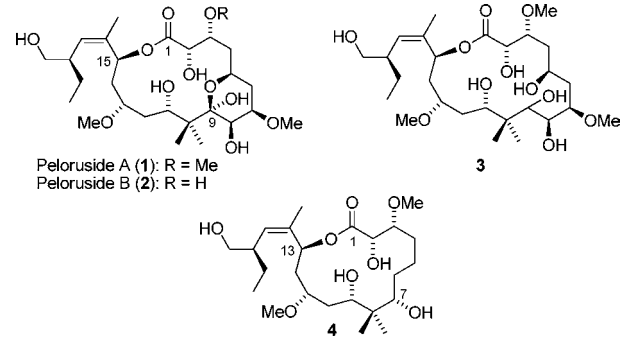



**Figure 1.** Structures of natural peloruside A (**1**) and B (**2**), the $NaBH_4$ reduction product of **1** (**3**), and target compound **4**.

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(1) West, L. M.; Northcote, P. T. *J. Org. Chem.* **2000**, *65*, 445.
(2) Jonathan, A.; Xu, C.-X.; Xu, X.; West, L. M.; Wilmes, A.; Chan, A.; Hamel, E.; Miller, J. H.; Northcote, P. T.; Ghosh, A. K. *J. Org. Chem.* **2010**, *75*, 2.
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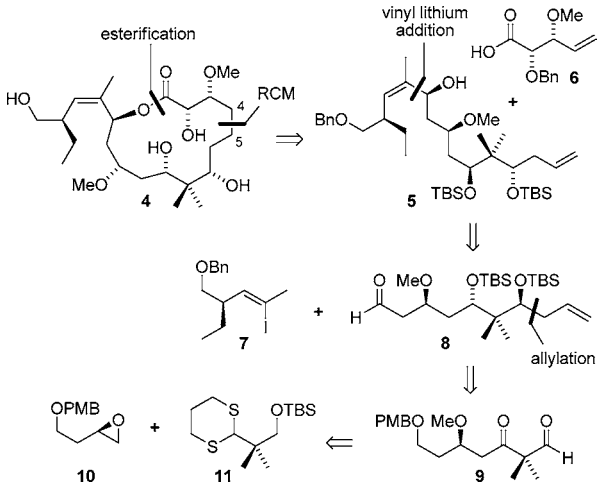
A total of five stereoselective syntheses of peloruside A have been reported to date,[9] including the non-natural (−)-enantiomer of **1**[9a] and 2-*epi*-peloruside A;[9e] the first total synthesis of peloruside B has been completed just recently.[2]

At the same time, virtually no structure−activity relationship (SAR) work has yet been performed on pelorusides. To the best of our knowledge, the only non-natural analogue of peloruside A that has been investigated so far is the $NaBH_4$ reduction product **3** (Figure 1), which was found to retain significant antiproliferative activity, despite the loss of the pyranose ring.[3] This suggests that even major structural changes in the macrolactone scaffold of **1** do not completely abolish the ability to interact with microtubules and to inhibit the growth of human cancer cells. In light of this finding we have initiated a program that aims at the exploration of the SAR of peloruside A (**1**) as it relates to the importance of the pyranose ring in the bicyclic core structure, with the ultimate objective to discover structurally simplified peloruside analogues that still retain potent biological activity.[10,11]

The retrosynthesis of peloruside A analogue **4** is outlined in Scheme 1 and in the first disconnection step entails

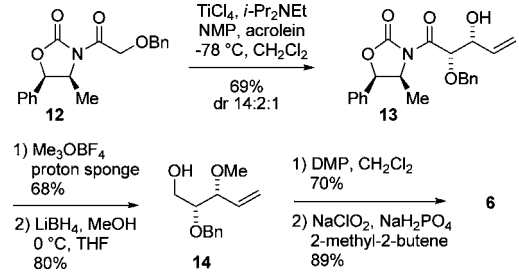
**Scheme 1.** Retrosynthetic Analysis for Target Structure **4**




breakage of the C4−C5 bond to produce a diene precursor for ring-closing metathesis (RCM). Reduction of the resulting macrocyclic alkene followed by (or concurrent with) deprotection of hydroxyl groups would then give the desired target structure. The diene itself would be obtained by esterification of acid **6** with alcohol **5**; the latter was envisaged to be produced through addition of vinyl iodide **7** to aldehyde **8**, which in turn would be the product of an asymmetric allylation reaction with $\beta$-keto aldehyde **9**. $\beta$-Keto aldehyde **9** was planned to be formed via epoxide opening of **10** with dithiane **11**.

Carboxylic acid **6** was originally envisioned to be accessed via the stereoselective aldol reaction of the boron-enolate of the Evans oxazolidinone **12** (Scheme 2) with acrolein.

**Scheme 2.** Synthesis of Building Block **6**




However, while the use of $Bu_2BOTf$ as a Lewis acid[12] did indeed produce aldol product **13** as a single isomer, only low conversion could be achieved in this reaction (15−50%), even in the presence of an excess of acrolein.[13] As a consequence, a different set of reaction conditions was employed for the preparation of **13**, building on previous work by Crimmins and co-workers on the reactions of glycolate imides with acrolein.[14] Thus, treatment of **12** with $TiCl_4$ as a Lewis acid and 1 equiv of NMP as an additive at −78 °C followed by reaction with acrolein gave aldol product **13** in good and reproducible yield (67−70%) and with 14:2:1 diastereoselectivity in favor of the desired 2*S*,3*R*-isomer (vide infra)[15] (Scheme 2). Clean separation of the diastereomeric mixture by flash chromatography (FC) was possible after the subsequent methylation step. As treatment of the resulting methylated imide with LiOOH did not give any conversion (i.e. the starting material remained unchanged), the elaboration of this intermediate into acid **6** was based on a three-step sequence, involving reductive removal of the chiral auxiliary (to give **14**) followed by two oxidation steps (DMP, Pinnick, Scheme 2).

To ascertain the (predicted) stereochemical outcome of the aldol reaction between **12** and acrolein in an independent way, **13** was also converted to the 2,3-*syn*-bis(benzyloxy)-

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(10) This work was also stimulated by the similar antiproliferative activity of the marine natural products neopeltolide[11a] and leucascandrolide A.[11b] Notably, neopeltolide and leucascandrolide A, although sharing a number of essential structural features, are distinguished by the lack of a second tetrahydropyran ring in neopeltolide. See also: Ulanovskaya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumacker, P. T.; Kron, S. J.; Kozmin, S. A. *Nat. Chem. Biol* **2008**, *4*, 418.

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(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

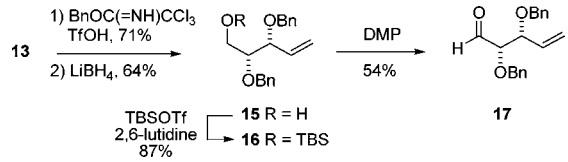
(13) A yield of 72% could be achieved on a single occasion, but this result could not be reproduced in several subsequent experiments.

(14) Crimmins, M. T.; She, J. *Synlett* **2004**, *8*, 1371.

(15) Three out of the four possible diastereomers were detected by NMR. The configuration of the minor diastereomers was not determined.

pentene derivatives **15** and **16** by treatment with benzyl 2,2,2-trichloroacetimidate followed by $LiBH_4$ reduction (to give **15**) and reaction with TBSOTf (to produce **16**; Scheme 3).

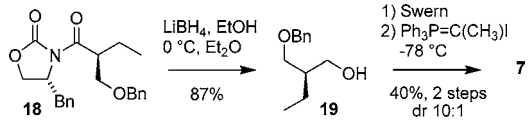
**Scheme 3.** Verification of the 2,3-*syn* Relationship in **6**




All analytical data collected for **15** and **16** (optical rotation, $^1H$ and $^{13}C$ NMR spectra) were identical with those reported in the literature, and the same is true for aldehyde **17**, which was obtained by DMP oxidation of **15**.[16]

As illustrated in Scheme 4, the synthesis of building block **7** commenced with the $LiBH_4$ reduction of the known

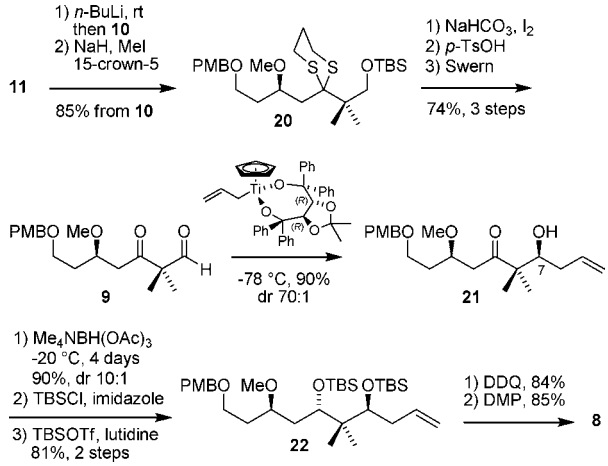
**Scheme 4.** Synthesis of Vinyl Iodide **7**




intermediate **18** (readily available via a highly diastereoselective Evans-alkylation of (*R*)-4-benzyl-3-butyryloxazolidin-2-one with BOMCl and $TiCl_4$).[17] The resulting alcohol **19** was then oxidized under Swern conditions, and the aldehyde was further converted to the desired vinyl iodide **7** by Wittig reaction with iodoethyl-phosphonium iodide;[18] this latter Wittig reagent gives *Z* olefins with high selectivity, albeit in moderate yields.[18,19]

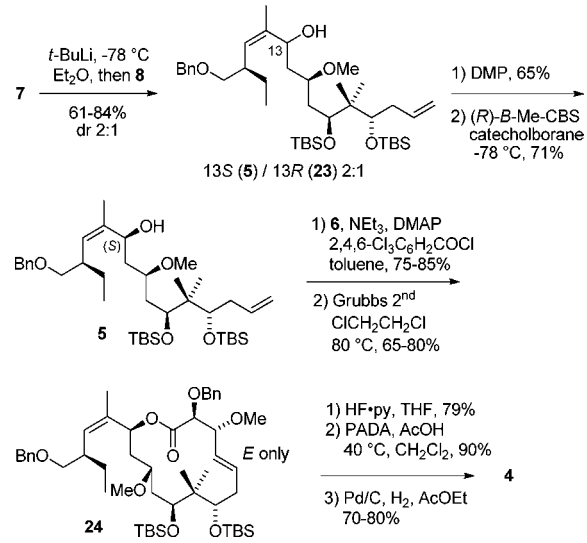
The preparation of aldehyde **8**, as the coupling partner for vinyl iodide **7** (cf. Scheme 1), is summarized in Scheme 5.

**Scheme 5.** Synthesis of Intermediate **8**




Epoxide ring-opening in **10** (available from (*S*)-aspartic acid in 3 steps and 50% overall yield)[20] with 1.8 equiv of lithiated dithiane **11** (available in 3 steps and 80% overall yield from 2,2-dimethylpropane-1,3-diol) gave a secondary alcohol, which was methylated with MeI in the presence of NaH and 15-crown-5 to provide methyl ether **20** in 85% yield for the two-step sequence from **10** (Scheme 5). Iodine-mediated dithiane cleavage followed by removal of the silyl protecting group with *p*-TsOH and Swern oxidation of the primary hydroxyl group gave $\beta$-keto aldehyde **9** (74%, 3 steps). This aldehyde was then submitted to asymmetric allyltitanation,[21] which gave homoallylic alcohol **21** in high yield (90%) and with excellent diastereoselectivity (dr up to 70:1). Notably, no conversion of **9** to **21** was observed under Keck allylation conditions,[22] whereas Brown allylation (with (−)-DIPCl)[23] gave only low yields (<30%) and moderate selectivity (2:1 to 10:1). The absolute configuration of the newly formed stereogenic center at C7 in **21** was verified by Mosher ester analysis.[24] 1,3-*anti*-Reduction of **21** with $Me_4NBH(OAc)_3$[25] (90%, dr 10:1) established the chiral center at C9 (analogue numbering, cf. Figure 1); unfortunately, separation of the minor diastereomer was not possible at this stage but could be accomplished after RCM (Scheme 6, compound **24**). The

**Scheme 6.** Assembly of Target Structure **4**




reduction product was then converted to the fully blocked tetrol **22**, which was further elaborated into intermediate **8**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via oxidative cleavage of the PMB protecting group with DDQ and subsequent DMP oxidation of the resulting primary hydroxyl group in 74% overall yield.

It should be noted here that the double silylation leading to **22** was best carried out in two separate steps, which involved reaction of the reduction product of **21** with 6 equiv of TBSCl and then treatment of the resulting 7:2-mixture of mono-TBS ethers with 1.6 equiv of TBSOTf. While this procedure provided **22** in 81% yield from the starting diol, direct treatment of the latter with 2.1 equiv of TBSOTf gave incomplete conversion, and reaction with a larger excess of TBSOTf was associated with the formation of several unidentified side products, thus furnishing only 57−69% of **22**.

To reconfirm the stereochemical outcome of the 1,3-reduction in **21** (Scheme 5), the resulting diol was converted to the corresponding acetonide (2,2-dimethoxypropane, cat. CSA, 75%). The $^{13}C$ chemical shifts of the two ketal methyl groups in this derivative were observed at 24.01 and 23.96 ppm, while the quaternary ketal carbon signal appeared at 100.96 ppm. These data are in excellent agreement with the predicted shifts for acetonides of *anti*-1,3-diols, which preferentially adopt a twist-boat conformation with both *anti*-substituents in equatorial positions.[26]

The elaboration of building blocks **6**, **7**, and **8** into peloruside A analogue **4** was initiated with the addition of the vinyl lithium species derived from **7**, by treatment with *t*-BuLi, to aldehyde **8** at −78 °C (Scheme 6). The reaction proceeded with modest selectivity to produce a ca. 2:1 mixture of allylic alcohols **5** and **23** (in favor of the desired diastereomer **5**) in scale-dependent yields. Thus, while **5**/**23** were obtained in 54% yield on a 0.15 mmol scale for **8**, yields increased to 61% and 84% for reactions with 0.41 and 0.82 mmol of **8**, respectively. As the mixture of **5** and **23** could not be separated by FC, it was oxidized with DMP and the resulting ketone was stereoselectively reduced with (*R*)-B-Me-CBS/catecholborane.[27] On the basis of this oxidation/reduction sequence, **5** could be obtained in stereochemically pure form and 46% yield for the two-step sequence from the **5**/**23** mixture. The absolute configuration of the newly established chiral center was again verified by Mosher ester analysis.[24]

Yamaguchi esterification[28] of acid **6** with allylic alcohol **5** followed by RCM of the resulting ester intermediate with Grubbs II catalyst[29] provided *E*-configured macrolactone **24** as the only isolable cyclization product in 65−80% yield. While RCM was initially performed in $CH_2Cl_2$, the use of 1,2-dichloroethane enabled the reaction to be conducted at higher temperature, thus resulting in shorter reaction times and allowing for reduced catalyst loads (<0.14 equiv of catalyst, 1.5 h at reflux versus >0.20 equiv of catalyst, 7 h at reflux in $CH_2Cl_2$). Removal of the TBS groups with HF·pyridine followed by selective reduction of the disubstituted endocyclic double bond with in situ generated diimide (from di-K azodicarboxylate (PADA), ca. 80 equiv)[30] and finally hydrogenolytic removal of the benzyl protecting groups furnished target structure **4** in very good overall yield (50−57% for the 3-step sequence from **24**). Direct catalytic hydrogenation (Pd/C; ambient pressure) of the partially deprotected diene obtained after TBS removal, i.e., without prior reduction of the endocyclic double bond, led to complete cleavage of the benzyl groups within 5 h. However, the reduction of the endocyclic double bond did not reach completion under these conditions, with the reaction failing to progress beyond ca. 70% conversion at 6 h. No attempts were made to conduct the hydrogenation at higher pressure, given the potential vulnerability of the side chain double bond under more forcing conditions.

Assessment of the antiproliferative activity of peloruside A analogue **4** in three human cancer cell lines revealed the compound to be several-hundred-fold less potent than peloruside A (**1**) or B (**2**). ($IC_{50}$ values against MCF-7/HCT116 > 20 $\mu$M; $IC_{50}$ against A549 = 16.4 $\mu$M). In light of the substantial structural changes relative to **1** or **2**, this result may not seem too surprising, but the observation of micromolar activity against the A549 cell line is still encouraging. On the basis of the chemistry developed for the synthesis of **4**, we will now attempt to improve the activity of this analogue through structural modifications in the C4−C6 region (analogue numbering, Figure 1). At the same time, the chemistry developed in the course of this work for the synthesis of intermediates **8** and **5** could offer a new entry into the synthesis of the natural products peloruside A and B. Studies along these lines are currently in progress in our laboratory.

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**Supporting Information Available:** Synthetic procedures, complete spectroscopic data, and $^1H$ and $^{13}C$ NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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