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Stereoselective Synthesis of the C9−C19 Fragment of Peloruside A

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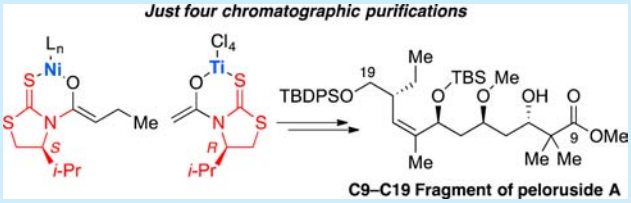
Supporting Information

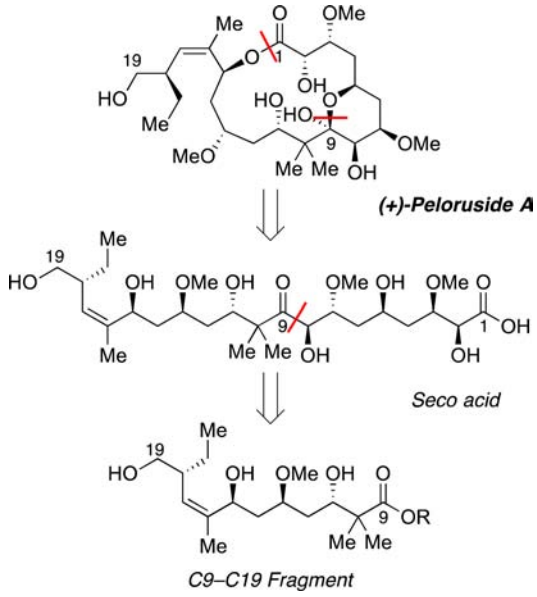
ABSTRACT: A concise synthesis of the C9−C19 fragment of peloruside A that is both highly stereoselective and efficient is described. Achieving an overall yield of 23% over 14 steps, this synthesis not only is high yielding but also involves four chromatography steps. This approach is based on the addition of metal enolates of chiral auxiliary scaffolds generated by either catalytic or stoichiometric amounts of nickel(II) or titanium(IV) Lewis acids.



(+)-Peloruside A is a polyketide macrolide that was first isolated by Northcote and co-workers in 2000 from the marine sponge *Mycale* found in Pelorus Sound, off the coast of New Zealand.[1] It displays potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng mL^{-1}.[2] In addition, peloruside A shows powerful microtubule-stabilizing activity similar to paclitaxel and is synergistic with it.[3−6] Structurally, it consists of a 16-membered lactone with an internal pyran ring and an unsaturated lateral chain, containing a total of 10 stereocenters (Scheme 1). The macrolide itself has a geminal dimethyl group and various hydroxyl and methoxy groups, while the unsaturated lateral chain contains a *Z*-olefin and a primary alcohol.

The first total synthesis of peloruside A was reported by De Brabander in 2003, confirming the absolute configuration of the natural product.[7] After this approach, other significant efforts have been directed to the total synthesis of peloruside A[8,9] or certain fragments of it.[10] More specifically, the synthesis of fragments containing the lateral chain of the macrolide has been a challenging goal due to the structural complexity.[9−11]

Scheme 1. (+)-Peloruside A and C9−C19 Fragment



In this context and considering the need for alternative routes toward such fragments, we envisaged a new and efficient approach to the C9−C19 fragment of peloruside A (Scheme 1) that could take advantage of several highly selective transformations based on chiral *N*-acyl thiazolidinethione scaffolds, developed in our group.[12−14] As seen in Scheme 2, our retrosynthetic analysis hinges on three asymmetric carbon−carbon bond forming reactions, involving the use of metal enolates of either the (*R*)- or (*S*)-enantiomer of *N*-acyl-4-isopropyl-1,3-thiazolidinethiones, and also a substrate-controlled Mukaiyama aldol reaction.[15] The use of highly effective chiral auxiliaries allows the control of reactional selectivity and also minimizes the steps needed in the synthesis by functionalization during removal of the auxiliary.[16−18] Beyond this we aimed to make the synthesis as concise and simple as possible and minimize the amount of purification processes. By doing this we would reduce both material used and time needed to carry out the synthesis, which in turn would reduce the cost and environmental impact of making the molecule.[19] In short, the aim was to create a simple and more effective synthesis of the C9−C19 fragment of peloruside A.

Our synthesis started with the first catalytic direct-type reaction applied to a peloruside A synthesis. This reaction is based on the catalytic addition of nickel(II) enolates to an oxocarbenium ion generated in situ.[14] The reaction was carried out using (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**1**)[20] as the substrate, trimethyl orthoformate as the electrophile, and a simple, robust, and commercially available $(Me_3P)_2NiCl_2$ as the precatalyst (Scheme 3); the addition of TESOTf was necessary to both activate the electrophile and

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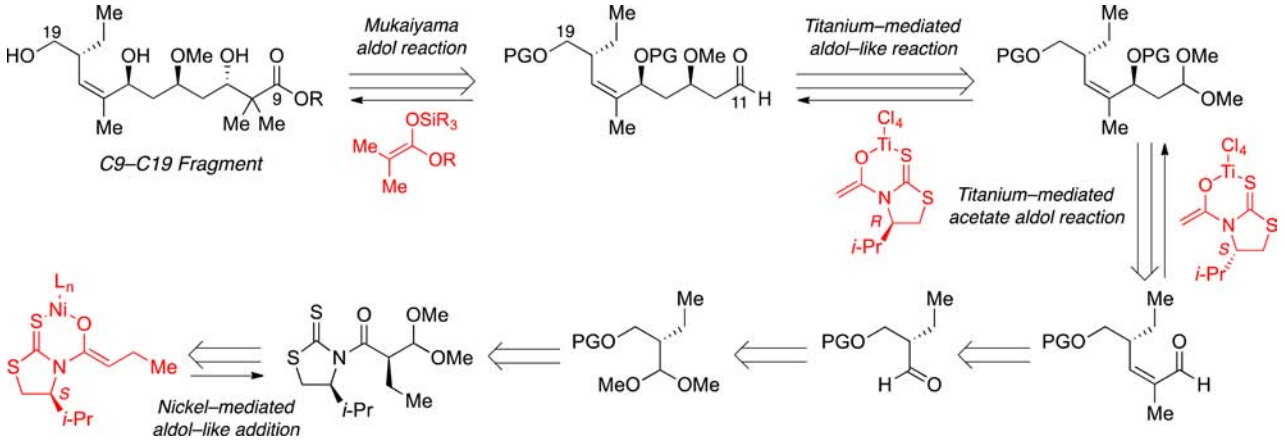
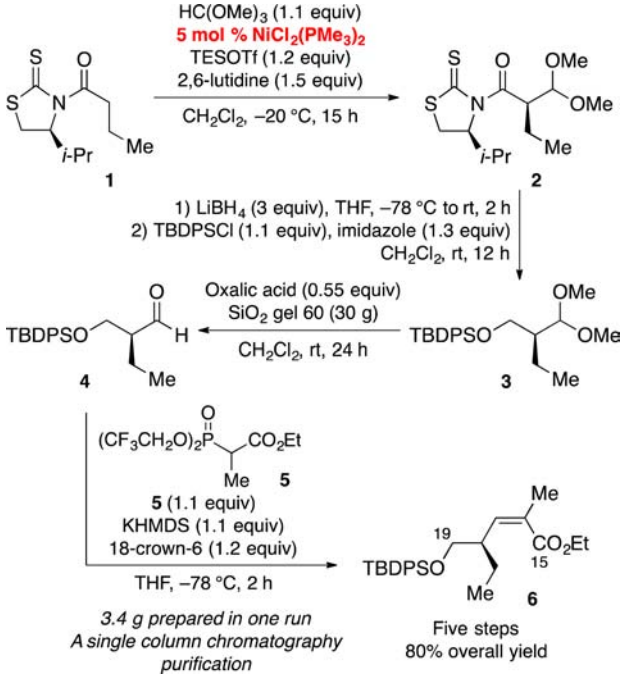
Scheme 2. Retrosynthetic Analysis of the C9−C19 Fragment



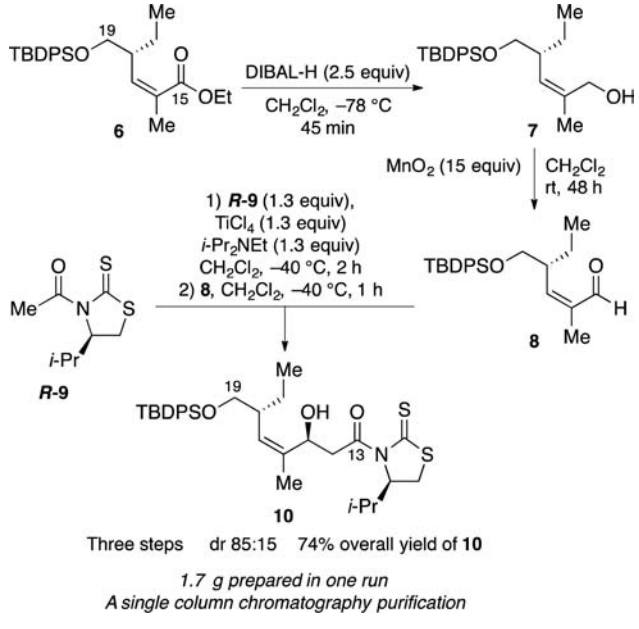
Scheme 3. Synthesis of the α,β-Unsaturated Ester 6 (C15−C19 Fragment)



create the truly active catalyst. Importantly, full conversion was achieved with only 5 mol % of $NiCl_2(PMe_3)_2$, which provided the corresponding adduct **2** as a single diastereomer with an 82% yield at a multigram scale. Removal of the chiral auxiliary with an excess of $LiBH_4$ and treatment of the resulting alcohol with TBDPSCl afforded the protected hydroxy acetal **3**. Furthermore, we were able to recover 90% of the auxiliary from this process; simple extraction in the workup allows for recycling and reuse of the chiral scaffold. Then, following a procedure described by Denmark, this acetal was converted into the aldehyde **4** using silica and oxalic acid in a simple and effective reaction.[21] Finally, the trisubstituted double bond was selectively inserted with a Still−Gennari reaction[22] using the phosphonate **5**[23] to obtain the α,β-unsaturated ester **6**. Because the aforementioned reactions proceeded efficiently and impurities were negligible, we could conduct all five reactions in sequence, with only one chromatographic purification process conducted after the Still−Gennari coupling. This led to the pure α,β-unsaturated ester **6** in a yield of 80% over five steps on a 10 mmol scale.

Continuing the synthesis, the reduction of α,β-unsaturated ester **6** with DIBAL-H[24] and the subsequent oxidation of the resultant allylic alcohol **7** with MnO_2 afforded the aldehyde **8** (Scheme 4), which served as the substrate for the next key aldol

Scheme 4. Synthesis of the Adduct 10 (C13−C19 Fragment)



reaction with the titanium(IV) enolate of (*R*)-*N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (***R*-9**).[20] Despite the challenge of such an acetate aldol reaction,[25] the application of the experimental conditions previously developed in our group[12] afforded the desired aldol adduct **10** with an excellent 85:15 diastereomeric ratio. Furthermore, we were able to carry out this reaction in succession, purifying only after the aldol step to achieve a 74% yield of pure single diastereomer **10** (C13−C19 fragment) over three steps at 8 mmol scale.

Treatment of **10** with TBSOTf afforded protected aldol **11**, which was reduced with DIBAL-H at −78 °C to give the desired aldehyde **12** (Scheme 5). Remarkably, this process was able to stop chemoselectively at the aldehyde stage, enabling removal of the chiral auxiliary and adjustment of the oxidation state in a single step. Also notable is our recovery of the chiral

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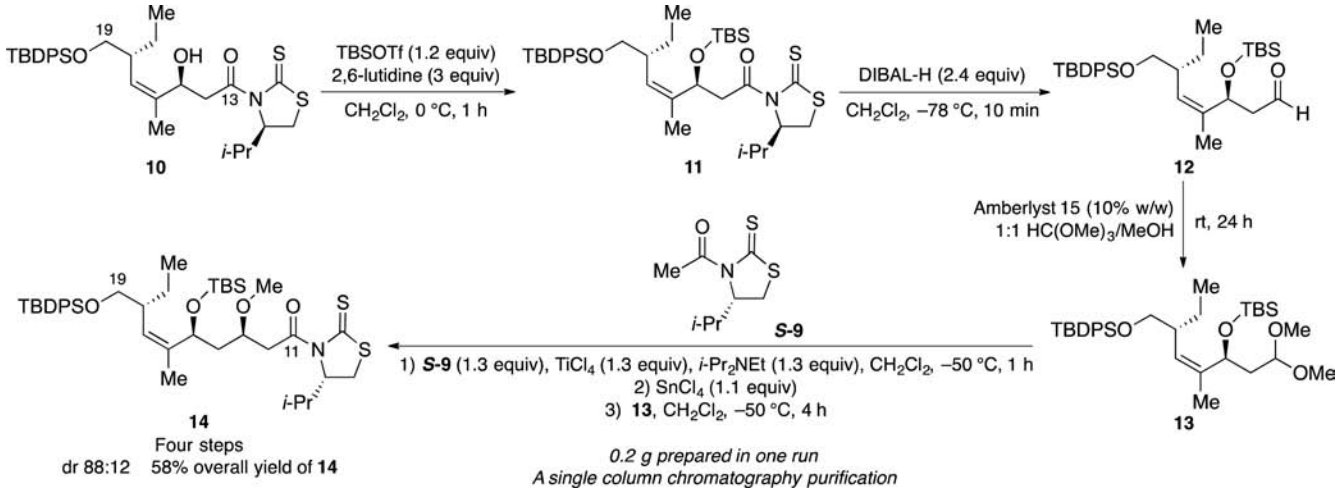
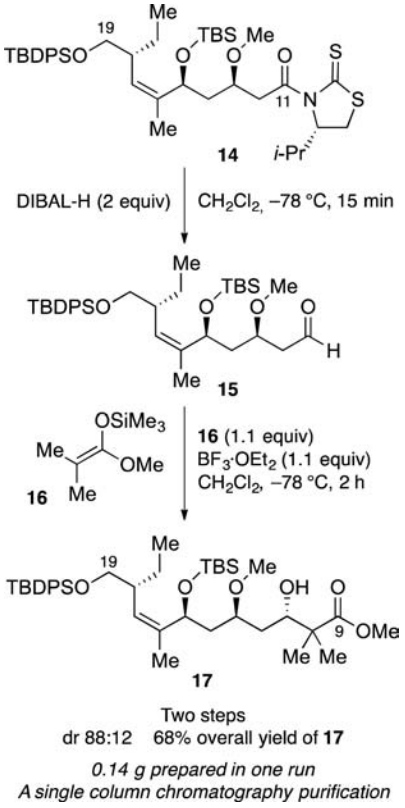
Scheme 5. Synthesis of the Adduct 14 (C11−C19 Fragment)



auxiliary in 85% purity from extraction. After various screening tests, dimethyl acetal **13** was efficiently prepared by treatment with MeOH, trimethyl orthoformate, and Amberlyst-15 without affecting the TBS protecting group. Differing from most strategies based on the stereoselective installation of the C13 hydroxyl group and subsequent methylation with energetic agents, we explored an alternative route. Indeed, we established that the Lewis acid-mediated addition of titanium enolates of *N*-acyl thiazolidinethiones to dimethyl acetals afforded *β*-methoxycarboxylic substructures stereoselectively in a single step.[13] As use of $SnCl_4$ as Lewis acid led to partial removal of the TBS protecting group, a comprehensive optimization was carried out. This was a lengthy process, balancing the maximum conversion against selectivity and the extent of deprotection of the TBS group that was occurring. Eventually, minimizing the equivalents of the enolate and the second Lewis acid, increasing the reaction time, and keeping the temperature at −50 °C afforded the desired adduct **14** (C11−C19 fragment) in a highly efficient manner. Indeed, we found that the addition of a slight excess of the titanium enolate from ***S*-9**[20] to **13** in the presence of 1.05 equiv of $SnCl_4$ (added as a 1 M solution in CH_2Cl_2) at −50 °C gave a full conversion and a selectivity of 88:12 alongside a small amount of the TBS-deprotected adduct. Again we were able to eliminate further purification processes by performing the protection, the removal of the auxiliary, the dimethyl acetal formation, and the addition in a continuous sequence, using only a single chromatographic purification at the end. This yielded 58% of a pure single diastereomer **14** over four steps.

Once again removal of the auxiliary with DIBAL-H gave the aldehyde **15** with a 92% recovery of the auxiliary. The last step involved a substrate-controlled Mukaiyama-aldol addition of silyl ketene acetal **16** to **15** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 6). The stereochemical outcome of this reaction relied heavily on the configuration of the chiral aldehyde **15**.[26] Particularly, comprehensive studies reported by Evans established that the Mukaiyama aldol addition to *β*-alkoxy aldehydes provides the corresponding *anti* aldol as the major diastereomer.[27] In accord with this model, the reaction of **15** and **16** produced a 88:12 mixture of diastereomers in a high yield. As in former sequences, we were able to run directly a two-step sequence after the removal of the chiral auxiliary to afford enantiomerically pure ester **17** in 68% yield with a single SiO_2 column purification. This final reaction concluded the synthesis

Scheme 6. Synthesis of the Ester 17 (C9−C19 Fragment)



of the C9−C19 fragment of peloruside A, and, with a methyl ester terminus, such an intermediate is suitably tailored for continuation of the total synthesis.

In conclusion, we have developed a concise synthesis of the C9−C19 fragment of peloruside A. The synthesis has been achieved in a total yield of 23% over 14 steps. Remarkably, not only have we achieved this very competitive yield compared to other attempts, but we have also been able to perform a very effective synthesis, by removing many of the purification steps, running just four chromatographic purifications over all 14 steps. The main benefit of this is a dramatic reduction of the time needed to execute the synthesis. It also permits work on a

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multigram scale. Further work is in progress to complete the total synthesis of peloruside following these ideas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01428.

Complete experimental procedures; physical and spectroscopic data for new compounds (PDF)

Copies of ^{1}H and ^{13}C spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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