Total Synthesis

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Highly Convergent Synthesis of Peluroside A

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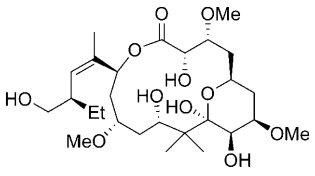
aldol reaction · asymmetric synthesis · macrocyclic compounds · natural products · reduction

A stated objective for many efforts in total synthesis is to provide access to structures that exhibit interesting biological activity. Although this goal is unquestionably worthy of pursuit, the impact that organic synthesis can have on the supply of natural products or their analogues for biological evaluation and, ultimately, therapeutic treatment is still limited by the structural complexity and size of the targets. Convergent strategies, in which two or more subunits of the target are prepared independently and coupled at a late stage in the sequence, have been developed to facilitate large-molecule synthesis. Although convergent approaches generally do not reduce the overall step count for a synthesis, they can greatly reduce the linear step count and improve throughput. Moreover, these modular approaches to molecular construction enable the preparation of analogues from structurally diverse subunits. There have been several spectacular examples of the preparation of natural products in substantial quantities through convergent approaches in the past decade.[1] Evans et al. recently reported[2] a highly convergent approach to peloruside A (**1**) that has the capacity



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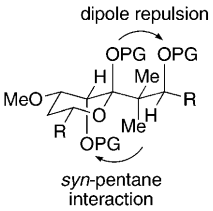
to provide useful amounts of this intriguing natural product and to supply analogues for biological evaluation.

Peloruside A was isolated from sponges of the *Mycale* genus in New Zealand by Northcote and co-workers.[3] Its connectivity and relative configuration were established by extensive NMR spectroscopic studies. Potent cytotoxicity was observed when P388 cells were exposed to **1**, and subsequent studies demonstrated that this activity arises from apoptosis induction through microtubule stabilization.[4] Although conflicting reports have emerged regarding the location of the binding site for peloruside A on microtubules,[5] it is clearly distinct from the paclitaxel binding site.[6] The presence of dual binding sites improves therapeutic potential by enabling paclitaxel and peloruside A to act synergistically.[7] The environmental sensitivity for peloruside A production from sponges,[8] however, suggests that synthesis will be the most reliable source for future biological studies.

De Brabander and co-workers reported[9] the first total synthesis of the enantiomer of peloruside A. Key elements of this landmark approach include the determination of the absolute configuration of the natural product and the identification of severe steric interactions that can hinder macrolactone formation when the hydroxy groups in proximity to the tetrahydropyran ring are protected (Scheme 1). Taylor and Jin completed the first synthesis of the natural enantiomer of **1** through a convergent sequence in which two advanced fragments were coupled through an aldol reaction.[10] Steric hindrance in the macrolactonization step was avoided in a creative manner through the use of a dihydropyrone intermediate that underwent oxidative functionalization to complete the synthesis. Ghosh et al. also approached the synthesis of **1**[11] by coupling two advanced fragments in an aldol reaction that involved an innovative reductive enolate formation. This sequence addressed the steric impediments to cyclization by delaying the construction of the tetrahydropyran ring until the macrolactone was formed. Several reports on the synthesis of peloruside A fragments or epimers have also contributed greatly to our understanding of the behavior of this densely functionalized structure.[12,13]



Scheme 1. Steric and electronic interactions in peloruside A.

The objective of Evans et al. in their synthesis of peloruside A was to design a route that was sufficiently flexible for analogue preparation. This flexibility was achieved by constructing the molecule from three fragments of approximately equal complexity (Scheme 2). Aldol reactions—the additions of enolates or their surrogates to aldehydes to form β-hydroxy carbonyl compounds—were used to couple the fragments because of the efficiency of these reactions even for large, densely functionalized substrates and their capacity for guiding stereocenter formation with high and predictable levels of control. A secondary strategic element in this approach was the application of directed ketone-reduction processes for the stereoselective

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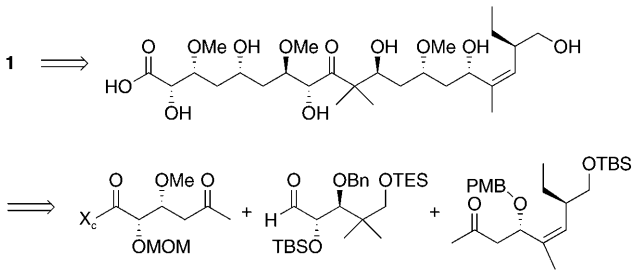
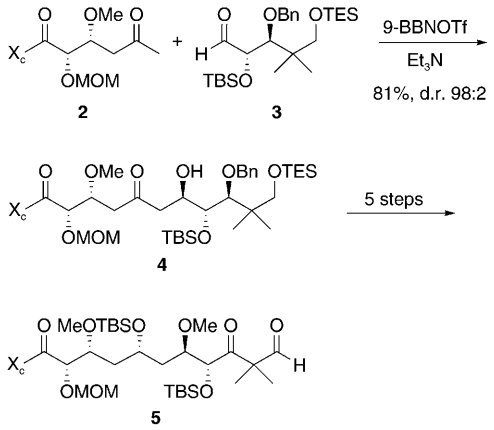


Scheme 2. Retrosynthetic analysis of peluroside A. X_c = benzyloxazolidinone, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl, TES = triethylsilyl, PMB = *para*-methoxybenzyl.

formation of secondary alcohols. This feature is particularly useful for the synthesis of analogues.

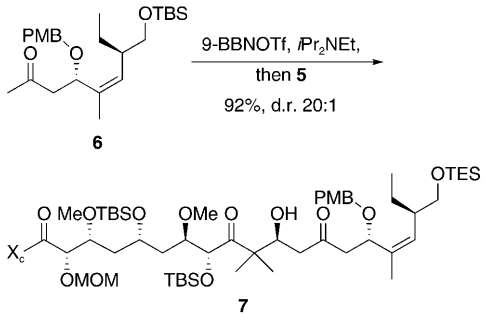
The coupling of **2**, prepared in six steps from (*S*)-4-benzyl-2-oxazolidinone, and **3**, prepared in seven steps from (*S*)-pantolactone, is an excellent application of the aldol reaction to form a key carbon–carbon bond, whereby stereochemical information in the nucleophile and electrophile guides the generation of a new stereocenter (Scheme 3). Boron enolates



Scheme 3. First fragment-coupling aldol reaction. 9-BBNOTf = 9-borabicyclononyl trifluoromethanesulfonate.

of β-alkoxy methyl ketones have been shown to undergo aldol reactions to provide products with the alkoxy group and the newly formed hydroxy group in an *anti* stereochemical arrangement with good to excellent levels of diastereoselectivity.[14] Aldehydes that contain alkoxy groups at the α and β positions in an *anti* arrangement generally react with boron enolates efficiently and selectively to provide a stereotriad with an *anti*, *anti* configuration.[15] This observation contrasts with predictions based on addition to α- or β-monoalkoxy aldehydes,[16] and has been explained on the basis of the minimization of steric interactions in Cornforth-type[17] transition states. Although these matching factors suggested that the coupling of **2** and with an aldehyde such as **3** would be efficient and highly stereoselective, the result of the aldol reaction was strongly dependent upon the alkyl groups on the boron atom and dependent to a lesser extent upon the bulk of the protecting groups. The best result was observed when the 9-borabicyclononyl (BBN) enolate of **2** was used, and the hydroxy groups at the α and δ positions of the aldehyde were protected with trialkylsilyl groups, as in **3**. Under these conditions, **4** was formed in 81% yield as a 98:2 mixture of diastereomers. Compound **4** was converted into aldehyde **5**, the electrophilic component for the next aldol coupling, through a five-step sequence.

The stereoselectivity in the coupling of **5** with the methyl ketone **6** (Scheme 4) was consistent with the previously discussed observation that β-alkoxy ketone boron enolates



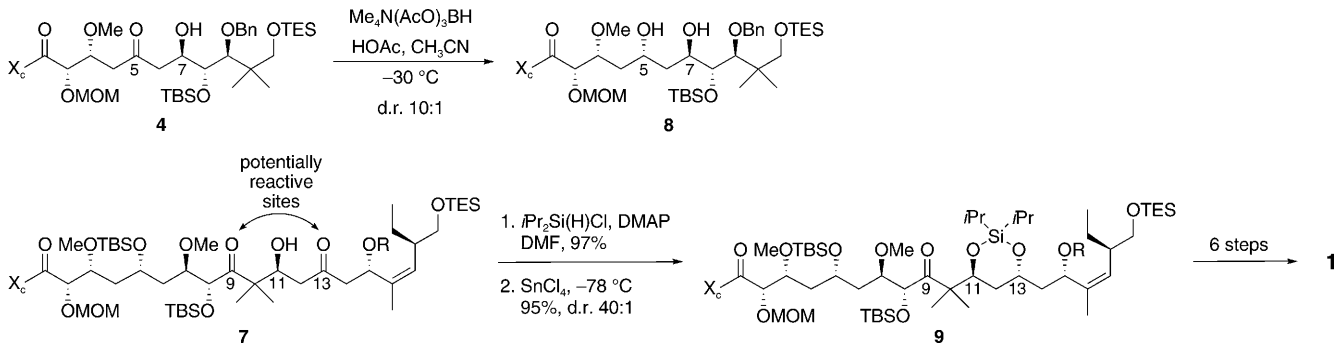
Scheme 4. Second fragment-coupling aldol reaction.

generally undergo 1,5-*anti*-selective aldol reactions. The steric hindrance that results from the geminal methyl groups in **5** significantly diminishes the electrophilic reactivity of the aldehyde group. Analogous compounds containing a reduced form of the β-keto group were found to be inert toward boron enolates. The aldol reaction between **5** and the 9-BBN enolate of **6**, however, was remarkably efficient and provided **7** in 92% yield as a 20:1 mixture of diastereomers. This transformation completed the construction of the linear carbon framework of peloruside A.

Stereoselective reduction of the ketone group immediately followed each of the fragment-coupling aldol reactions (Scheme 5). The synthesis of the natural product required both reduction steps to proceed with *anti* selectivity with respect to the hydroxy groups that had been formed in the coupling reactions. Reduction of the C5 carbonyl group in **4** with $Me_4N(AcO)_3BH$[18] was directed by the hydroxy group at C7 as expected to form diol **8** in essentially quantitative yield as a greater than 10:1 mixture of diastereomers.

The reduction directed by the C11 hydroxy group of **7** was complicated by the presence of ketone groups at C9 and C13. $Me_4N(AcO)_3BH$ showed no selectivity between the carbonyl groups, despite the presence of geminal methyl groups at C10. This result led to the development of a stepwise reduction protocol that proceeded through diisopropylsilyl ether formation and $SnCl_4$-mediated ketone hydrosilylation[19] to form disilyloxane **9** in 95% yield as a 40:1 mixture of diastereomers. The regioselectivity of this reaction apparently arises from enhancement of the steric impact of the geminal methyl groups through the use of a bulkier reducing agent.

Each of these reductions ultimately led to the need to differentiate one hydroxy group from the other. Steric and electronic differences were exploited for monofunctionaliza-



Scheme 5. Stereo- and regioselective reduction of the aldol products **4** and **7**. DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide.

tion with excellent regioselectivity. An efficient six-step sequence in which macrolactonization preceded tetrahydropyran formation completed the synthesis. The longest linear sequence in this route was 22 steps from pantolactone.

The objective of this synthesis was to develop a highly convergent approach to peloruside A that would enable facile analogue preparation. In principle, analogues can be prepared by incorporating fragments with different substituents and/or substituents in different stereochemical orientations into the sequence. This approach is likely to be successful with respect to carbon–carbon bond formation; however, the exquisite stereochemical control that was observed in the synthesis of the natural product could be hard to match because of the complex effects of proximal functional groups on competitive transition states in aldol reactions. Although this factor might impact the capacity of the route to deliver bulk quantities of analogues, it is unlikely to be an impediment for the exploration of structure–activity relationships. The hydroxy-group-directed reduction reactions provide additional opportunities for the preparation of stereoisomers of peluroside A: Numerous protocols have been developed for the *syn*-selective reduction of β-hydroxy ketones.[20] These procedures could be incorporated readily into the synthetic sequence to enhance the stereochemical diversity of a series of analogues.

The preparation of suitable amounts of material for intensive studies on the biological activity of peloruside A was not identified as an objective of the synthesis by Evans et al. An analysis of the amounts of each subunit that have been prepared and the efficiencies of the reactions, however, strongly suggests that this route has the potential to deliver hundreds of milligrams of the natural product. The ability to prepare significant quantities of a target structure and a range of analogues by convergent synthetic strategies can have an impact on the use of complex natural products to study important biological processes and, potentially, on the development of lead structures into drugs.

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