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Synthesis of the C(1)–C(12) Segment of Peloruside A by an α-Benzyloxymethyl Ketone Aldol Strategy

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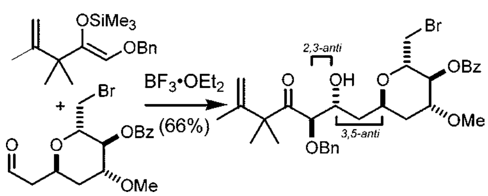
ABSTRACT



The C(1)–C(12) segment of 16-membered antitumor macrolide peloruside A has been prepared by a $BF_3 \cdot OEt_2$-catalyzed Mukaiyama aldol reaction between a glucose-derived C(1)–C(7) aldehyde and a C(8)–C(12) α-benzyloxymethyl ketone. Exclusive 2,3-anti and moderate 3,5-anti/syn facial selectivity (3.5:1) was observed in the aldol reaction. The key C(1)–C(7) aldehyde contains the required stereochemistry at carbons two, three, and five, and has been efficiently prepared on multigram scales from commercial triacetyl D-glucal.

The sponges of the *Mycale* genus have proven to be a valuable source for spectacular new antiviral and antitumor natural products. In 2000, Northcote reported the isolation of the 16-membered macrolide peloruside A (**1**, Figure 1) from a select subpopulation of deep-sea *Mycale* sea sponges, along with known natural products mycalamide A and pateamine.[1] Peloruside A shows potent cytotoxicity at nanomolar concentrations toward multiple tumor cell lines, and is thought to function like Taxol by inducing apoptosis in the G2-M phase of the cell cycle through microtubule stabilization.[2,3] The promising therapeutic potential of peloruside A coupled with severely limited availability from natural sources (3.0 mg was isolated from 170 g of frozen sponge) necessitates that additional quantities for biological evaluation be supplied through synthesis in the laboratory. Recently De Brabander completed an elegant total synthesis of *ent*-**1**, thus establishing absolute configuration and confirming structural assignment;[4] Several other groups have reported the synthesis of peloruside fragments.[5−9]

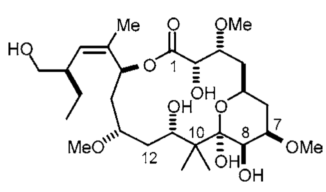


Figure 1. Peloruside A (**1**).

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(3) Hood, K. A.; West, L. M.; Rouwe, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, St. J.; Miller, J. H. *Cancer Res*. **2002**, *62*, 3356−3360.

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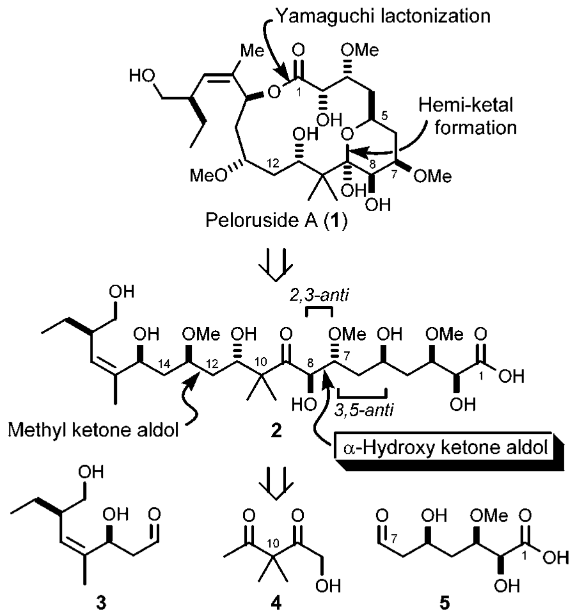
Our retrosynthetic strategy for peloruside A is shown in Scheme 1. After hydrolysis of the 16-membered macrocyclic lactone and C(9) hemi-ketal to afford carboxylic acid **2**, we plan to join fully elaborated left- and right-hand segments **3** and **5** to central unit **4** containing the C(10) geminal dimethyl group. This synthetic strategy required the development of an unknown α-hydroxy ketone aldol reaction for C(7)−C(8) bond construction. While glycolate anti aldols are well established,[10] α-hydroxy ketone aldols are underdeveloped, particularly with ketones flanked by a quaternary carbon.[11−13]

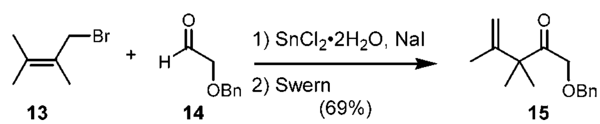
Scheme 1



The synthesis of **12**, an equivalent of the right-hand aldehyde **5** but with functional groups suitably protected, is shown in Scheme 2. Reaction of commercial triacetyl D-glucal **6** with methanol and catalytic Ph_3P•HBr under conditions described by Mioskowski and Falk et al. gave the 2-deoxypyranoside **7** in 96% yield.[14] Acetate cleavage and benzylidene acetal formation (Et_2NH; $PhCH(OMe)_2$, cat. TsOH; 60% for both steps) followed by methylation (NaH, MeI) provided **9** in 90% yield. Selective cleavage of the primary benzylidene ether under Hanessian−Hullar[15] radical bromination conditions (NBS, $BaCO_3$, CCl_4, reflux) gave the known pyranoside **10** in 99% yield.[16] Allylation of **10** (Me_3-SiOTf, allyl-$SiMe_3$; MeCN, 95%) afforded exclusively the expected diastereomer **11**.[17] It was convenient to stockpile the material at this stage and prepare the aldehyde only as needed. Olefin cleavage by ozonolysis proved fickle and at best a 70% yield of aldehyde was obtained. However, stepwise dihydroxylation and glycol cleavage (OsO_4, NMO; $NaIO_4$, 96%) consistently delivered aldehyde **12** in excellent yield. The entire optimized sequence was repeated with 50 g of triacetyl D-glucal **6** and provided approximately ∼31 g of aldehyde **12** (46% overall). Aldehyde **12** contains atoms C(1)−C(7) of peloruside A with the correct stereochemistry at C(2), C(3), and C(5).

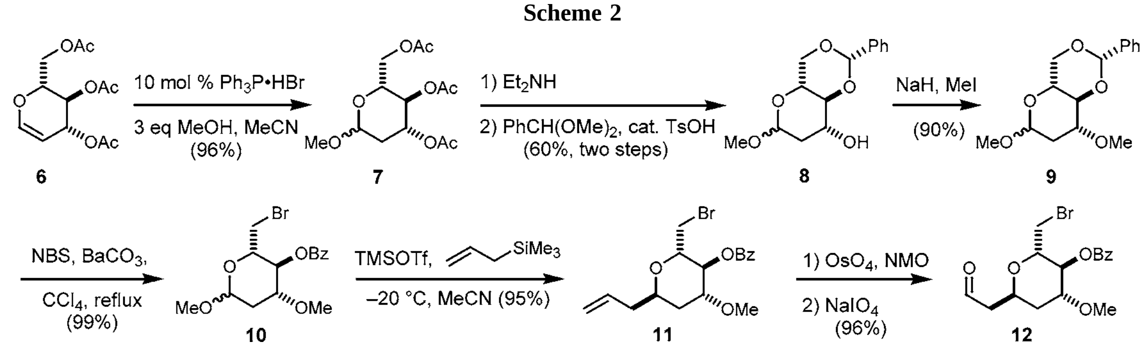
Ketone **15**, an equivalent of central piece **4**, was prepared in 69% overall yield by S_E2' addition of an allylic stannane generated in situ from Barbier-type reaction of **13** with $SnCl_2$•$2H_2O$ and benzyloxy acetaldehyde **14** (Scheme 3).[18]

Scheme 3

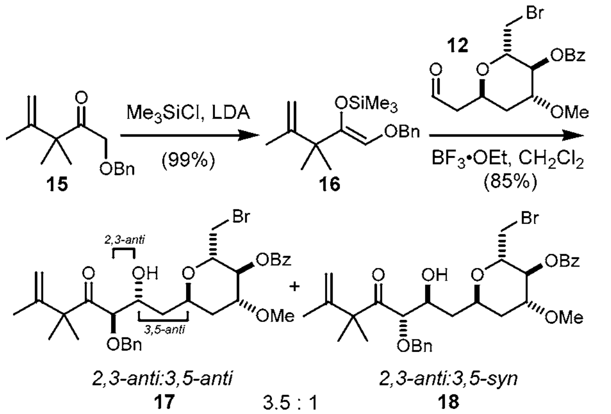


Aldol reactions between ketone **15** and aldehyde **12** were extensively studied under a variety of conditions to discover strategies for selectively accessing each of the four possible diastereomeric products.[19] The most effective method identified for securing the 2,3-anti-3,5-anti diastereomer required for the peloruside A synthesis is a Mukaiyama aldol reaction promoted by BF_3•OEt_2 (Scheme 4). The optimized aldol procedure consists of adding 1.1 equiv of BF_3•OEt_2 to a −20 °C solution of silyl enol ether **16** and aldehyde **12** in dichloromethane, allowing the reaction to warm to 0 °C and maintaining it at this temperature for 2 h. These conditions provide an 85% isolated yield of the 2,3-anti-3,5-anti (**17**) and 2,3-anti-3,5-syn (**18**) diastereomers in a 3.5 to 1 ratio. This modest level of selectivity is none the less noteworthy given the lack of an α stereocenter and the complexity of the aldehyde. Other Lewis acids that were investigated but failed to improve stereochemistry include the following:

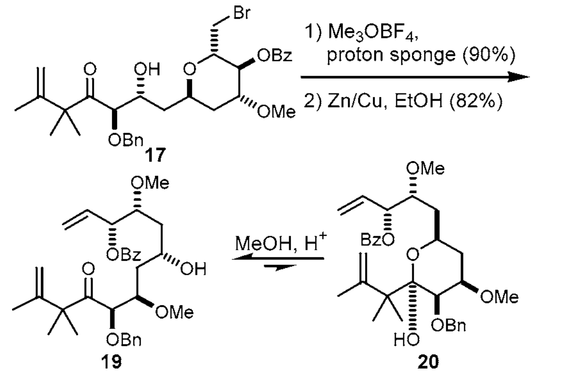
Scheme 2



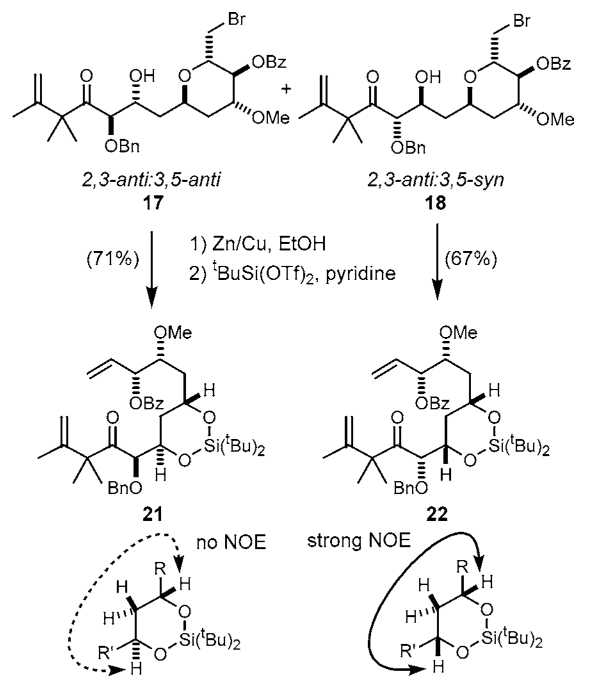
Scheme 4



Scheme 5



Scheme 6



BF_3·SMe_2, Et_2AlCl, $TiCl_4$, $SnCl_4$, and $MgBr_2$·OEt_2. Evans reported good facial selectivities in aldol reactions with β-heterosubstituted aldehydes under similar nonchelation control conditions using BF_3·OEt_2 as the Lewis acid.[20]

The synthesis continued with methylation of the C(7) hydroxyl group of the major 2,3-*anti*-3,5-*anti*-aldol product **17**, using Meerwein's salt under conditions described by Evans (Me_3OBF_4, proton sponge, 90%) (Scheme 5).[21] Vasella ring cleavage by spontaneous β-elimination of the alkyl zinc generated in situ by reduction of the alkyl bromide with zinc–copper couple provided acyclic diol **19**.[22] At this point we expected that conditions could be established such that equilibrium would favor the hemiketal **20** (or the methyl ketal) over ketone **19**, thereby providing a locked cyclic structure that would greatly facilitate stereochemical assignment by NOE analysis. However, reliably obtaining **20** proved elusive.

To ascertain the 3,5-anti or syn stereochemistry, both aldol diastereomers were carried forward by Vasella ring cleavage and conversion of the resulting diols to their di-*tert*-butylsilylene ethers (Scheme 6).[23] Analysis of these diastereomers by NOE spectroscopy clearly showed a strong enhancement between the quasi-1,3-diaxial methine hydrogens in the syn diastereomer **22**, and similar NOEs were absent in **21**.[24] The 2,3-anti stereochemistry is based on comparison of coupling constants of the other three diastereomers and literature precedence with *tert*-butyl ethyl ketones.[13,19,25]

With stereochemistry established, we decided to proceed with the C(10) ketone intact (Scheme 7). The C(5) hydroxyl

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(19) These results along with additional stereochemical proofs will be described elsewhere.

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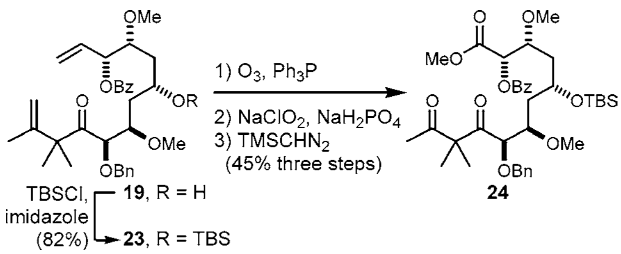
Scheme 7



in **19** was first protected as its TBS ether (^{t}Bu(Me)$_2$SiCl, imidazole, DMF, 82%). Both alkenes were then cleaved by ozonolysis (O_3, $NaHCO_3$, CH_2Cl_2; PPh_3), and the aldehyde was immediately oxidized to the carboxylic acid ($NaClO_2$, NaH_2PO_4) in the presence of 2-methyl-2-butene as an acid trap. Esterification (Me_3SiCHN_2; MeOH, PhH) afforded methyl ester **24** in 45% isolated yield for the three steps.

In summary, an α-hydroxy ketone anti−anti aldol between silyl enol ether **16** and aldehyde **12** was developed and applied to the synthesis of the C(1)−C(12) segment of peloruside A (Figure 2, in red). A practical and readily scaleable preparation of aldehyde **12** from commercial triacetyl D-glucal **6** was executed on a 50-g scale in approximately 46% overall yield with use of standard laboratory-sized glassware and equipment. Full details regarding protocols for selectively accessing other diastereomeric aldol products from reactions between ketone **15** and aldehyde **12**, as well as aldol reactions with related structures, will be described elsewhere.

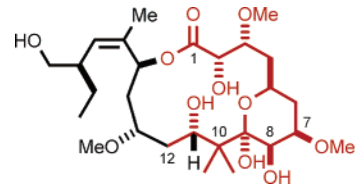


Figure 2. Peloruside A, with the segment prepared here in red.

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Supporting Information Available: Structural data for key compounds **12**, **17**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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