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Toward the Total Synthesis of Natural Peloruside A: Stereoselective Synthesis of the Backbone of the Core

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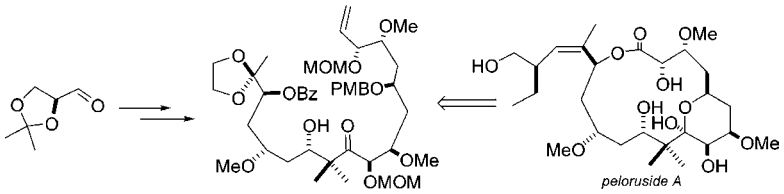
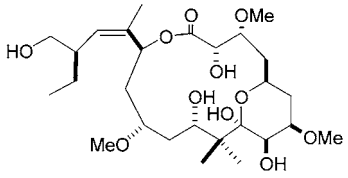
ABSTRACT



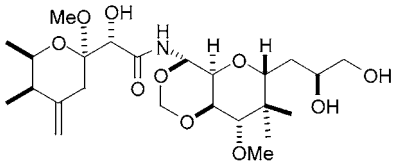
An asymmetric synthesis of the backbone of the core of natural peloruside A is described. Key elements include reiterative application of enantioselective allylation to establish the stereochemistry of the backbone and a double asymmetric aldol reaction to successfully couple two fragments.

Marine sponges have been extensively investigated as an important source of biologically active marine natural products that have proven to be invaluable as agents for pharmacological manipulation of cellular biochemical pathways. Peloruside A (**1**), together with mycalamide A (**2**) and pateamine (**3**), was isolated from the New Zealand marine sponge *Mycale* sp. by Northcote and coworkers.[1] Its structure and relative stereochemistry were determined by extensive NMR studies, which showed that peloruside A is a polyoxygenated 16-membered macrolide with a branched and *Z*-configured trisubstituted olefin, containing a densely functionalized pyranose ring adjacent to a *gem*-dimethyl moiety. Although peloruside A bears some structural features of both mycalamide A (*gem*-dimethyls and polyhydroxylation) and pateamine (macrolide ring), it does not appear to be closely related biochemically.[1a]

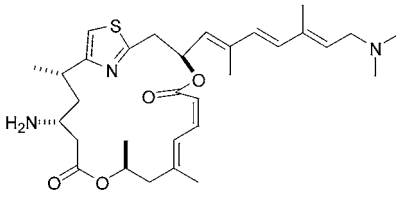
Peloruside A (**1**) was found to be cytotoxic to P388 murine leukemia cells at approximately 10 ng/mL (18 nM).[1a] It induces biochemical changes consistent with apoptosis in a number of cultured mamalian cell lines.[1b] Further studies have revealed that it exhibits microtubule-stabilizing activity



1: *peloruside A*



2: *mycalamide A*



3: *pateamine*

(1) (a) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445. (b) Hood, K. A.; Bäckström, B. T.; West, L. M.; Northcote, P. T.; Berridge, M. V.; Miller, J. H. *Anti-Cancer Drug Des.* **2001**, *16*, 155. (c) Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356.

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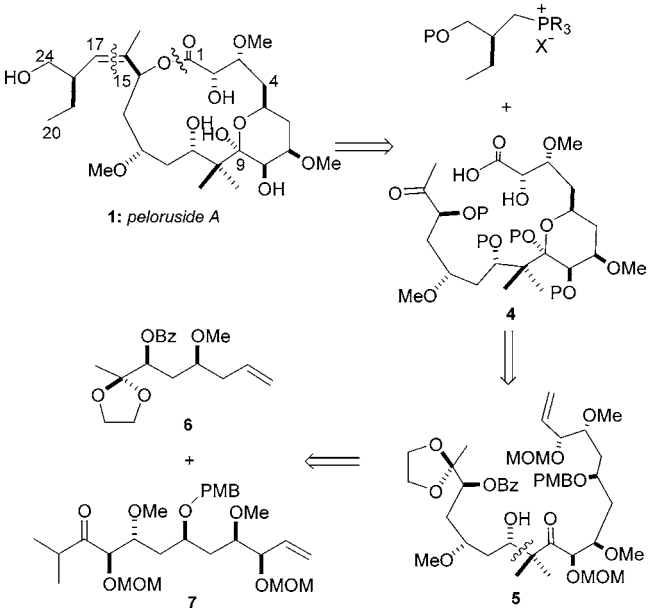
and arrests cells in the G2-M phase of the cell cycle, similar to paclitaxel (Taxol).[1c]

The unusual structure, potent biological activity, and scarcity of peloruside A make it an attractive target for total synthesis. Recently, an elegant total synthesis, followed by comparison of the optical rotation and the biological activity of the synthetic sample to those of the natural sample, established the absolute configuration of peloruside A.[2] Synthetic studies toward the fragments of it have been reported by Paterson's group[3] and Ghosh's group.[4] Unfortunately, since its absolute configuration was not clear in advance, all their synthetic efforts were devoted to the antipode of peloruside A. Herein, we would like to report an asymmetric synthesis of the backbone of the core of *natural* peloruside A.

Our retrosynthetic plan is outlined in Scheme 1. Peloruside A (**1**) can be achieved from a suitable seco acid (**4**) via

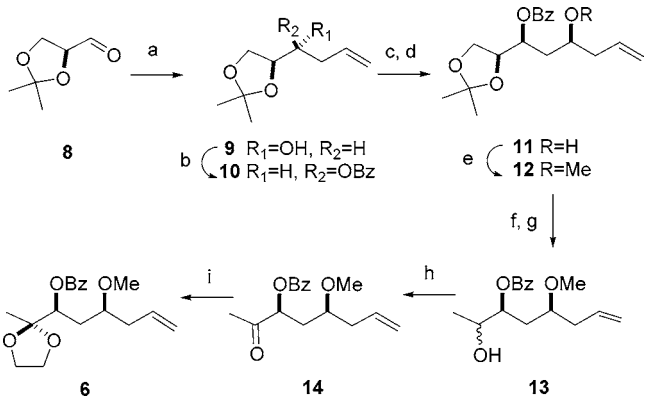
Scheme 1



macrolactonization with simultaneous disconnection at C16−C17 via Wittig reaction. Retrosynthetic analysis of advanced intermediate **5** revealed the two subunits **6** and **7** with disconnections at C10−C11 via an aldol transformation. Although examples of analogous disconnection were infrequently encountered in total synthesis of natural products structurally similar to peloruside A, we considered it applicable if suitable protective groups on the subunits were selected wisely. Both fragment **6** and fragment **7** can be derived from *L*-glyceraldelyde acetonide **8**, which is readily accessible.[5]

A concise and stereoselective synthesis of **6** is illustrated in Scheme 2. A substrate-control stereoselective allylation[6]

Scheme 2 [a]



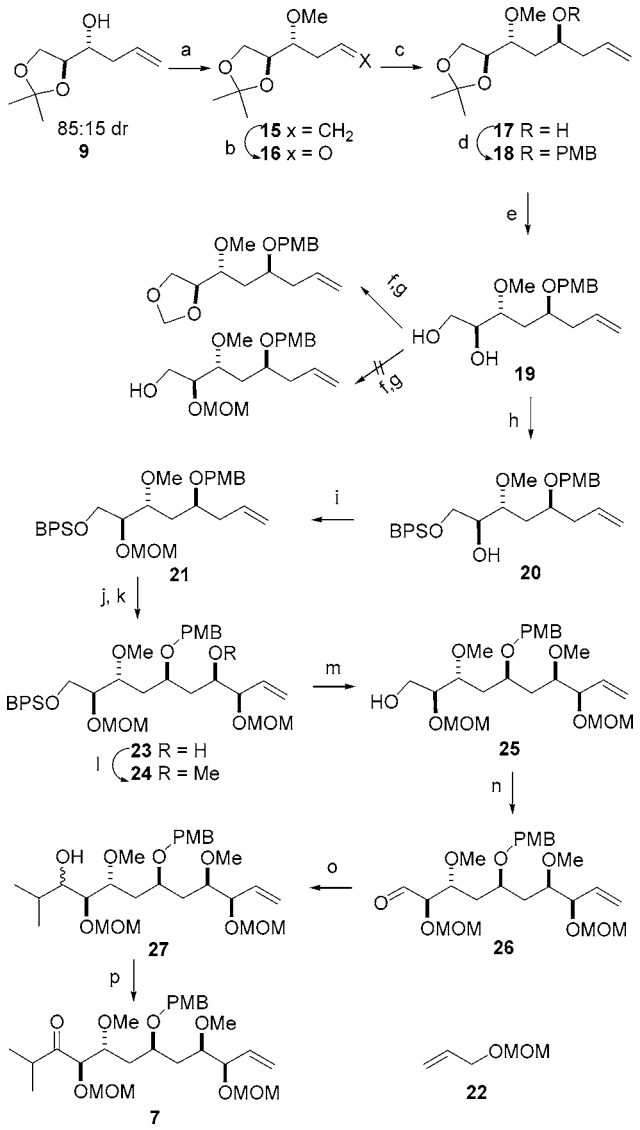
[a] Reagents and conditions. (a) Ref 6: diallyl zinc, THF, −10 to 20 °C, 85:15 dr, 83%. (b) PhCOOH, Ph_3P, DIAD, THF, rt; separation of diastereoisomers, 67%. (c) Cat. OsO_4, $NaIO_4$, THF−H_2O, rt. (d) allylB[(−)-Ipc_2], ether, −78 °C, 72% for two steps (after isolation of the diastereoisomer of **11**). (e) MeI, NaH, THF, rt, 92%. (f) H_5IO_6, EtOAc, 0 °C. (g) Me_3Al, CH_2Cl_2, 0 °C. (h) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 81% for three steps. (i) Ethylene glycol, cat. TsOH, PhH, reflux, 97%.

of **8** in THF afforded **9** as a mixture of diastereoisomers (85:15 dr) that were separated on silica gel after Mitsunobu conversion of the free hydroxyl of **9** to give **10**. Johnson−Lemieux oxidation of **10**, followed by stereoselective allylation[7] of the resultant aldehyde with *B*-allyldiisopino campheyl borane in ether, resulted in alcohol **11**, whose absolute configuration was confirmed by ^{1}HNMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters. After methylation of the free hydroxyl of **11**, the resulting compound **12** then provided a facile entry to ketone **14** by a three-step sequence, including oxidative cleavage of acetonide,[8] chemoselective addition of trimethyl aluminum to the aldehyde group in the presence of the ester group,[9] and Dess−Martin oxidation of the corresponding alcohol. Protection of ketone **14** with ethylene glycol in benzene in the presence of catalytic TsOH under reflux completed the synthesis of fragment **6**.

Our synthesis of fragment **7** commenced from alcohol **9** (85:15 dr), which acted as a common intermediate with the synthesis of fragment **6** (Scheme 3). Methyl ether formation, Johnson−Lemieux oxidation, and asymmetric allylation provided alcohol **17**, whose absolute configuration was confirmed by ^{1}HNMR spectra of its (*R*)- and (*S*)-MTPA esters. It was notable that asymmetric allylation of aldehyde

(2) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648.
(3) Paterson, I.; Di Francesco, M. E.; Kühn, T. *Org. Lett.* **2003**, *5*, 599.
(4) (a) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967. (b) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659.
(5) (a) Hubschwerlen, C. *Synthesis* **1986**, 962. (b) Hubschwerlen, C.; Specklin, J.-L.; Higelin, J. *Org. Synth.* **1993**, *72*, 1.
(6) Mulzer, J.; Angermann, A.; Münch, W. *Liebigs Ann. Chem.* **1986**, 825.
(7) (a) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
(8) Li, L.; Wu, Y.; Wu, Y. *J. Carbohydr. Chem.* **1999**, *18*, 1067.
(9) Liu, B.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 4933.

Scheme 3 [a]

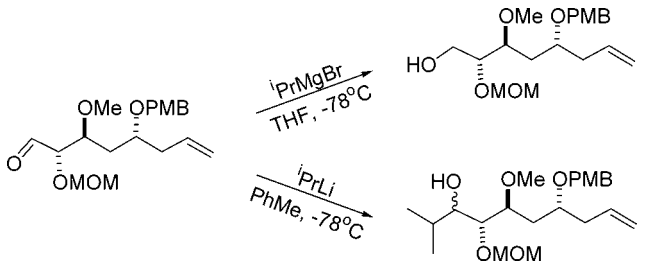


[a] Reagents and conditions. (a) MeI, KOH, DMSO, rt, 81%. (b) Cat. OsO_4, $NaIO_4$, THF−H_2O, rt. (c) allylB[(−)-Ipc$_2$], ether, −78 °C, 75% for two steps (after isolation of the diastereoisomer of **17**). (d) PMBCl, cat. TBAI, NaH, THF, reflux, 92%. (e) Cat. TsOH, MeOH, rt, 96%. (f) $HC(OMe)_3$, CH_2Cl_2, rt. (g) DIBAL-H, THF, −78 °C to room temperature, 72% for two steps (after isolation of the diastereoisomer of **17**). (h) TBDPSCl, cat. DMAP, Et_3N, CH_2Cl_2, rt, quant. (i) MOMCl, $^iPr_2NEt$, CH_2Cl_2, rt, 91% based on the recovery of starting material. (j) Cat. OsO_4, $NaIO_4$, THF−H_2O, rt. (k) **22**, ^{s}BuLi, THF, −78 °C, 40 min; then (−)-Ipc$_2$BOMe, −78 °C, 1.5 h; then aldehyde, −78 °C, 3.5 h; NaOH, 30% H_2O_2, ether, rt, 8 h, 75% from **21**. (l) MeI, NaH, THF, rt, 85%. (m) TBAF, THF, rt, 96%. (n) Dess−Martin periodinane, CH_2Cl_2, rt. (o) isopropyllithium, toluene, −78 °C to room temperature. (p) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 62% for three steps based on the recovery of **25**.

16 using (+)-DIPT modified allylboronate failed,[10] while using enantiopure *B*-allyl diisopinocampheyl borane delivered a good result. Protection of alcohol **17** as a PMB ether did not occur under the normal conditions (NaH, PMBCl, cat. TBAI, rt) but afforded **18** at an elevated temperature in excellent yield. Compound **18** was advanced to diol **19** by deprotection of the acetonide catalyzed by TsOH in methyl alcohol. Since the selective protection of the secondary hydroxyl as a MOM ether via formation of cyclic orthoformate and then DIBAL-H reduction proved not to be feasible,[11] we turned to protection of the primary hydroxyl as a TBDPS ether and then protection of the secondary hydroxyl as a MOM ether **21**. Johnson−Lemieux oxidation and addition of (*Z*)-alkoxyallylborane,[12] generated in situ, to the corresponding aldehyde at low temperature produced the desired homoallyl alcohol **23**, which was methylated (NaH, MeI) to provide **24**. Following conversion into aldehyde **26** after deprotection and then oxidation of the primary hydroxyl of **25**, an efficient isopropyl addition was required to complete the synthesis of fragment **7**.

A model study (Scheme 4) revealed that with a Grignard reagent as a nucleophilic agent, the aldehyde was mainly

Scheme 4



reduced to an alcohol via the transfer of hydride from the isopropyl Grignard reagent. However, after several trials, we found out that isopropyllithium[13] *freshly* prepared from isopropyl chloride and lithium was able to give the desired product in a satisfactory yield (70%). Thus, isopropylation of aldehyde **26** with isopropyllithium and Dess−Martin oxidation of the resultant alcohol **27** produced ketone **7** smoothly.

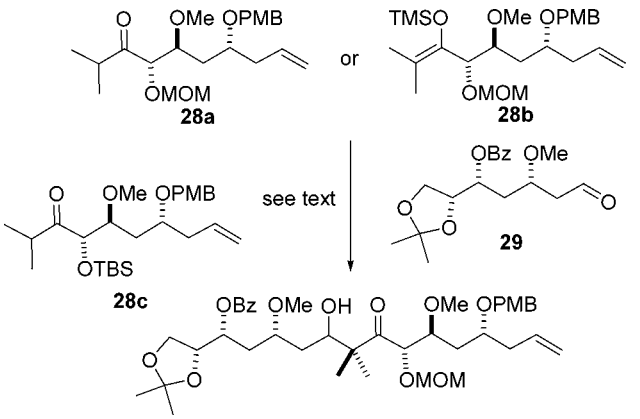
The planned aldol coupling of fragment **6** and fragment **7** was crucial in our synthetic plan toward the backbone of the core of peloruside A. To probe the optimal reaction conditions, we decided to study related model reactions (Scheme 5) patiently and carefully.

It was frustrating that no reaction occurred under standard conditions of either BF_3Et_2O-[14] or $TiCl_4$-promoted[15] Mu-

(10) Ratio of the desired diastereoisomer of alcohol **17** to the undesired one was determined to be ca. 1:4 on the basis of their isolated yields.

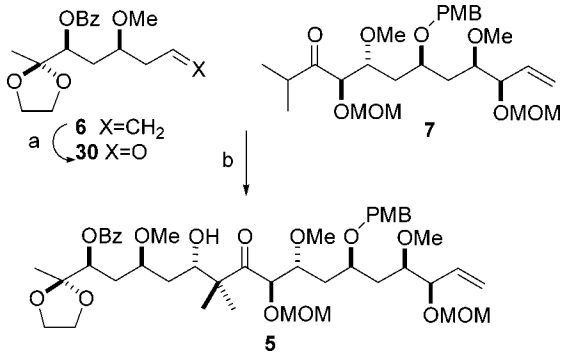
(11) Yang, W.-Q.; Kitahara, T. *Tetrahedron* **2000**, *56*, 1451.
(12) (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimota, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612.
(13) Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862.
(14) (a) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *57*, 6311. (b) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439.
(15) (a) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840. (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **2001**, *66*, 2747.

Scheme 5



kaiyama aldol reaction of **29** and **28b**, which was easily derived from **28a**. In the presence of $TiCl_4$ and $^{i}Pr_2NEt$ at −78 °C,[16] ketone **28a** was prone to decomposition and the titanium enolate could not be formed to initiate the following aldol reaction. Similarly, boron-mediated aldol conditions (Cy_2BCl, Et_3N, ether, −78 °C)[17] turned out to be another failure, although they are extensively applied in the syntheses of natural products. The amazing difficulty created by the lack of reactivity of the aldol coupling, we think, might be attributed to the structure of isopropyl ketone, which is resistant to enolation or forms a bulky tetrasubstituted olefin after enolation, preventing the approach of the aldehyde **29**. Thus, it is not surprising that LiHMDS proved to be another ineffective agent due to its hindered structure. To our delight, LDA-induced aldol reaction occurred in THF at −78 °C giving an acceptable yield.[18] It can be argued that a less hindered base than LDA (such as $LiNEt_2$) should be screened experimentally. Indeed, we have observed that the α-stereogenic center of **28a** experienced racemization to a small extent, which indicates that a less hindered base would give a lower regioselectivity in the course of enolation and thus lead to more serious racemization of the adjacent stereogenic center of ketone **28a**. With these results in hand, we effected the aldol coupling induced by LDA with 74:26 dr in 60% yield based on 31% recovery of ketone **7**. The orientation of the newly formed hydroxyl of **5** was determined by ^{1}-HNMR analysis of its MTPA esters (modified Mosher's method)[19] to be the desired α form (Scheme 6).

Scheme 6 [a]



[a] Reagents and conditions. (a) Cat. OsO_4, $NaIO_4$, THF−H_2O, rt. (b) **7**, LDA, THF, −78 °C; then aldehyde **30**, THF, −78 to −40 °C, 74:26 dr, 60%.

In summary, we accomplished the stereoselective synthesis of the backbone of the core of peloruside A based on a convergent strategy. A distinguishing feature is the reiterative application of asymmetric allylation in either a substrate-control or reagent-control manner to install the *syn*- and *anti*-1, 3-diol functionality stereoselectively. This also allows the homoallyl alcohol to act as an equivalent of a *β*-hydroxyl aldehyde to ensure the stability of intermediates and the feasibility in the course of diverse protection of hydroxyls. Another feature can be attributed to the novel double asymmetric aldol coupling in the last step, which provides a distinct method for asymmetric synthesis of structural analogues. Work toward the total synthesis of peloruside A is in progress in our laboratory and will be reported in due course.

Supporting Information Available: Spectroscopic data for compounds **5**−**7**, **10**−**12**, **14**, **15**, **17**−**20**, and (*R*)- and (*S*)-MTPA esters of **5**, along with selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036058A

(16) Koch, G.; Loisekur, O.; Fuentes, D.; Jantsch, A.; Altmann, K. H. *Org. Lett.* **2002**, *4*. 3811.

(17) Enders, D.; Ince, S. J. *Synthesis* **2002**, 619.

(18) Protective groups of the α-hydroxyl group also proved to be important since ketone **28c** (Scheme 5) could not give an aldol product with aldehyde **29** even under the LDA conditions.

(19) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 729.