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Synthesis of the C12–C19 Fragment of (+)-Peloruside A through a Diastereomer-Discriminating RCM Reaction

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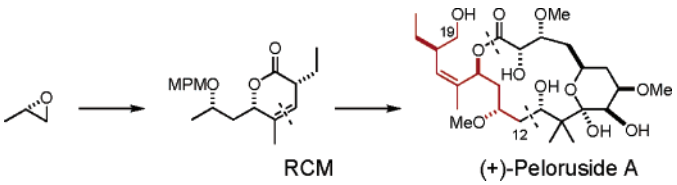
ABSTRACT

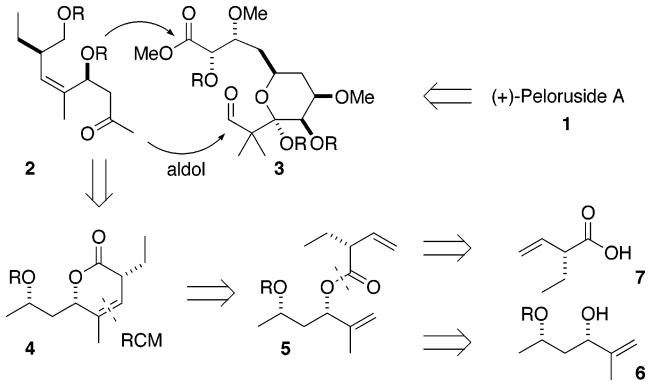


A short and efficient asymmetric synthesis of the C12–C19 fragment of the cytotoxic macrolide (+)-peloruside A has been achieved via a highly diastereomer-discriminating RCM of α-branched but-3-enoate ester of a methallylic alcohol derived from hydrolytically resolved (*S*)-(–)-propylene oxide.

(+)-Peloruside A **1** is a secondary metabolite isolated from a New Zealand marine sponge, *Mycale hentscheli*.[1] This 16-membered macrolide possesses potent taxol-like cytotoxic properties acting on the cell mitotic process at the G2 stage through a mechanism blocking microtubule depolymerization.[2] Peloruside A is less lipophilic than paclitaxel and binds to a different site on tubulin. These properties make this compound a promising candidate for the development of new anticancer agents, especially for multidrug-resistant solid tumors. The structure and relative stereochemistry of peloruside A have been determined by spectroscopic methods, while its absolute stereochemistry was presumed to be related to another cytotoxic natural product, bryostatin. A number of synthetic approaches toward peloruside A were built upon this assumption,[3] culminating in the total synthesis of the nonnatural (−)-peloruside A,[3a] the subsequent efforts being directed toward the naturally occurring enantiomer **1**.[4]

We envisioned completion of the synthesis of (+)-peloruside A **1** (Scheme 1) occurring through an aldol

Scheme 1. Retrosynthetic Scheme



reaction between ketone **2** and aldehyde **3** to create the C11−C12 bond followed by stereoselective reduction of the C11 ketone function and macrolactonization. The synthesis of the

(1) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445−449.

(2) (a) Hood, K. A.; Bäckström, B. T.; West, L. M.; Northcote, P. T.; Berridge, M. V.; Miller, J. H. *Anti-Cancer Drug Des.* **2001**, *16*, 155−166. (b) Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356−3360.

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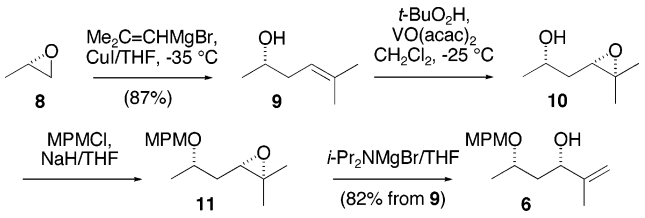
C12−C19 fragment **2** relies on the ring-closing metathesis (RCM) of the diene ester **5** derived from the secondary methallylic alcohol **6** and α-branched but-3-enoic acid **7**, as a method for stereospecific creation of the *Z* double bond. In the course of our work, we discovered an unprecedented example of diastereomer-discriminating RCM that dramatically shortens the synthesis.

The allylic alcohol **6** (Scheme 2) was obtained from (*S*)-propylene oxide **8** (98% ee) conveniently prepared in bulk by hydrolytic kinetic resolution of the cheap racemate using the (*S*,*S*)-salen−Co(III) complex.[5]

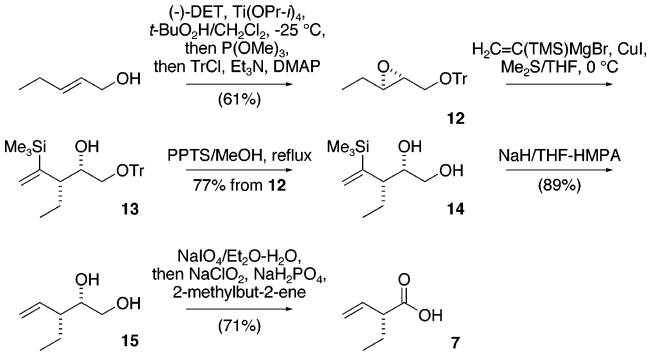
Scheme 2. Synthesis of Allylic Alcohol **6**



The reaction of epoxide **8** with 2-methyl-propenylmagnesium bromide in the presence of a catalytic amount of CuI led to homoallylic alcohol **9**.[6] $VO(acac)_2$-catalyzed epoxidation of **9** afforded the volatile, water-soluble epoxy alcohol **10**, which could not be isolated in high yield using the standard aqueous workup procedure.[7] Therefore, crude epoxy alcohol **10**, obtained by a careful concentration of the reaction mixture, was directly protected as 4-methoxybenzyl (MPM) ether **11**. Without further purification, the epoxide was rearranged by treatment with *i*-Pr_2NMgBr[8] furnishing methallylic alcohol **6** (dr 95:5, by GC and NMR) in 71% overall yield from **8**. The preparation of **6** only required one short column chromatography, the final purification being performed by distillation.

The required (*R*)-2-ethylbut-3-enoic acid **7** was prepared in ca. 30% overall yield from the commercially available (*E*)-pent-2-en-1-ol by adapting the known method[9] using a regioselective oxirane ring opening of the protected epoxy alcohol **12**, as shown in Scheme 3.

Scheme 3. Synthesis of (*R*)-2-Ethylbut-3-enoic Acid **7**



The coupling of alcohol **6** and acid **7** using classical DCC/DMAP esterification conditions proceeded in a disappointingly low yield (40−57%) and was accompanied by a severe racemization of the acid to give an inseparable mixture of esters **5*R*** and **5*S***. A concurrent ketene pathway[10] is suspected for this loss of stereointegrity. Prior to tackling the ester preparation issue, we subjected a small sample of diene (**5*R***/**5*S*** = 6/4) to a RCM test with second-generation Grubbs' catalyst, $(PCy_3)(H_2IMes)Cl_2Ru{=}CHPh$, in refluxing CH_2Cl_2. The reaction was sluggish and appeared incomplete after 3 days. However, when the main components of the reaction were isolated, we were delighted to find that an unexpected resolution of the diastereomers had taken place. Thus, unreacted diene ester was recovered as an almost pure **5*S*** isomer, while diene **5*R*** underwent the RCM giving the required *syn*-lactone **4**. The relative stereochemistry of the substituents of lactone **4** was proved by the NOE observed between H15 and H18 (Scheme 4).

In a scale-up preparation, two additional minor lactones were also isolated in comparable yields (ca. 5% of each). The first of them, **4a**, possessed anti relative stereochemistry, as evidenced by the observed H14/H18 NOE. To confirm the structure of **4a** as a RCM product from (*S*)-2-ethylbut-3-enoate **5*S***, a sample of recovered pure ester **5*S*** was treated with Grubbs' catalyst (10 mol %) for an extended reaction time (5 days). Indeed, lactone **4a** was isolated but was found to be a minor product, the major one being *syn*-lactone **4** (**4**/**4a** = 2/1), along with a mixture of linear dimers. Thus, (*R*)-2-ethylbut-3-enoate **5*R*** undergoes a RCM, while the slow-reacting ester **5*S*** mainly isomerizes into **5*R***, thus rendering a dynamic kinetic resolution possible. However, this isomerization is slow, and more investigations are necessary to understand the mechanism involved in this step and to make the overall process truly efficient. Studies on the mechanism of this isomerization are currently in progress in our laboratory.

The second minor lactone **4b** (syn isomer, as determined by NOE) was identified as the RCM product derived from the allylic alcohol **6a** present in **6** (vide supra). This was proved by its directed synthesis, as shown in the Scheme 4.

(3) (−)-Peloruside A: (a) Liao, X.; Wu, Y.; De Brabander J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648−1652. (b) Paterson, I.; Di Francesco, M. E.; Kühn, T. *Org. Lett.* **2003**, *5*, 599−602. (c) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967−3969. (d) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659−7661. (e) Gurjar, M. K.; Pedduri, Y.; Ramana, C. V.; Puranik, V. G.; Gonnade, R. *Tetrahedron Lett.* **2004**, *45*, 387−390.

(4) (+)-Peloruside A: (a) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959−4961. (b) Lui, B.; Zhou, W.-S. *Org. Lett.* **2004**, *6*, 71−74. (c) Engers, D. W.; Bassindale, M. J.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 663−666. (d) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303−1305 (*total synthesis*).

(5) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, 936−938. (*S*)-Propylene oxide (99% ee) is also commercially available from Aldrich.

(6) Wolfe, S.; Zhang, C.; Johnston, B. D.; Kim, C.-K. *Can J. Chem.* **1994**, *72*, 1066−1075.

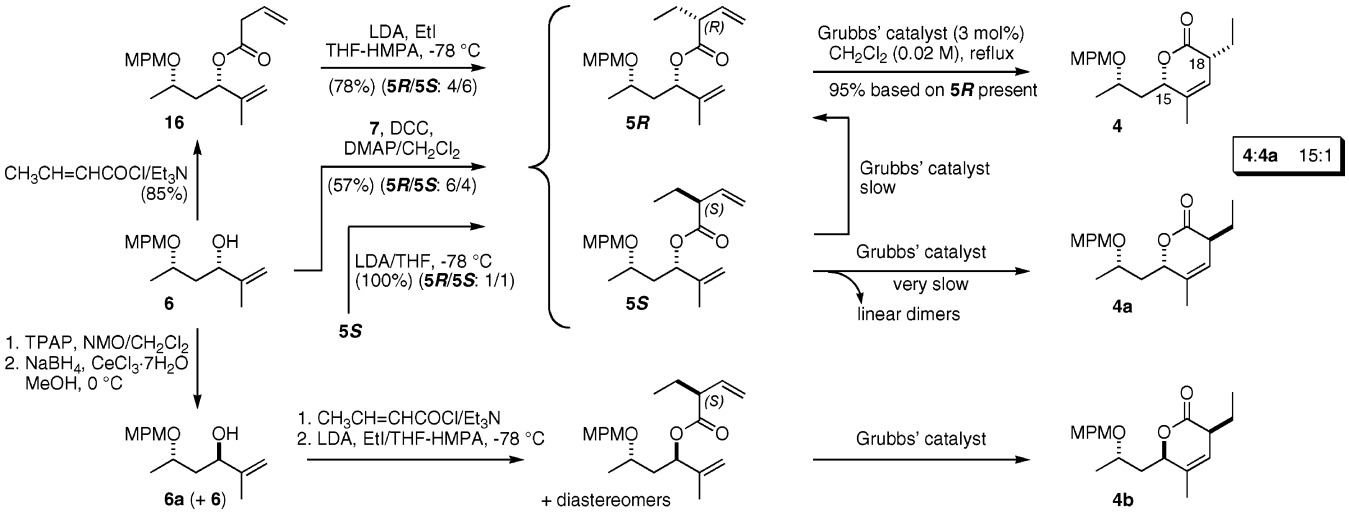
(7) Minhelich, E. D.; Daniels, K.; Eickhoff, D. E. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692.

(8) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433−1435.

(9) Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1985**, 498−499.

(10) (a) Lombardo, L. *Tetrahedron Lett.* **1985**, *26*, 381−384. (b) Hudicky, T.; Radesca, L.; Rigby, H. L. *J. Org. Chem.* **1987**, *52*, 4397−4399.

Scheme 4. Preparation of Diene Esters and RCM



Both minor isomers **4a** and **4b** were easily separable from our target lactone **4** that ensured a high enantiomeric purity of the C12−C19 fragment **2**.

The lactone product distribution, determined at 15% conversion, revealed the unprecedented level of diastereomer discrimination in RCM for this archetype of diene substrates (**4**/**4a** ≥ 44/1, starting from **5*R***/**5*S*** = 44/56). Several selective RCM reactions have recently been reported;[11] however, to the best of our knowledge, no prominent selectivity for the metathesis cyclization leading to β,γ-unsaturated δ-lactones[12] or lactams[13] has been described so far.

The theoretical investigation of credible reaction pathways by semiempirical (MP3) calculations allowed us to locate the transition states of RCM for ester dienes **5** and to identify synergetic steric interactions responsible for the observed selectivity. The bulky ruthenium catalyst occupies an equatorial position (Figure 1).

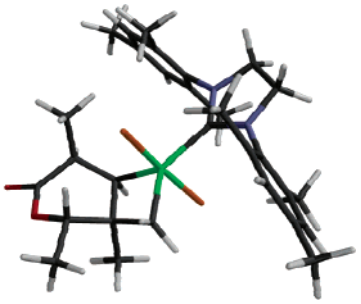


Figure 1. Transition state of RCM for **5*S*** (truncated).

The difference in the transition state energies for the diastereomeric substrates is mainly due to the steric interaction between the *endo*-Cl atom, a substituent at C2 (H for **5*R***, Et for **5*S***), and H5 of the lactone cycle. The steric interaction between methyl group at C4, the substituent at C5, and the *exo*-Cl of the catalyst maintains the lactone ring puckering, which reinforces the essential steric strains on the *endo* side of the transition state. Consistently, the calculations predict a significant loss of selectivity for diene esters lacking the branching methyl at this position. This is in accordance with available experimental observations.[13]

The lowest energy transition state for RCM of diene **5*S*** was calculated to be ca. 4 kcal/mol less favorable, as compared to its **5*R*** isomer, in good qualitative agreement with the data calculated from the selectivity observed ($\Delta\Delta E_{calcd} \geq 2.52$ kcal/mol). Assuming the entirely reversible mechanism of olefin metathesis reaction,[14] the slow-reacting diene ester **5*S*** should mainly be regenerated from the corresponding ruthenium carbene complex by the available terminal alkenes or should undergo a cross-metathesis reaction to give a linear dimer.

It became obvious that the serious problems of esterification of alcohol **6** could be circumvented, and the synthesis advantageously simplified, by exploiting the discovered diastereomer-discriminating RCM reaction. Indeed, the esterification of alcohol **6** with crotonoyl chloride in triethylamine gave the β,γ-unsaturated ester **16**, which was alkylated by ethyl iodide to furnish a mixture of dienes **5*R*** and **5*S*** (ca. 4/6 by ^{1}H NMR). Under the RCM conditions described, this mixture afforded lactone **4** in a 36% yield (95% based on **5*R*** present) along with the unreacted diene ester that was recovered as an almost pure diastereomer **5*S*** (>95% by ^{1}H NMR). The recovered ester was then treated with LDA in

(11) (a) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734−1737 and references therein. (b) Van de Weghe, P.; Aoun, D.; Boiteau, J.-G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105−4108. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (d) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211.

(12) Andeana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875−3878.

(13) Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron* **2002**, *58*, 7275−7290.

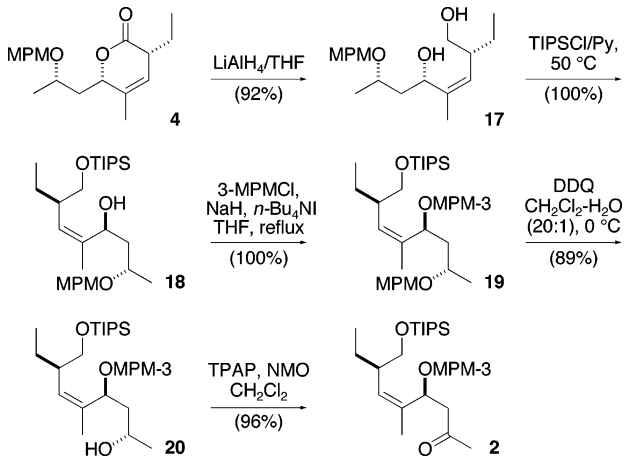
(14) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Chem. Soc., Chem. Commun.* **1997**, 3887−3897.

THF at −78 °C, and the enolate thus formed was quenched by addition of acetic acid to provide a mixture of diene esters **5*R*** and **5*S*** (ca. 1/1 as estimated by NMR), which can be directly recycled in a new RCM sequence.

Despite the inconvenience of a recycling procedure, this method has a significant advantage since it avoids a lengthy preparation of (*R*)-2-ethylbut-3-enoic acid **7**. The unique source of chirality of lactone **4** thus becomes the highly efficient, recyclable (*S*,*S*)-salen−Co(III) catalyst.

The enantiomerically pure lactone **4** was then cleanly reduced to diol **17** using $LiAlH_4$ in THF (Scheme 5). The primary alcohol function of diol **17** was selectively silylated (**18**), and the secondary alcohol function was protected as a 3-methoxybenzyl (3-MPM) ether to give **19**. The following selective oxidative cleavage[15] of the 4-methoxybenzyl ether led to alcohol **20** from which the targeted C12−C19 fragment of (+)-peloruside A, the ketone **2**, was obtained using Ley's oxidation (TPAP/NMO).

Scheme 5. C12−C19 Fragment of (+)-Peloruside A



The optical rotation of ketone **2** ($[\alpha]^{23}_D$ −21.3 (*c* 1.3, $CHCl_3$)) is in good agreement with the data reported for the closely related MPM-protected enantiomer described by Paterson ($[\alpha]^{20}_D$ +22.4 (*c* 1.3, $CHCl_3$)).[3b]

In summary, the C12−C19 fragment **2** of (+)-peloruside A has been synthesized in 11 steps from epoxide **8** in a 13% overall yield (not taking into account the possibility of recycling the unreacted diene **5*S***; average step efficiency = 83%) or in ca. 20% yield after one two-step recycling of diene ester **5*S*** (average step efficiency = 88%). The key step of this synthesis, an unprecedented diastereomer-discriminating RCM reaction leading to lactones, seems to have significant potential in the synthesis of polyketide natural products. Further investigations along this line are currently in progress and will be reported in due course.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050588K

(15) Nakajima, N.; Abe, R.; Yonemitsu, O. *Chem. Pharm. Bull.* **1988**, *36*, 4244−4247.