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Synthetic studies of microtubule stabilizing agent peloruside A: an asymmetric synthesis of C_{10}–C_{24} segment

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Abstract

An asymmetric synthesis of the C_{10}–C_{24} fragment of the potent antitumor macrolide, peloruside A is described. All three stereogenic centers have been enantioselectively constructed utilizing Evans alkylation, Brown asymmetric allylboration, and a substrate controlled epoxide formation. Other key reactions involved Grubbs's ring-closing olefin metathesis and Ando's *Z*-selective olefination reaction.

Peloruside A, a 16-membered macrolide, was recently isolated from the New Zealand marine sponge *Mycale hentscheli*.[1] It exhibited potent cytotoxicity against P388 murine leukemia cells with an IC_{50} value of 10 ng/mL.[1] Like paclitaxel, peloruside A has shown microtubule-stabilizing activity and arrests cells in the G_2-M phase.[2] It has structural resemblance to epothilones which are undergoing clinical trials.[3] Important antitumor activities of peloruside A along with its unique structural features have stimulated immense interest in the synthesis and structure–function studies. Peloruside A's initial structure and relative stereochemistry were established by NMR studies.[1] However, its absolute stereochemistry was conclusively established only recently after the first total synthesis[4] followed by its chemical and biological correlation with the natural peloruside A. To date, De Brabander and co-workers have reported the only total synthesis. Synthetic approaches toward fragments of peloruside A have been reported by Paterson et al.[5] We recently reported an enantioselective synthesis of the C_1–C_9 segment of peloruside A.[6] In continuation of our on-going studies, we now report a stereocontrolled route to the C_{10}–C_{24} segment (**3**) of peloruside A where all three stereocenters have been created by asymmetric synthesis.

As shown in Figure 1, our convergent synthetic plan for peloruside A involves the assembly of C_1–C_9 segment (**2**) and C_{10}–C_{24} (**3**) by an aldol reaction followed by a macrolactonization between the C_{15}-hydroxyl group and the C_1-carboxylic acid. We plan to synthesize the fragment **3** by a nucleophilic addition of isopropylmagnesium halide to the functionalized δ -lactone derived from acrylate ester **4**. The corresponding homoallyl alcohol will be derived from protected alcohol **5** by oxidation, olefination and subsequent asymmetric allylboration of the resulting aldehyde utilizing Brown's protocol. Protected alcohol **5** will be readily available by Evans' asymmetric alkylation reaction.[7]

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As depicted in Scheme 1, asymmetric alkylation of chiral imide **6** was carried out with benzyloxymethyl chloride using Evans' protocol[7a] to provide the alkylated product **7** as a single isomer in 80% yield (from benzyloxazolidinone). Reduction of imide **7** by $LiBH_4$ in THF–MeOH at 23°C afforded alcohol **8**. Swern oxidation of **8** and subsequent Horner–Emmons reaction of the resulting aldehyde with sodium enolate of (*o*-cresol)$_2$P=O(CH$_3$)CHCO$_2$Et as described by Ando[8] furnished tri-substituted *Z*-olefin **9** in 90% yield over two steps. The *Z*-selectivity was >99:1 as revealed by ^{1}H and ^{13}C NMR analysis. Our next synthetic plan was to install an α,β-unsaturated δ-lactone with appropriate stereochemistry and then elaborate the *syn*-1,3-diol functionality by a substrate-controlled diastereoselective epoxidation followed by reductive opening of the resulting epoxide. For the synthesis of α,β-unsaturated δ-lactone, ester **9** was first reduced by Dibal-H to deliver the corresponding alcohol. Dess-Martin periodinane oxidation provided the aldehyde which was subjected to the Brown asymmetric allylboration protocol[9] with allyldiisopinocampheylborane to afford homoallylic alcohol **10** as the major diastereomer (dr=93:7 by ^{1}H and ^{13}C NMR). Alcohol **10** was obtained in 65% yield over two steps after silica gel chromatography.

For synthesis of α,β-unsaturated δ-lactone, we relied upon ring-closing olefin metathesis protocol described in our recent work.[10] Reaction of **10** with acryloyl chloride and triethylamine at 0°C furnished acryloyl ester **11**. Exposure of **11** to a catalytic amount (10 mol%) of first generation commercial Grubb's catalyst[11] in CH2Cl2 at reflux for 12 h provided α,β-unsaturated δ-lactone **12** in 83% yield after one recycle of the recovered starting material.[12] The use of titanium tetra-isopropoxide as a co-catalyst (40 mol%) significantly lowered the yield (62%) of δ-lactone **12**. Reaction with second generation Grubb's catalyst did not improve the overall yield (74%) either. For elaboration of the hydroxy γ-lactone with appropriate stereochemistry, δ-lactone **12** was exposed to nucleophilic epoxidation with alkaline hydrogen peroxide in methanol at 0°C to furnish the corresponding epoxide in 74% yield as a single isomer. Treatment of the resulting epoxide with diphenyldiselenide and sodium borohydride in 2-propanol afforded exclusively hydroxylactone **13** in quantitative yield.[13] Lactone **13** possesses the required *syn*-1,3-diol stereochemistry necessary for peloruside A synthesis. Protection of alcohol **13** under standard condition provided TBDPS ether **14** in quantitative yield.

For conversion of -lactone **14** to the C_{10}–C_{24} fragment, we first attempted direct opening of lactone ring with isopropylmagnesium chloride. However, reaction of **14** with excess isopropylmagnesium chloride under a variety of reaction conditions did not provide the desired ketone. In an alternative approach, δ-lactone **14** was transformed into C_{10}–C_{24} fragment ketone **16** as follows (Scheme 2). Reaction of **14** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum in CH_2Cl_2 according to Weinreb procedure[14] furnished the corresponding hydroxy Weinreb amide. Protection of the resulting alcohol as MEM–ether provided Weinreb amide **15** in 86% yield (from **14**). Treatment of **15** with isopropylmagnesium chloride (5 equiv.) in THF at 23°C for 5 h afforded C_{10}–C_{24} fragment ketone **16**[15] in 61% yield. It turned out that both MEM-and TBDPS-protecting groups were critical to form **16**. Replacement of the MEM-group with a PMB-group resulted in substantial β-elimination as well as degradation of starting material.

In summary, a highly stereoselective synthesis of C_{10}–C_{24} segment of peloruside A has been accomplished. The key steps involved an Evans asymmetric alkylation, Ando's *Z*-selective olefination, Brown asymmetric allylboration, Grubbs's ring-closing olefin metathesis, and substrate controlled stereoselective epoxidation. Work toward the total synthesis of peloruside A is in progress.

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12. Initially, lactone **12** was obtained in 68% along with 23% of unreacted starting material. After one recycling of starting material overall isolated yield was 83%.

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15. All new compounds gave satisfactory spectroscopic andanalytical results. **16**: $[\alpha]_D^{20}$=+87.5 (*c* 0.4, $CHCl_3$); IR (thin film) 2932, 1713, 1429, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.67 (m, 4H), 7.42–7.26 (m, 11H), 5.06 (d, *J*=10.3 Hz, 1H), 4.54 (m, 1H), 4.49–4.42 (m, 4H), 4.34 (d, *J*=6.8 Hz, 1H), 3.57 (m, 1H), 3.43–3.27 (m, 8H), 2.75 (dd, *J*=16.0, 4.6 Hz, 1H), 2.63(dd, *J*=6.0, 7.3 Hz, 1H), 2.59–2.52 (m, 2H), 1.95 (m, 1H), 1.56 (m, 1H), 1.46 (m, 1H), 1.42 (d, *J*=0.9 Hz, 3H), 1.15 (m, 1H), 1.06–1.01 (m, 15H), 0.79 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 213.2, 139.2, 136.4, 136.3, 135.6, 134.3, 131.5, 130.0, 129.9, 128.7, 127.9, 127.8 (2C), 92.5, 74.2, 73.3, 72.2, 70.5, 68.4, 67.6, 59.4, 46.9, 42.1, 41.1, 39.5, 27.4 (3C), 25.4, 19.7, 18.3, 18.2, 12.1; HRMS (ESI) *m/z* calcd for $C_{42}H_{60}O_6Si$ (M^++Na) 711.4057, found 711.4045.

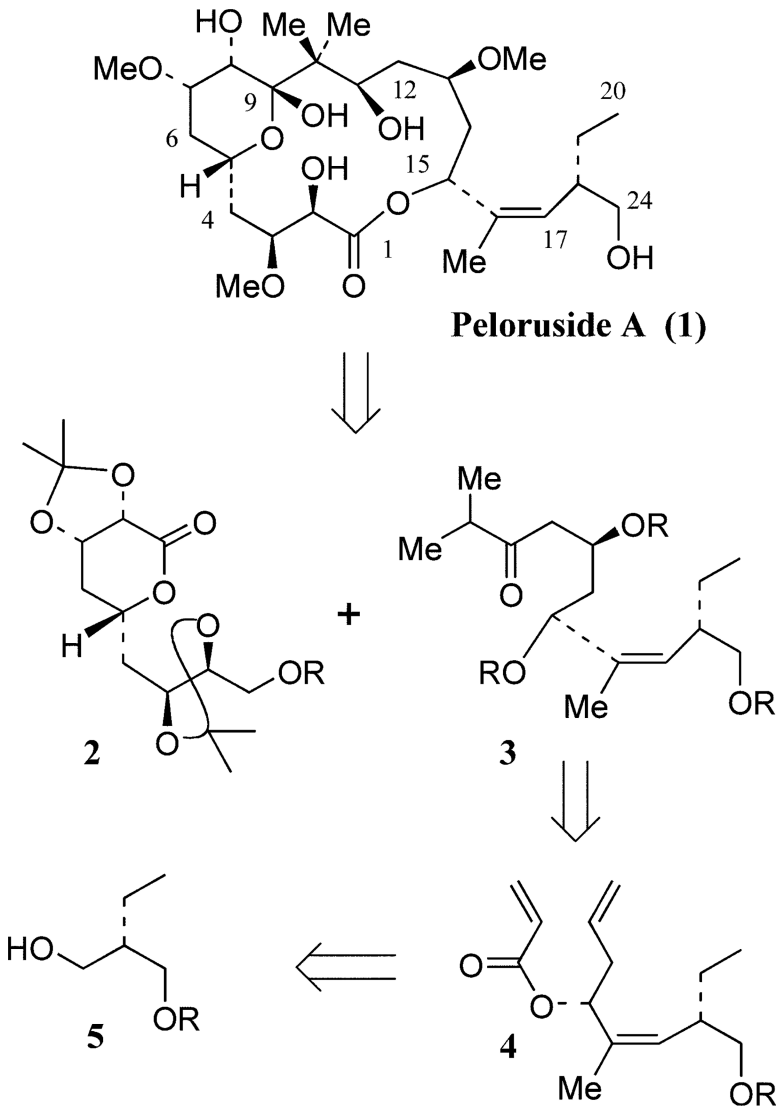
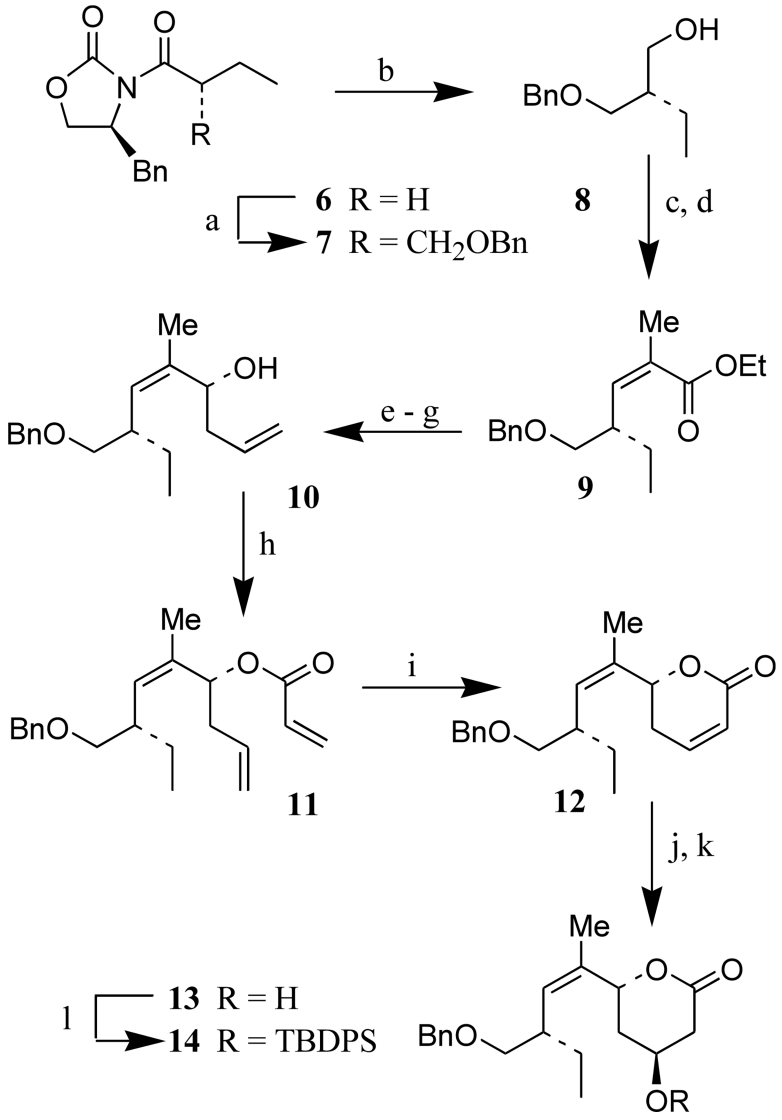
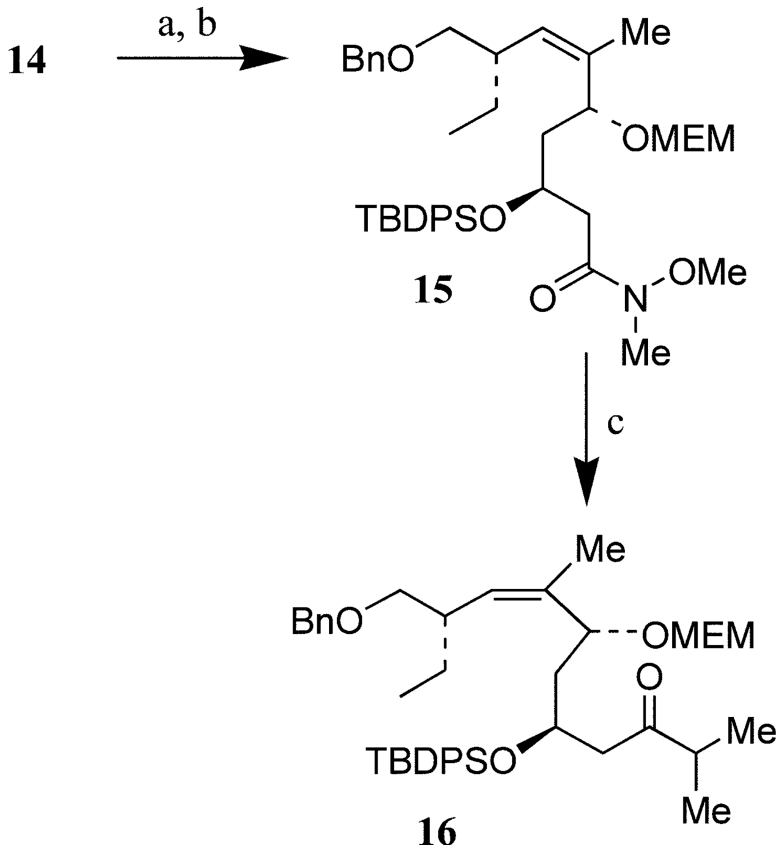


Figure 1.



Scheme 1. Reagents and conditions:

(a) $TiCl_4$, Et_3N, CH_2Cl_2, $PhCH_2OCH_2Cl$, 0°C, 1.5 h; (b) $LiBH_4$, MeOH, THF, 23°C, 1 h (94%); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 45 min; (d) $(o\text{-cresol})_2{}^{P}O(CH_3)CHCO_2Et$, NaH, THF, −78 to −20°C, 2 h (90% over two steps); (e) Dibal-H, CH_2Cl_2, −78° to −40°C, 1 h (96%); (f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 23°C, 1.5 h; (g) $CH_2CHCH_2B[(+)\text{-Ipc}]_2$, Et_2O, −80°C, 3 h (65% over two steps); (h) $CH_2CHCOCl$, Et_3N, CH_2Cl_2, 0°C, 2 h (77%); (i) $Cl_2(Pcy)_2RuCHPh$, CH_2Cl_2, 40°C, 12 h (83%); (i) H_2O_2, 6N-aq NaOH, MeOH, 1.5 h (74%); (k) $NaBH_4$, PhSeSePh, AcOH, $^{i}PrOH$, 0°C, 30 min (quant.); (l) TBDPSCl, imidazole, DMAP, DMF, 23°C, 13 h (quant.).



Scheme 2. Reagent and conditions:

(a) $AlMe_3$, $HN(OCH_3)$-CH_3·HCl, CH_2Cl_2, 23°C, 2.5 h (93%); (b) MEMCl, DIPEA, 23°C, 9 h (92%); (c) ^{i}PrMgCl, THF, 23°C, 5 h (61%).