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An enantioselective synthesis of the C_1–C_9 segment of antitumor macrolide peloruside A

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Abstract—A stereocontrolled synthesis of the C_1–C_9 segment of the marine natural product peloruside A is described. The key steps involve Sharpless's catalytic asymmetric dihydroxylation reaction, a chelation-controlled reduction of chiral β-alkoxy ketones to elaborate the *syn*-1,3-diol functionality and a ring-closing olefin metathesis of a homoallylic alcohol-derived acrylate ester to form an α,β-unsaturated δ-lactone.

Macrocyclic marine natural products continue to be a rich source for potent antitumor agents with unique structural features.[1] However, in many instances scarcity of natural abundance has hindered subsequent in-depth biological studies. Peloruside A, a 16-membered macrolide was recently isolated from the New Zealand marine sponge *Mycale hentscheli*.[2] It displayed potent cytotoxicity against P388 murine leukemia cells at 10 ng/mL. It induces biochemical changes consistent with apoptosis in a number of cultured mammalian cell lines.[3a] More recently, it has been shown that peloruside A exhibits microtubule-stabilizing activity and arrests cells in the G_2-M phase of the cell cycle similar to paclitaxel.[3b] Peloruside A has structural similarity to epothilones which are undergoing clinical trials.[4] Peloruside A contains ten stereogenic centers and its structure and relative stereochemistry have been elucidated by extensive NMR studies.[2] As part of our continuing interest in the chemistry and biology of complex natural products with potent antimitotic properties,[5] we became intrigued by the unique structural features of peloruside A along with its significant antitumor properties. Moreover, scarcity of its supply has precluded its in-depth biological evaluation. Thus far, Paterson and co-workers have only reported the synthesis of various fragments of peloruside A.[6] Herein, we describe a convenient enantioselective synthesis of the C_1–C_9 segment of peloruside A where all five stereogenic centers have been constructed by asymmetric synthesis.

As depicted in Figure 1, our synthetic strategy to peloruside A is convergent and involves the assembly of fragments **2** (C_1–C_9 segment) and **3** (C_{10}–C_{24} segment) by an aldol reaction and subsequent macrolactonization between the C_1-carboxylic acid and C_{15}-hydroxyl group. The synthesis of the C_1–C_9 segment commenced with the preparation of α,β-unsaturated ester **4** using known procedures.[7] As shown in Scheme 1, ester **4** was transformed into optically active alcohol **5** by a three-step sequence involving: (1) Sharpless asymmetric dihydroxylation[8] reaction with AD mix-α in the presence of methanesulfonamide in a mixture (1:1) of *t*-BuOH and H_2O at 0°C provided the corresponding diol in 90% ee;[9] (2) exposure of the resulting diol to dimethoxypropane in the presence of a catalytic amount of PPTS to form the isopropylidene derivative; and (3) reduction of the ester with lithium borohydride.

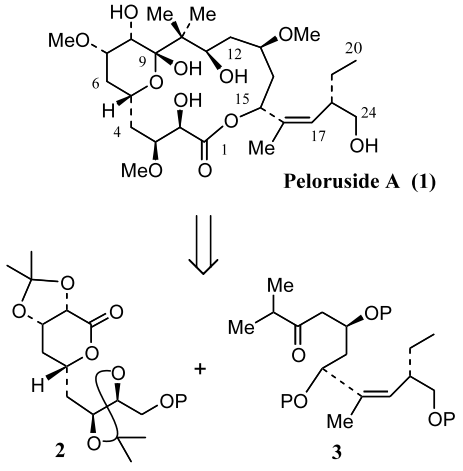

Figure 1.

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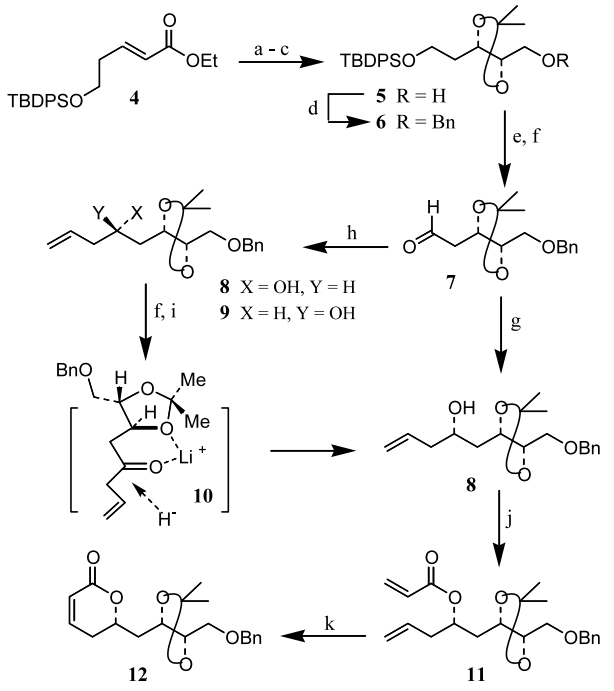
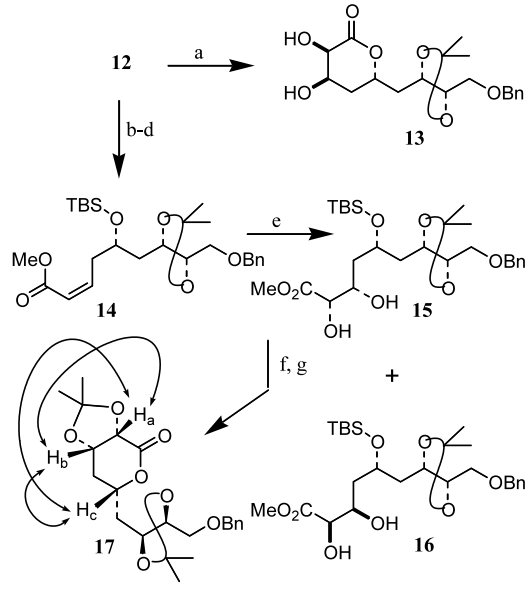


Scheme 1. *Reagents and conditons*: (a) AD mix-α, $CH_3SO_2NH_2$, ^tBuOH–H_2O (1:1), 0°C, 36 h, (89%); (b) $Me_2C(OMe)_2$, PPTS (cat.), Me_2CO, 23°C, 5 h (92%); (c) $LiBH_4$, THF, 0°C, 2 h (97%); (d) NaH, BnBr, DMF, 23°C, 4 h (69%); (e) $nBu_4N^+F^-$, THF, 23°C, 2 h (99%); (f) Dess–Martin, $NaHCO_3$, CH_2Cl_2, 23°C, 2 h; (g) CH_2=$CHCH_2B[(-)$-$Ipc]_2$, THF, −78°C, 3 h (71%); (h) CH_2=$CHCH_2MgBr$, Et_2O, 0°C, 1 h (74%); (i) $LiAlH_4$, LiI, Et_2O, −78°C, 30 min (87%); (j) CH_2=CHCOCl, Et_3N, CH_2Cl_2, 0°C, 1 h (62%); (k) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, 40°C, 14 h (90%).

The overall procedure is very convenient and provided desired optically active alcohol **5** in 80% yield (three steps) after silica gel chromatography $\{[\alpha]_D^{23} = -9.62$ (c 0.52, $CHCl_3$)$\}$. Protection of alcohol **5** as a benzyl ether provided **6** in multigram quantities. Removal of the TBDPS group followed by Dess–Martin oxidation[10] of the resulting alcohol in CH_2Cl_2 in the presence of $NaHCO_3$ for 2 h provided aldehyde **7** in 87% yield.

To install the 1,3-diol functionality selectively, aldehyde **7** was subjected to Brown's asymmetric allylboration protocol with allyldiisopinocampheylborane to provide homoallylic alcohol **8** diastereoselectively in 71% yield.[11] A diastereomeric ratio of 83:17 was determined by ^1H and ^{13}C NMR analysis. In an alternative procedure, aldehyde **7** was also converted to alcohol **8** diastereoselectively using chelation-controlled reduction as the key step. Thus, treatment of **7** with allylmagnesium bromide provided a diastereomeric mixture (syn:$anti$ = 42:58 by ^1H NMR analysis) of alcohols **8** and **9** in 74% yield. The mixture of alcohols **8** and **9** was oxidized by Dess–Martin periodinane[10] to give the corresponding β-ketone in 88% yield. A chelation-controlled reduction by LAH in the presence of LiI at −78°C in ether provided alcohol **8** diastereoselectively (syn:$anti$ = 91:9 by ^1H NMR analysis) in 87% yield.[12] The observed diastereoselectivity can be rationalized by stereochemical model **10** in which, due to the presence of the *gem*-dimethyl group on the β-face, the carbonyl reduction proceeded from the less hindered α-face providing **8** selectively. This three-step sequence is operationally simple and provided convenient access to desired alcohol **8**. Our next plan was to form an α,β-unsaturated δ-lactone and then elaborate the 1,2-diol functionality at C_7 and C_8 stereoselectively. For the synthesis of the corresponding α,β-unsaturated δ-lactone, we utilized the ring-closing olefin metathesis protocol described by us recently.[13] As shown, alcohol **8** was reacted with acryloyl chloride and Et_3N in CH_2Cl_2 at 0°C to afford acrylate ester **11**. Acrylate ester **11**, upon exposure to a catalytic amount of first generation commercial Grubbs's catalyst[14] (10 mol%) in CH_2Cl_2 at 40°C for 14 h, provided α,β-unsaturated δ-lactone **12** in 90% yield after silica gel chromatography.

To append the C_7 and C_8-1,2-diol functionality, we attempted catalytic osmylation of α,β-unsaturated δ-lactone **12** in aqueous acetone (Scheme 2). This has however, provided undesired diol **13** as a single diastereomer in 67% yield. The depicted stereochemistry was assigned based upon NOESY experiments. Sharpless's asymmetric dihydroxylation[8] of **12** with AD mix-β did not proceed even after prolonged (24 h) reaction time at 23°C. This prompted us to investigate asymmetric dihydroxylation of the corresponding open chain α,β-unsaturated ester. Thus, saponification of lactone **12** with aqueous sodium hydroxide was followed by protection of the resulting hydroxy acid as the corresponding TBDMS protected derivative.[15] Esterification of the resulting acid with diazomethane afforded



Scheme 2. *Reagents and conditons*: (a) OsO_4 (cat.), NMO, Me_2CO:H_2O (7:1), 23°C, 12 h (72%); (b) NaOH, THF–H_2O, 0°C, 14 h; (c) TBDMSCl, imidazole, DMF, 23°C, 18 h; (d) CH_2N_2, Et_2O, 0°C, 0.5 h (80% for three steps); (e) AD mix-β, $CH_3SO_2NH_2$, ^tBuOH–H_2O (1:1), 0°C, 72 h (72%); (f) $nBu_4N^+F^-$, THF, 23°C, 3 h; (g) $Me_2C(OMe)_2$, PPTS (cat.), Me_2CO, 23°C, 24 h (63% for two steps).

methyl ester **14** in 80% yield over three steps. This *cis*-α,β-unsaturated ester was then subjected to asymmetric dihydroxylation with AD mix-β at 0°C for 72 h. This afforded a mixture of diastereomeric *cis*-1,2-diols in 72% yield with the major product (**15**) being the desired diastereomer (diastereomeric ratio 91:9 was determined by ^{1}H and ^{13}C NMR analysis). The diastereomers were separated by silica gel chromatography. The depicted stereochemistry of **15** and **16** are based upon subsequent stereochemical assignment of lactone **17**. It should be noted that catalytic osmylation of **14** at 23°C for 6 h afforded the *cis*-1,2-diols **15** and **16** as a 1:1 mixture of diastereomers in 85% yield. Diol **15** was converted to δ-lactone **17** as follows. Treatment of **15** with $n\mathrm{Bu_4N^+F^-}$ in THF resulted in removal of TBDMS group and concomitant lactonization. Protection of the diol functionality with dimethoxypropane and a catalytic amount of PPTS furnished isopropylidene derivative **17** in 63% over two steps.[16] Stereochemical assignment of **17** was based upon NOESY experiments. The spatial proximity of the protons H_a (δ 4.24 ppm), H_b (δ 4.58 ppm) and H_c (δ 4.44 ppm) is clearly evident in the NOESY spectrum. Either derivative of **15** or **17** is now suitable for the synthesis of peloruside A.

In summary, a stereocontrolled synthesis of the C_1–C_9 fragment of peloruside A has been achieved. The key steps are the Sharpless asymmetric dihydroxylation reaction, Grubbs' ring-closing olefin metathesis and a chelation-controlled reduction of a chiral β-alkoxy ketone to install the *syn*-1,3-diol functionality stereoselectively. Further work toward the total synthesis of peloruside A is in progress.

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16. All new compounds gave satisfactory spectroscopic and analytical results. Lactone **17**: $[\alpha]_D^{20} = +43.28$ (*c* 0.67, $CHCl_3$); IR (thin film) 1758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.30 (m, 5H), 4.60–4.51 (m, 3H), 4.44 (m, 1H), 4.24 (d, $J = 7.7$ Hz, 1H), 4.0 (m, 1H), 3.88 (m, 1H), 3.67 (dd, $J = 9.9$, 5 Hz, 1H), 3.54 (dd, $J = 9.9$, 5.7 Hz, 1H), 2.47 (ddd, $J = 14.2$, 8.1, 1.4 Hz, 1H), 2.08 (ddd, $J = 14.3$, 7.6, 6.2 Hz, 1H), 1.89 (ddd, $J = 14.3$, 6.1, 4.8 Hz, 1H), 1.72 (ddd, $J = 14.2$, 12.1, 8.0), 1.50 (s, 3H), 1.40 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (125 MHz): δ 170.6, 138.1, 128.9, 128.3 (2C), 112.1, 109.5, 80.1, 75.3, 74.1, 73.1, 72.9, 72.2, 70.8, 38.6, 34.8, 27.6, 27.3 (2C), 25.7; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{51}O_7$ (M^++H): 407.2070; found: 407.2071.