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A stereoselective synthesis of the C11–C19 fragment of (+)-peloruside A

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This work is dedicated to Professor Xi-kui Jiang on the occasion of his 80th birthday

Abstract—A new route to the synthesis of the C11–C19 fragment of peloruside A is described, which includes an aldol reaction with ethyl acetoacetate, β-hydroxyl-directed reduction of β-hydroxy ketone, as well as methylation of C13 hydroxyl moiety in the system of MeI–Ag_2O–$MgSO_4$–CH_2Cl_2.

(+)-Peloruside A **1** (Fig. 1) is a cytotoxic marine natural product,[1] isolated from a marine sponge, *mycale sp* in New Zealand.[2] The structure and relative stereochemistry of peloruside A features a polyoxygenated 16-membered macrolide with a branched and *Z*-trisubstituted olefin, containing a multi-functionalized pyranose ring.

Preliminary biological experiments showed that peloruside A had paclitaxel-like microtubule-stabilizing activity and was cytotoxic even at nanomolar concentrations.[2] In addition, recent research demonstrated that peloruside A could effectively inhibit cell (such as human (HL-60) and mouse (32D-ras) myeloid leukemic cells) growth, which could induce cell death.[3]

As it has potent anticancer properties, multi-functionalized pyranose and scarcity in nature, peloruside A became an attractive target molecule for total synthesis.

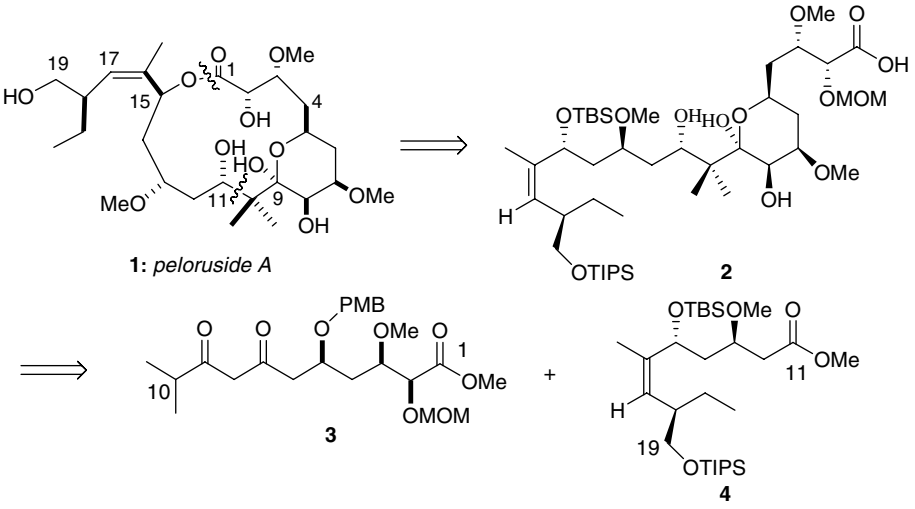

Figure 1.

Keywords: Synthesis; Fragment; Peloruside A.
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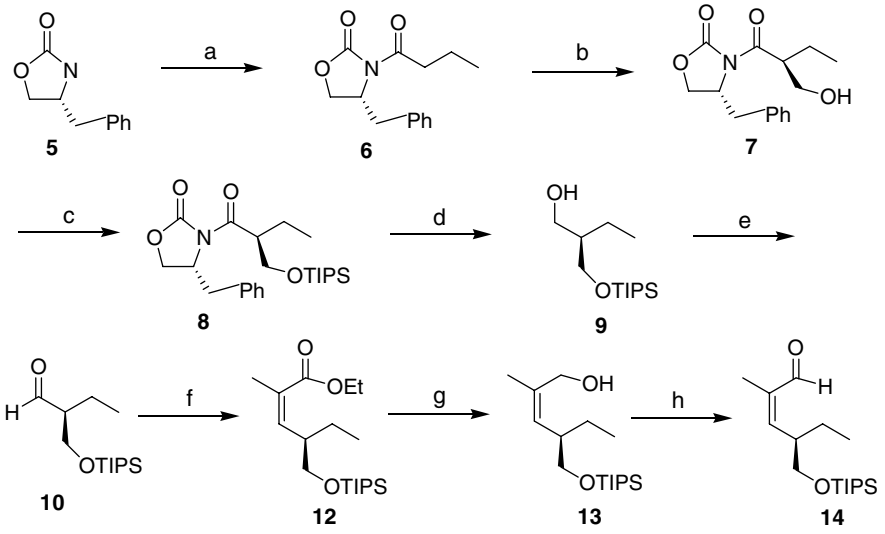
The first elegant total synthesis of (+)-peloruside A was reported by De Brabander and co-workers in 2003 and then the absolute configuration of peloruside A was determined.[4] Recently, Taylor and Jin have also completed the total synthesis of **1**.[5] In addition, many other research groups have reported their synthetic study of peloruside A.[6] In our previous letter, we reported the synthesis of the important backbone of the core of **1**.[6c] However, we encountered some problems in establishment of the *Z*-trisubstituted olefin. Therefore, we had to adjust our synthetic strategy. Herein, we would like to report our new efforts towards the synthesis of peloruside A.

Our new retrosynthetic analysis of **1** was outlined in Figure 1. Peloruside A could be obtained from a suitable intermediate (**2**) via macrolactonization. Precursor **2** could be achieved from the two subunits C1–C10 segment **3** and C11–C19 segment **4** via an aldol transformation at C10–C11. In this letter, we would like to report a new route to the synthesis of segment **4**.

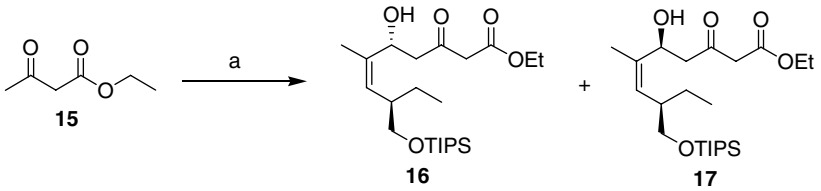
As depicted in Scheme 1, oxazolidone **6** could be obtained by using Evans auxiliary **5** in 96% yield. Aldol reaction of **6** with *s*-trioxane according to Fukumoto and co-workers protocol[7] and subsequent protection of the hydroxyl group of the product with triisopropylsilyl group provided **8** in 49% overall yield. The reduction of **8** with $LiBH_4$ in THF–ether at room temperature afforded alcohol **9** in 88% yield.[7] Exposure to Swern oxidation of **9** and subsequent Horner–Emnos reaction of the resulting aldehyde **10** with sodium enolated of $(o\text{-cresol})_2PO(CH_3)CHCOOEt$ (**11**) as described by Ando[8] furnished tri-substituted *Z*-olefin **12** in 58% yield over two steps. Compound **11** could be prepared from $P(OMe)_3$ according to the Ando procedure.[8] α,β-Unsaturated ester **12** was reduced by Dibal-H to give the corresponding alcohol **13**. Dess–Martin periodinane oxidation of **13** provided aldehyde **14**, which was subjected to aldol reaction with ethyl acetoacetate according to the literature protocol.[9] The aldol products **16** (34%) and **17** (35%) were obtained and the absolute configurations were confirmed by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters (Scheme 2).

As the initial test, aldol product **16** was transformed to **18**, which was reduced with $NaBH_4$ to give two diastereomers of **19** (Scheme 3). However, The diastereomers of **19** were unable to be separated by silica gel chromatography. Evans et al. reported that β-hydroxy ketone could be reduced by $NaBH(OAc)_3$ or $Me_4NBH(OAc)_3$ to give anti diol product.[10] We thus followed his idea. Fortunately, as expected, **16** was reduced by $NaBH(OAc)_3$ to give anti diol **20** in 80.5% yield as a 90:10 mixture of isomers (Scheme 4), which can be easily separated by silica gel chromatography.

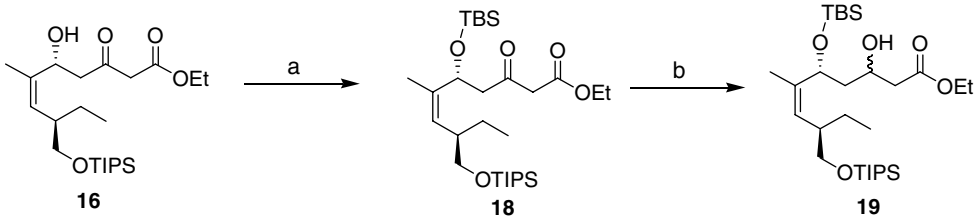
Cyclization under acidic conditions (PTS[11] could only afford lactone **21** (Scheme 4) in very low yield with little starting material recovered. The use of PPTS[12] as



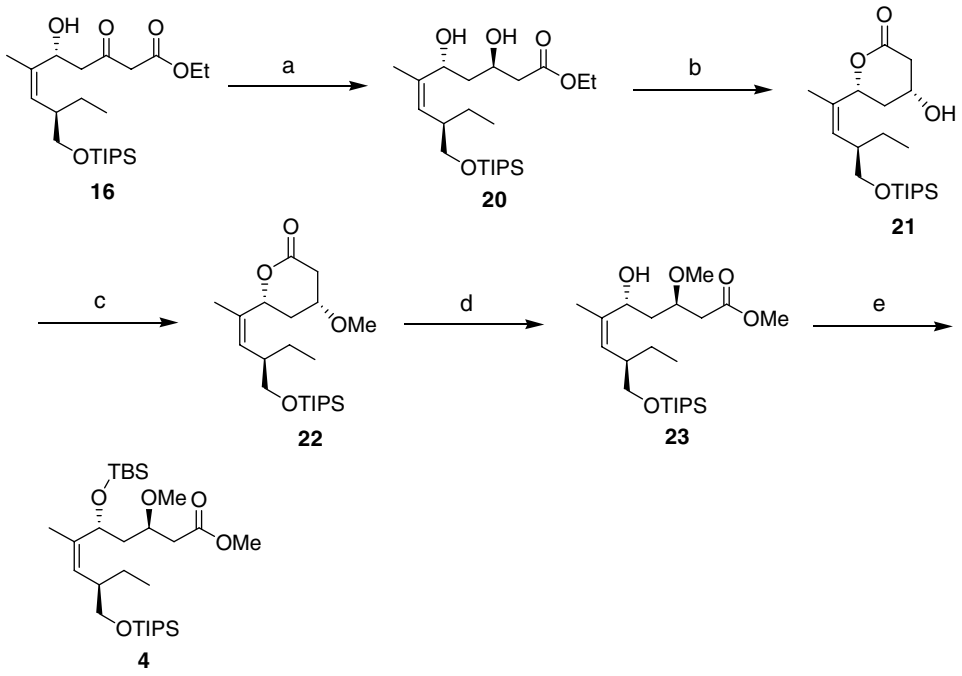
Scheme 1. Reagents and conditions: (a) BuLi, butanoyl chloride, THF, −78 °C, 96%; (b) $TiCl_4$, *s*-trioxane, Et_3N, 0 °C; (c) TIPSCl, Et_3N, rt, 49% for two step; (d) $LiBH_4$, Et_2O/THF, rt, 88%; (e) $(COCl)_2$, DMSO, Et_3N, −78 °C; (f) NaH, $(o\text{-cresol})_2PO(CH_3)CHCOOEt$ (**11**), THF, −78 °C, 58.2% for two step; (g) Dibal-H, CH_2Cl_2, −78 °C, 86%; (h) Dess–Martin periodinane, CH_2Cl_2, 0 °C.



Scheme 2. Reagents and conditions: (a): (1) NaH, THF, 0 °C; (2) BuLi, THF, −78 °C; (3) **14**, THF, −78 °C, **16** (34%), **17** (35%).



Scheme 3. Reagents and conditions: (a) TBSCl, imidazole, DMF, DMAP, rt; (b) $NaBH_4$, EtOH, rt, 59.7% for two step.



Scheme 4. Reagents and conditions: (a) $NaBH(OAc)_3$, THF, 0 °C, 80.5%; (b) PPTS, CH_2Cl_2, rt, 46% (95% corr); (c) MeI, Ag_2O, $MgSO_4$, CH_2Cl_2, rt, 66.6% (88.3% corr); (d) PPTS, MeOH, rt, 71%; (e) TBSCl, imidazole, DMF, DMAP, rt, 57.8%.

a catalyst at high temperature also gave low yield with little starting material recovered. But at room temperature, the use of PPTS in CH_2Cl_2 could give 46% yield (95% corr) with 51.5% starting material recovered.

In the following steps, initially it was found that the methylation of C13 hydroxyl was troublesome. Under various conditions,[10b] such as MeI/NaH and freshly prepared Ag_2O/MeI, both gave unsatisfactory results. Finally, the system of MeI–Ag_2O–$MgSO_4$–CH_2Cl_2 was found to be effective to methylate. It proved reliable and afforded the desired compound **22**[13] (Scheme 4) in a reproducible 66.6% yield (88.3% corr) with 24.5% starting material recovered (Fig. 2). Using PPTS as catalyst, methanolysis of **22** provided δ-hydroxy methyl ester **23** in 71% yield. Silylation of the hydroxyl of ester **23** with *tert*-butyldimethylchlorosilane (TBSCl) afforded C11–C19 fragment **4**[14] (Scheme 4) in 57.8% yield. During silylation, compound **22** was found, which could be a reason for the low yield.

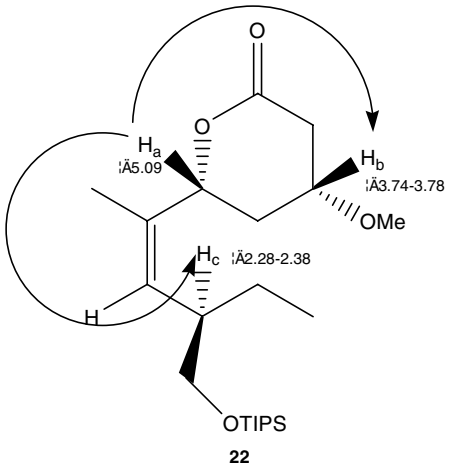


Figure 2.

In summary, we have accomplished a new stereoselective synthesis of C11–C19 fragment **4** of peloruside A. The feature of our new route is the application of aldol reaction of ethyl acetoacetate, β-hydroxyl-directed reduction of β-hydroxy ketone, as well as methylation of C13 hydroxyl in the system of MeI–Ag_2O–$MgSO_4$–CH_2Cl_2. Work towards segment **3** and the total synthesis of peloruside A is in progress in our laboratory and will be reported in due course.

Acknowledgements

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13. Stereochemical assignment of compound **22** was based upon NOESY experiments. The spatial proximity of the protons H_a (δ 5.09 ppm), H_b (δ 3.74–3.78 ppm) and H_c (δ 2.28–2.38 ppm) is clearly evident in the NOESY spectrum.
14. Fragment **4**: $[\alpha]_D^{21}$ −10.4 (*c* 0.47, $CHCl_3$); FT-IR (film, cm^{-1}): 682, 775, 836, 883, 1014, 1077, 1095, 1162, 1251, 1379, 1438, 1464, 1745, 2866, 2895, 2934, 2958; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.02 (s, 3H), 0.07 (s, 3H), 0.87–0.92 (m, 12H), 1.01–1.13 (m, 21H), 1.14–1.30 (m, 1H), 1.40–1.48 (m, 1H), 1.67 (s, 3H), 1.70–1.78 (m, 1H), 2.32–2.44 (m, 2H), 2.59 (dd, $J = 6.3$, 15.0 Hz, 1H), 3.38 (dd, $J = 6.9$, 9.6 Hz, 1H), 3.33 (s, 3H), 3.40 (dd, $J = 6.9$, 9.6 Hz, 1H), 3.56 (dd, $J = 5.1$, 9.3 Hz, 1H), 3.67 (s, 3H), 3.86–3.78 (m, 1H), 4.75 (d, $J = 10.5$ Hz, 1H), 4.92 (d, $J = 9.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: −5.1, −4.6, 11.9, 12.0, 17.97, 18.03, 18.1, 24.7, 25.8, 39.4, 41.7, 42.7, 51.5, 56.3, 66.6, 67.2, 74.4, 127.5, 139.4, 172.0; MS (ESI) *m*/*z*: 567.4 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{29}H_{60}O_5Si_2Na$: 567.3877 ($[M+Na]^+$), found 567.3872.