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Toward a synthesis of the antitumor macrolide peloruside A: a chiral pool approach for the C(1)–C(11) segment

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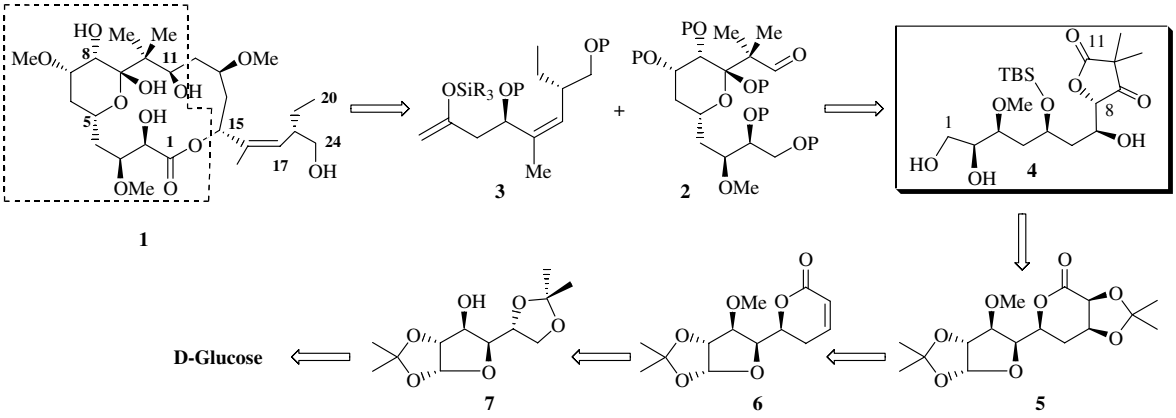
Abstract—Dihydroxylation of the glucose derived α,β-unsaturated lactones **6** and **13** was found to be on the α-face of the pyranolactone ring exclusively. The resulting dihydroxylated compound from **13** has been used in a synthesis of the lactone **4**, which corresponds to C(1)–C(11) of peloruside A.

Peloruside A **1** is a recently discovered antimitotic macrolide isolated from the New Zealand marine sponge *Mycale* sp. Northcote and co-workers[1] established its structure as a polyoxygenated 16-membered macrolide with an integrated pyranose ring and a branched unsaturated side chain, and its relative stereochemistry. Peloruside A was found to be cytotoxic to P388 murine leukemia cells as well as to other cancer cells and recent studies demonstrated that peloruside functions by promoting tubulin polymerization and by interfering with microtubule dynamics like taxol and other microtubule stabilizing agents.[2] In the light of the inherent interest generated by its promising biological activity, and with the necessity of determining its absolute configuration, peloruside A has been identified as an appropriate target for total synthesis. During our work DeBrabander and co-workers[3] reported the first total synthesis of (−)-peloruside A and confirmed that natural peloruside has a stereochemistry opposite to that shown in Scheme 1. Meanwhile Paterson,[4] Ghosh[5] and their co-workers have



Scheme 1. Retrosynthetic analysis of **1**.

Keywords: Barbier reaction; Ring closing metathesis; Dihydroxylation; Barton–McCombie deoxygenation; Mitsunobu reaction; Dess–Martin periodinane.
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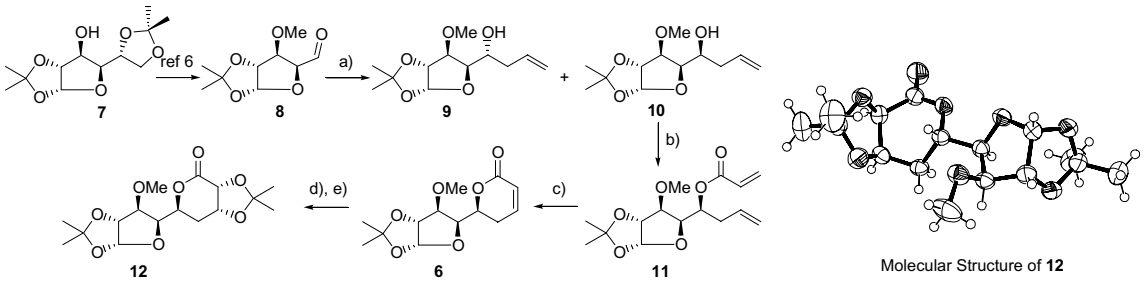


Scheme 2. Reagents and conditions: (a) Zn, aq NH_4Cl/THF (2:3), allyl bromide, 0 °C, 0.5 h, **9**/**10** (9:1), 95%; (b) acryloyl chloride, EtN^iPr_2, CH_2Cl_2, 0 °C, 0.5 h, 76%; (c) 5 mol% **A**, benzene, ↑↓, 1 h, 72%; (d) (i) OsO_4 (cat), 50% aq NMO, acetone/H_2O (9:1), 10 h; (ii) PTSA (cat), 2,2-dimethoxypropane, acetone, rt, 0.5 h, 66%.

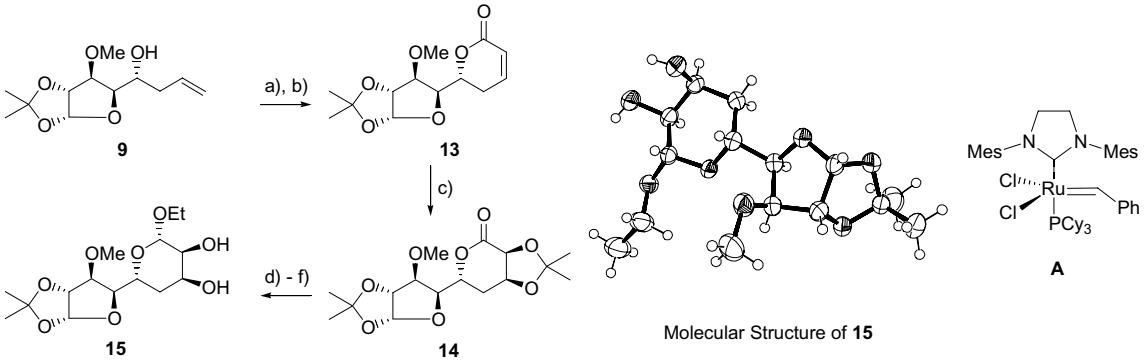
independently reported the synthesis of different fragments corresponding to **1**. Herein we describe our chiral pool approach for the synthesis of **4**, an advanced intermediate corresponding to the C(1)–C(11) sector of **1**.

Our projected program for the total synthesis of **1** envisaged a Mukaiyama aldol reaction between **2** and **3** as the main key transformation for fabricating the total carbon unit of peloruside A and subsequent macrolactonization. We noted the resemblance between the stereochemistry of C(2) and C(3) to that of glucose diacetonide **7** and the feasibility of the selective methylation of C(3), and anticipated that dihydroxylation of the unsaturated lactone **6** should dispose the other two hydroxyl groups at C(7) and C(8) with the required stereochemistry (Scheme 1).

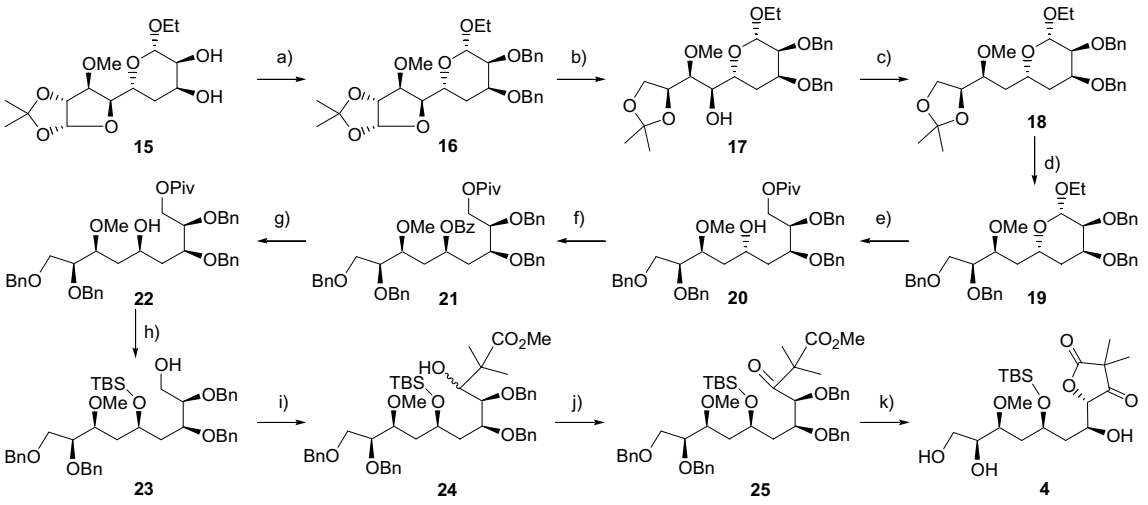
The synthesis of **6** began with allylation of **8**[6] under Barbier conditions[7] using allylbromide and Zn. The (5*R*)- and (5*S*)-isomers **9** and **10** were obtained in a 95% (9:1) yield. The minor isomer **10** was treated with acryloyl chloride to provide diene **11** (Scheme 2). Ring closing metathesis of **11** with the second generation Grubbs' catalyst[8] gave the α,β-unsaturated δ-valerolactone **6**. Dihydroxylation[9] of **6** gave only one isomer, which was characterized as its acetonide **12**.[10] NOE experiments with **12** clearly indicated that the dihydroxylation of **6** had resulted exclusively from the undesired α-face,[5] this being further confirmed by single crystal X-ray diffraction studies (Scheme 2).

As the dihydroxylation of lactone **6** having the correct (*S*) stereochemistry at C(5) gave the undesired diastereomer **12**, we studied the same sequence of reactions with the major isomer **9**, anticipating a similar diastereoselectivity from the α-face since inversion of the stereochemistry at C(5) by means of Mitsunobu reaction could be carried out at a later stage. Indeed the dihydroxylation of the α,β-unsaturated δ-valerolactone **13** derived from **9** gave exclusively one diastereomer and the resulting diol was characterized as its acetonide **14** (Scheme 3). NOE studies of **14** as well as single crystal X-ray diffraction studies of the ethyl glycoside **15**[11] derived from **14** following selective DIBAL-H reduction and anomeric *O*-ethylation using NaH, EtI and clearly established that the stereochemistry of the dihydroxylation was as expected.

Having an easy access to the key intermediate **15**, we addressed the inversion at C(5) and the chain extension at C(9). As shown in Scheme 4, benzylation of the diol **15** gave the ethyl pyranoside **16** in 90% yield. Following a sequence of reactions (i) hydrolysis of the furanoside acetonide, (ii) reduction of the resulting acetal with $LiAlH_4$, and (iii) selective acetonide protection, **16** was converted to **17** in an overall yield of 61%. The Barton–McCombie deoxygenation protocol[12] was successfully applied to the deoxygenation of the C(4)–OH in **17** and the deoxygenated product **18** was obtained in good yield. Deprotection of the isopropylidene system with PPTS in methanol and protection of the resulting diol as



Scheme 3. Reagents and conditions: (a) acryloyl chloride, EtN^iPr_2, CH_2Cl_2, 0 °C, 0.5 h, 76%; (b) 5 mol% **A**, benzene, ↑↓, 1 h, 72%; (c) (i) OsO_4 (cat), 50% aq NMO, acetone/H_2O (9:1); (ii) PTSA (cat), 2,2-dimethoxypropane, benzene, ↑↓, 0.5 h, 66%; (d) DIBAL-H, toluene, −78 °C; (e) NaH, DMF, EtI, 0 °C, 1 h; (f) PPTS (cat), MeOH, rt, 1 h, 71% (three steps).



Scheme 4. Reagents and conditions: (a) NaH, DMF, BnBr, 0 °C, 1 h, 90%; (b) (i) TFA/H_2O (4:1); 0 °C, 1 h; (ii) $LiAlH_4$, THF, rt, 3 h; (iii) PTSA (cat), 2,2-dimethoxypropane, CH_2Cl_2, rt, 0.5 h, 61%; (c) (i) NaH, THF, CS_2, MeI, 0 °C, 1.5 h; (ii) Bu_3SnH, AIBN (cat), toluene, ↑↓, 1 h, 55%; (d) (i) PPTS (cat), MeOH, rt, 8 h; (ii) NaH, DMF, BnBr, 0 °C, 1 h, 90%; (e) (i) H_2SO_4 (cat), AcOH/H_2O (4:1), ↑↓, 0.5 h; (ii) $LiAlH_4$, THF, rt, 1 h; (iii) pivalolyl chloride, pyridine, 0 °C, 0.5 h, 62%; (f) DIAD, TPP, $PhCO_2H$, THF, 0 °C, 0.5 h, 79%; (g) (i) DIBAL-H, toluene, 0 °C, 1 h; (ii) pivalolyl chloride, pyridine, 0 °C, 0.5 h, 81%; (h) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; (ii) DIBAL-H, toluene, −78 °C, 2 h, 92%; (i) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h; (ii) $(Me)_2CH–CO_2Me$, LDA, THF, −78 °C, 0.5 h, 69%; (j) Dess–Martin periodinane, CH_2Cl_2, 1.5 h, 79%; (k) 10% Pd–C/H_2, MeOH, AcOH (cat), 1 atm, rt, 82%.

the benzyl ether using NaH and benzyl bromide gave the fully protected pyranoside **19**. Removal of the glycosidic ethyl protection of **19**, reduction of the cyclic acetal with $LiAlH_4$, and selective protection of the 1°-OH with pivaloyl chloride in pyridine at 0 °C gave the pivaloyl ester **20**[13] in 62% overall yield.

Inversion of the C(5) center in **20**, as envisioned at the planning stage was accomplished under Mitsunobu conditions[14] using diisopropyl azodicarboxylate (DIAD)/PPh_3 and benzoic acid to give the diester **21** in 79% yield. For convenience in comparison of spectral data, **21** was treated with DIBAL-H and the 1°-OH of the resulting diol was protected selectively as its pivaloyl ester **22**.[15] Spectral data of **20** and **22** clearly confirmed the inversion at C(5). The TBS ether **23** obtained from **22** (following a sequence of 2°-OH protection as its TBS ether and depivaloylation using DIBAL-H) was subjected to oxidation using Dess–Martin[16] periodinane. The resulting aldehyde was treated with the lithium enolate of methyl 2-methylpropionate and oxidation of the condensed product **24** with the Dess–Martin periodinane gave **25** in good yield. As anticipated, hydrogenation of **25** with 10% Pd–C gave the ketolactone **4**. The spectral data of **4**[17] are in agreement with the assigned structure.

In conclusion, a compound corresponding to the C(1)–C(11) fragment of peloruside A has been synthesized using a chiron approach from D-glucose.[18] Efforts are underway to complete a synthesis of (−)-peloruside A, a total synthesis of the natural product (+)-peloruside A, as well as to apply the resulting strategy to generate structural analogues of (+)-peloruside A with useful in vivo activity.

Acknowledgement

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9. During their synthesis of the C(1)–C(9) fragment of (−)-peloruside A, Ghosh et al. noticed a similar undesired α-face selective dihydroxylation of the corresponding unsaturated lactone. See Ref. 5.
10. Spectral data of **12**: $[\alpha]_D^{25}$ −65.33 (*c* 0.96, $CHCl_3$); mp 121–124 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32, 1.36 (2s, 6H),

1.48, 1.50 (2s, 6H), 1.87 (ddd, 1H, $J = 14.8, 11.5, 3.6$ Hz), 2.01 (dt, 1H, $J = 14.8, 1.8$ Hz), 3.40 (s, 3H), 3.75 (d, 1H, $J = 3.8$ Hz), 4.22 (dd, 1H, $J = 7.5, 3.8$ Hz), 4.58 (d, 1H, $J = 6.7$ Hz), 4.60 (d, 1H, $J = 3.9$ Hz), 4.66 (br ddd, 1H, $J = 6.7, 3.6, 1.9$ Hz), 4.90 (ddd, 1H, $J = 11.5, 7.5, 1.8$ Hz), 5.95 (d, 1H, $J = 3.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.1 (q), 25.8 (q), 26.2 (q), 26.7 (q), 29.9 (t), 57.5 (q), 71.6 (d). 72.8 (d), 74.2 (d), 80.8 (d), 81.0 (d), 83.9 (d), 105.1 (d), 110.6 (s), 111.9 (s), 167.1 (s). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C, 55.73; H, 7.21.

11. Spectral data of **15**: $[\alpha]_{25}^{D}$ +34.08 (c 1.4, $CHCl_3$); mp 142–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, 3H, $J = 7.1$ Hz), 1.31, 1.48 (2s, 6H), 1.65 (t, 1H, $J = 13.3$ Hz), 2.19 (br dt, 1H, $J = 13.3, 2.8$ Hz), 2.47 (br s, 1H, OH), 2.51 (br s, 1H, OH), 3.40 (dt, 1H, $J = 7.7, 2.8$ Hz), 3.44 (s, 3H), 3.57 (dq, 1H, $J = 9.3, 7.2$ Hz), 3.78 (d, 1H, $J = 2.9$ Hz), 3.92 (dq, 1H, $J = 9.3, 7.2$ Hz), 4.02 (dd, 1H, $J = 8.9, 2.9$ Hz), 4.17 (ddd, 1H, $J = 11.6, 8.9, 2.8$ Hz), 4.22–4.24 (m, 1H), 4.53 (d, 1H, $J = 3.7$ Hz), 4.63 (d, 1H, $J = 7.7$ Hz), 5.85 (d, 1H, $J = 3.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7 (q), 25.7 (q), 26.2 (q), 34.6 (t), 57.6 (q), 64.4 (t), 66.0 (d), 66.8 (d), 71.0 (d), 81.3 (d), 82.9 (d), 99.8 (d), 104.4 (d), 110.9 (s). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84. Found: C, 53.73; H, 8.19.
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13. Spectral data of **20**: $[\alpha]_{25}^{D}$ −9.67 (c 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 1.48 (dd, 1H, $J = 6.3, 2.8$ Hz), 1.58 (br dt, 1H, $J = 14.2, 4.0$ Hz), 1.64 (ddd, 1H, $J = 14.2, 4.0, 2.8$ Hz), 1.83 (dt, 1H, $J = 14.7, 8.8$ Hz), 3.39 (s, 3H), 3.56 (dd, 1H, $J = 9.9, 6.3$ Hz), 3.63 (br dt, 1H, $J = 9.1, 3.8$ Hz), 3.65–3.71 (m, 2H), 3.76 (dt, 1H, $J = 6.3, 3.8$ Hz), 3.84 (dt, 1H, $J = 8.3, 3.8$ Hz), 3.90–3.94 (m, 1H), 4.18 (dd, 1H, $J = 11.9, 6.3$ Hz), 4.38 (dd, 1H, $J = 11.9, 3.8$ Hz), 4.53 (s, 2H), 4.57 (d, 1H, $J = 11.6$ Hz), 4.63 (d, 1H, $J = 11.6$ Hz), 4.64 (d, 1H, $J = 12.0$ Hz), 4.70 (br d, 2H, $J = 11.6$ Hz), 4.73 (d, 1H, $J = 12.0$ Hz), 7.17–7.38 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2 (q), 38.5 (t), 38.6 (t), 38.7 (s), 59.0 (q), 63.5 (t), 66.9 (d), 70.3 (t), 72.3 (t), 72.6 (t), 72.9 (t), 73.3 (t), 77.8 (d), 78.7 (d), 78.9 (d), 79.2 (d), 127.4–128.4 (several arom. ds), 137.7 (s), 138.0 (s), 138.3 (s), 138.6 (s), 178.1 (s). Anal. Calcd for $C_{43}H_{54}O_8$: C, 73.90; H, 7.79. Found: C, 73.95; H, 7.75.
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15. Spectral data of **22**: $[\alpha]_{25}^{D}$ −12.64 (c 1.22, $CHCl_3$); ^{1}H NMR (300 MHz $CDCl_3$) δ 1.20 (s, 9H), 1.47–1.74 (m, 4H), 3.39 (s, 3H), 3.52–3.63 (m, 3H), 3.67–3.78 (m, 2H), 3.91–4.02 (m, 2H), 4.12 (dd, 1H, $J = 11.8, 6.3$ Hz), 4.32 (dd, 1H, $J = 11.8, 3.8$ Hz), 4.47 (s, 2H), 4.54 (d, 1H, $J = 11.4$ Hz), 4.55 (d, 1H, $J = 11.8$ Hz), 4.59 (d, 1H, $J = 11.4$ Hz), 4.64 (d, 1H, $J = 11.8$ Hz), 4.66 (d, 1H, $J = 11.4$ Hz), 4.70 (d, 1H, $J = 11.8$ Hz), 7.25–7.40 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0 (q), 37.3 (t), 38.6 (s), 38.9 (t), 58.1 (q), 63.5 (t), 67.1 (d), 69.9 (t), 72.3 (t), 72.8 (t), 72.9 (t), 73.3 (t), 76.0 (d), 78.4 (d), 79.3 (d), 80.9 (d), 127.4–128.2 (several arom. ds), 138.0 (s), 138.2 (s), 138.3 (s), 138.4 (s), 178.1 (s). Anal. Calcd. for $C_{43}H_{54}O_8$: C, 73.90; H, 7.79. Found: C, 73.49; H, 7.66.
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17. Spectral data of **4**: $[\alpha]_{25}^{D}$ −7.15 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz $CDCl_3$) δ 0.10, 0.12 (2s, 6H), 0.88 (s, 9H), 1.32, 1.33 (2s, 6H), 1.68 (ddd, 1H, $J = 14.7, 5.0, 2.2$ Hz), 1.88 (t, 2H, $J = 6.3$ Hz), 2.22 (ddd, 1H, $J = 15.0, 11.3, 4.2$ Hz), 3.37–3.40 (m, 1H), 3.42 (s, 3H), 3.64–3.67 (m, 2H), 3.73 (dd, 1H, $J = 13.3, 6.3$ Hz), 4.11–4.19 (m, 1H), 4.38 (td, 1H, $J = 11.2, 2.5$ Hz), 4.59 (d, 1H, $J = 2.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7 (q), −4.6 (q), 17.9 (s), 19.2 (q), 21.9 (q), 25.7 (q), 36.1 (t), 44.7 (s), 57.9 (q), 63.9 (t), 67.9 (d), 68.9 (d), 72.5 (d), 78.8 (d), 85.9 (d), 177.7 (s), 211.5 (s). Anal. Calcd for $C_{20}H_{38}O_8Si$: C, 55.27; H, 8.81. Found: C, 54.89; H, 8.96.
18. The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition Nos. CCDC-219593 (**15**) and CCDC-219594 (**12**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc. cam. ac.uk].