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Synthesis and Biological Activity of 7,8,9-Trideoxy- and 7*R* DesTHP-Peloruside A

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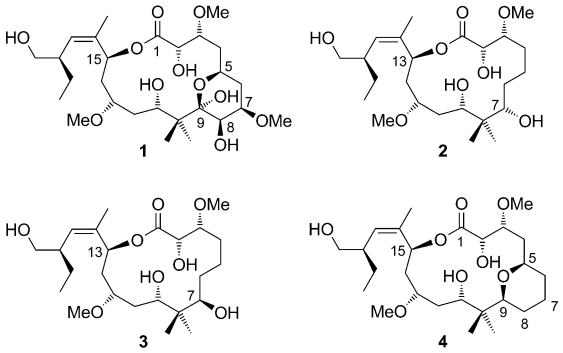
Abstract: The stereoselective syntheses of 7,8,9-trideoxypeloruside A (**4**) and a monocyclic peloruside A analogue lacking the entire tetrahydropyran moiety (**3**) are described. The syntheses proceeded through the PMB-ether of an ω-hydroxy β-keto aldehyde as a common intermediate which was elaborated into a pair of diastereomeric 1,3-*syn* and -*anti* diols by stereoselective Duthaler–Hafner allylations and subsequent 1,3-*syn* or *anti* reduction. One of these isomers was further converted into a tetrahydropyran derivative in a high-yielding Prins reaction, to provide the precursor for bicyclic analogue **4**. Downstream steps for both syntheses included the substrate-controlled addition of a vinyl lithium intermediate to an aldehyde, thus connecting the peloruside side chain to C15 (C13) of the macrocyclic core structure in a fully stereoselective fashion. In the case of monocyclic **3** macrocyclization was based on ring-closing olefin metathesis (RCM), while bicyclic **4** was cyclized through Yamaguchi-type macrolactonization. The macrolactonization step was surprisingly difficult and was accompanied by extensive cyclic dimer formation. Peloruside A analogues **3** and **4** inhibited the proliferation of human cancer cell lines in vitro with micromolar and sub-micromolar IC_{50} values, respectively. The higher potency of **4** highlights the importance of the bicyclic core structure of peloruside A for nM biological activity.

Keywords: natural products · peloruside A · structure–activity relationships · total synthesis · tubulin

Introduction

Peloruside A (**1**) is a polyketide-derived 16-membered macrolide that was isolated from the marine sponge *Mycale hentscheli* by Northcote and co-workers and shown to exhibit potent in vitro antitumor activity.[1] The compound was subsequently found to be a microtubule-stabilizing agent (MSA)[2] with a tubulin binding site distinct from that of most other natural product MSAs,[3] which almost uniformly bind to the taxol site on β-tubulin.[4,5] As a result, peloruside A (**1**) exhibits synergistic effects with a number of taxol site agents on tubulin assembly[6] and cancer cell growth.[7]

Peloruside A (**1**) has been a frequent target for total synthesis;[8,9] in addition, the synthesis or semisynthesis of a number of (simplified) analogues of **1** has been reported for SAR studies.[2,10,11] Biological studies have also been performed on a limited number of natural congeners of **1**,[9,10b] but the overall SAR picture for peloruside-type structures is still spotty at this point.



We have recently reported the stereoselective synthesis of the 14-membered monocyclic peloruside A analogue **2**, as part of a program directed at the exploration of the importance of the pyranose ring in the bicyclic core structure of peloruside A (**1**) and its particular substitution pattern.[11] While **2** retained measurable antiproliferative activity against A549 cells, it was generally >1000-fold less potent than **1**; it remained unclear, however, to what extent the biological activity of **2** was affected by the configuration of the C7 chiral center (corresponding to C9 in natural **1**), although calculations had indicated that in order for the C7-hydroxyl group to mimic the anomeric hydroxyl group in peloruside A (**1**) the preferred configuration would have to

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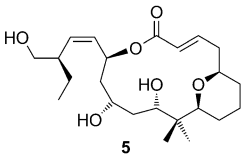
be 7*S* (as in **2**) rather than 7*R*.[12] In order to clarify this question experimentally, we have now also prepared 7*R* analogue **3** and we have assessed its effects on cancer cell proliferation. At the same time we felt that the lack of significant antiproliferative activity of **2** might point to the need for a conformationally more restricted and/or larger sized macrocycle as a prerequisite for potent biological activity (see also ref. [2]). As a consequence, we have started to investigate the stepwise reconstruction of natural **1** from monocyclic analogues **2**/**3** and to assess the changes in activity that would be associated with the restoration of individual modules or substituents of the peloruside structure that are not present in **2**/**3**. In a first step in this process we have investigated the greatly simplified bicyclic peloruside A analogue **4**, which served to assess the importance of the bicyclic core structure of **1** for biological activity, independent of any substituents on the tetrahydropyran (THP) ring. In an independent parallel study Zimmermann et al. have investigated the related analogue **5**;[10d] this compound was found to exhibit only moderate antiproliferative activity (IC_{50} values between 10 and 20 μM).

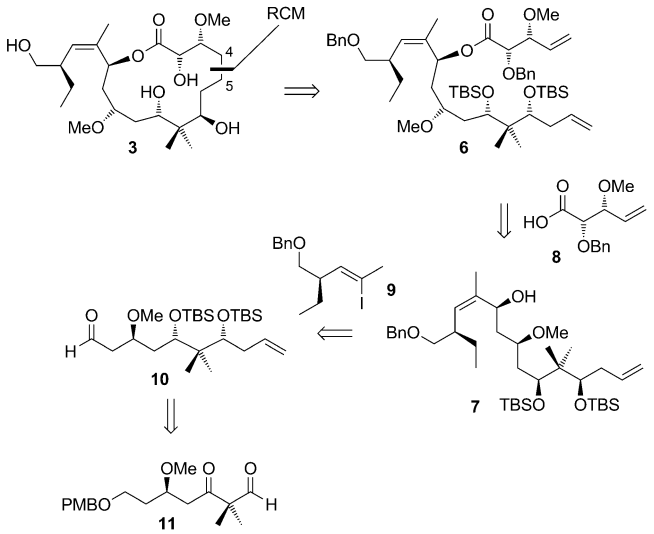


Results and Discussion

Synthesis of 7*R* DesTHP-peloruside A (3): In analogy to our previous work on analogue **2**,[11] the core element of our synthetic strategy towards 7*R* desTHP-peloruside A (**3**) was the anticipated RCM-based macrocyclization of diene **6**, which would be followed by TBS removal, double-bond reduction and (if possible simultaneous) cleavage of the benzyl protecting groups (Scheme 1). Diene **6** would be obtained by esterification of acid **8** with alcohol **7**; the latter was to be produced through addition of a vinyl metal intermediate derived from vinyl iodide **9** to aldehyde **10**, which in turn would be derived from β-keto aldehyde **11** by asymmetric allylation and subsequent 1,3-*syn* reduction as the defining steps. The synthesis of aldehyde **11**, vinyl iodide **9**, and acid **8** has been described.[11]

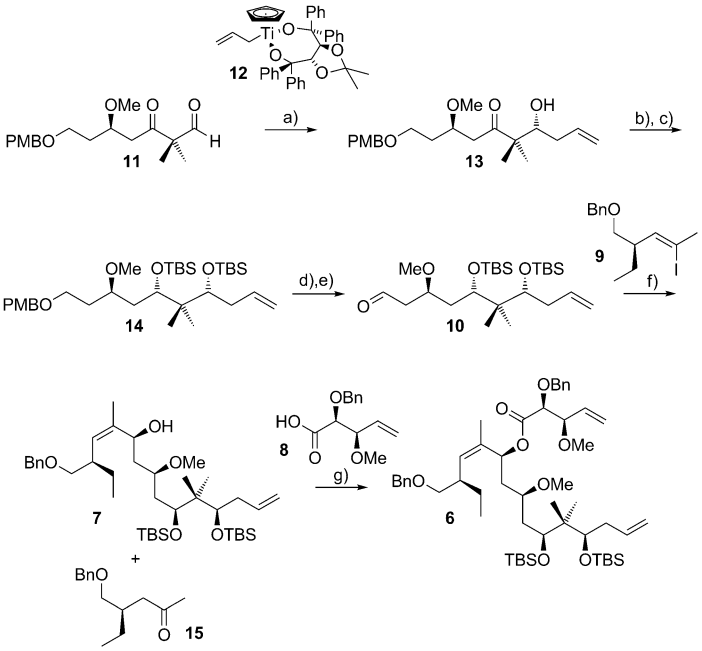
The implementation of these concepts in the first step entailed the asymmetric allylation of aldehyde **11** under Duthaler–Hafner conditions (Scheme 2).[13] When the allyltitanation of **11** was performed with a 1.4-fold excess of **12** the desired 7*R* homoallylic alcohol **13** was obtained in 93% yield and with excellent diastereoselectivity (d.r. >25:1); an excess of **12** was crucial for complete conversion of the starting aldehyde **11**.

After treatment of **13** with DIBALH in THF the desired *syn*-diol could be isolated in excellent yield (84%). (The reaction proceeded with a d.r. of 15:1, the minor isomer could be removed by FC.) The reduction product was then converted into the corresponding bis-TBS-ether **14** by reaction with TBSOTf; subsequent oxidative cleavage of the PMB-ether with DDQ[14] followed by Dess–Martin oxidation of the ensuing primary alcohol gave the required aldehyde **10** in 58% overall yield for the 4-step sequence from homoallylic alcohol **13**.



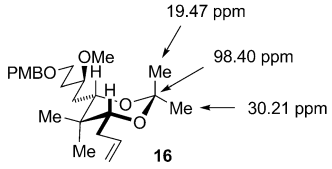
Scheme 1. Retrosynthesis of 7*R* desTHP-peloruside A (**3**).

In order to ascertain the predicted 1,3-*syn* relationship of the diol obtained by DIBALH reduction of **13**, the former



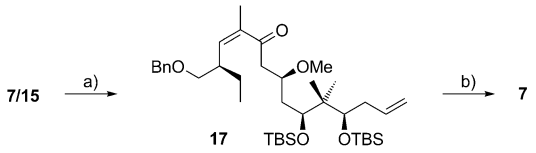
Scheme 2. a) **12**, Et_2O, −78 °C, 2.5 h, 93% (d.r. >25:1); b) slow addition of DIBALH (1.0 equiv over 80 min), THF, −78 °C, then 4.0 equiv DIBALH, −78 °C, 2 h, 84%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C → RT, 3.5 h, 95%; d) DDQ, CH_2Cl_2/H_2O 12:1, 0 °C, 3 h, 93%; e) DMP, CH_2Cl_2, RT, 90 min, 78%; f) 2.1 equiv **9**, 4.0 equiv *t*BuLi, Et_2O, −78 °C, 30 min, then 1.0 equiv **10**, −78 °C, 18 h; **7**: 58%, **15**: 18% (based on **9**); g) **8**, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, RT, 1 h, then **7**, DMAP, RT, 90 min, 83%.

was converted into the corresponding acetonide **16** by treatment with CSA in 2,2-dimethoxypropane. The ^{13}C chemical shifts for the ketal methyl groups of **16** (19.47 ppm, axial methyl group; 30.21 ppm, equatorial methyl group) and for



its quaternary carbon (98.40 ppm) are in perfect agreement with the predicted shifts for acetonides of *syn*-1,3-diols.[15]

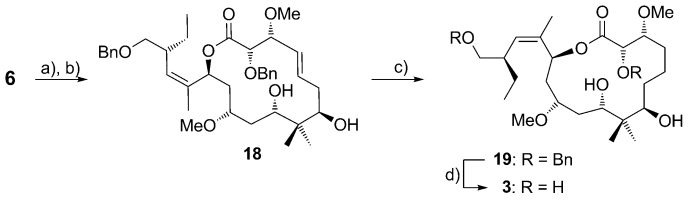
Reaction of aldehyde **10** with the vinyllithium reagent derived from vinyl iodide **9** by treatment with *t*BuLi at −78 °C[11] gave the desired 13*S* alcohol **7** (numbering for **3**) as the sole isomer (in 58 % yield), but the product was contaminated with methyl ketone **15** (18 %, based on **9**) which could not be removed chromatographically.[16] However, the stereoselectivity of this transformation was not immediately recognized, as the signals originating from **15** in the NMR spectra of the **7**/**15** mixture were initially believed to arise from the 13*R* diastereoisomer of **7**. The mixture was thus oxidized to enone **17**, which was then re-reduced with catecholborane in the presence of the (*R*)-Corey–Bakshi–Shibata (CBS) catalyst,[17] to provide **7** as a single isomer and free of ketone **15** (Scheme 3); the latter could be readily removed by FC at the enone stage.



Scheme 3. a) DMP, $NaHCO_3$, CH_2Cl_2, RT, 90 min, 89 % (based on the amount of **7** in the starting mixture); b) catecholborane, (*R*)-B-Me-CBS oxazaborolidine, toluene, −78 → 0 °C, 7 h, 87 %.

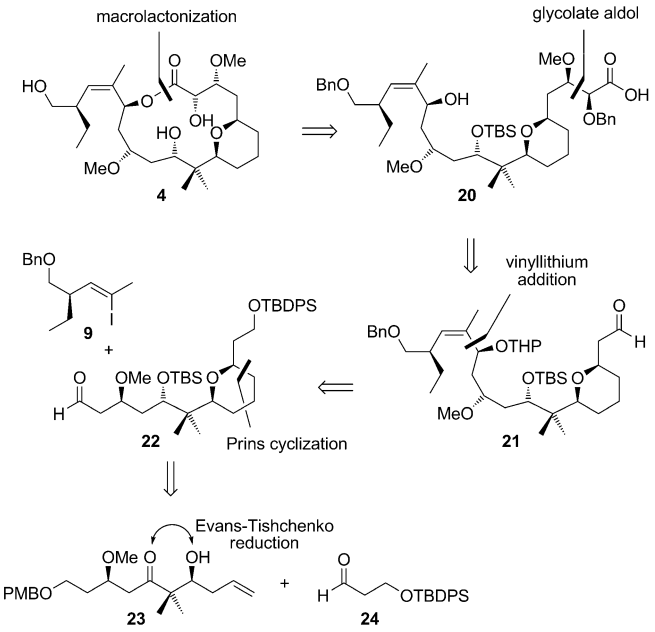
The *S* configuration of the chiral center formed in the CBS-reduction of enone **17** was established by Mosher ester analysis;[18] this stereochemical outcome is in perfect agreement with a large body of information on the stereodirecting properties of CBS catalysts.[17] Importantly, the product of the CBS-reduction was spectroscopically indistinguishable from the allylic alcohol obtained in the reaction between aldehyde **10** and the vinyllithium reagent derived from vinyl iodide **9**. The esterification of **7** and carboxylic acid **8** under Yamaguchi conditions[19] then gave the desired diene **6** in 83 % yield (Scheme 2).

As shown in Scheme 4, treatment of **6** with Grubbs second-generation catalyst[20] in 1,2-dichloroethane at 80 °C provided the *E*-configured macrolactone as the only isolable cyclization product in yields around 60 %, thus reproducing the outcome of the corresponding step in the synthesis of analogue **2**.[11] Subsequent cleavage of the two TBS-ethers with HF·pyridine in THF gave partially deprotected macrolactone **18** in 89 % yield. When submitting **18** to catalytic hydrogenation conditions (Pd/C, H_2 at ambient pressure in AcOEt), complete decomposition was observed within 2 h. In contrast, the endocyclic double bond could be selectively reduced with diimide (PADA, AcOH, CH_2Cl_2, reflux temperature, 30 h)[21] to deliver the saturated macrolactone **19** in excellent yield (83 %); interestingly, however, the reaction appeared to be significantly more sluggish than the same transformation with the 7*S* isomer of **18**, that is, longer reaction times (30 h vs. 17 h) and more equivalents of PADA/AcOH (260 equiv vs 80 equiv) were required to drive the reaction to completion. The final benzyl ether cleavage from **19** was first attempted by catalytic hydrogenation in AcOEt (Pd/C, H_2, room temperature, ambient pressure); while these conditions had been successfully employed for the debenzylation of the 7*S* isomer of **19**, for **19** they only led to decomposition. Likewise, treatment of **19** with BCl_3 did not produce any of the desired des-THP-peloruside **3**. These problems could be finally overcome by changing the solvent for the hydrogenation from AcOEt to ethanol, which led to a significant enhancement in reaction rate. At the same time decomposition pathways could be suppressed by limiting the amounts of Pd/C to 2–4.5 %. Under these conditions the debenzylation of **19** went to completion within ca. 7 h at room temperature and ambient pressure to give **3** in 73 % yield. Only minor amounts of polar side products were formed (TLC: < 5–10 %) and the trisubstituted side chain double bond remained unaffected (according to MS-based reaction monitoring).

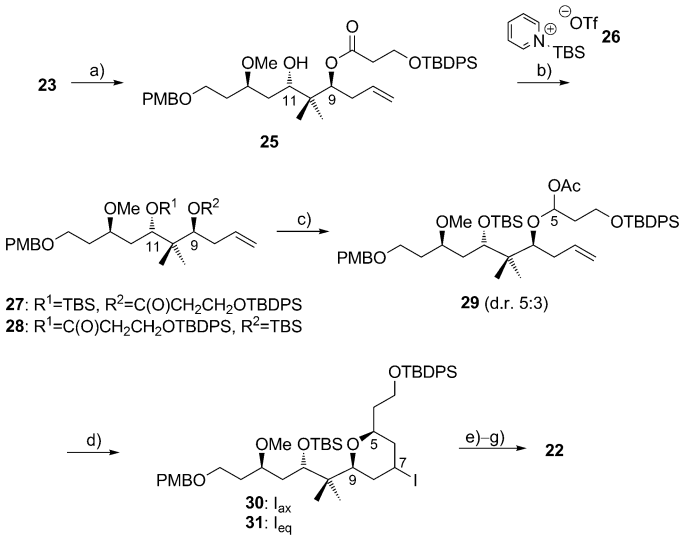


Scheme 4. a) Grubbs II catalyst, 1,2-dichloroethane, 80 °C, 5 h, 60 %; b) HF·py, THF, RT, 19 h, 89 %; c) PADA, AcOH, CH_2Cl_2, reflux, 30 h, 83 %; d) Pd/C, H_2 (atmospheric pressure), EtOH, RT, 6.5 h, 73 %.

Synthesis of 7,8,9-trideoxy-peloruside A (4): Due to the presence of the tetrahydropyran ring in **4** and its particular positioning, RCM-mediated macrocyclization at the site exploited in the synthesis of **3** (and also **2**[11]) was no longer feasible for **4**. As a consequence, the synthesis of **4** was to be based on ring-closure by macrolactonization of an appropriately protected seco-acid, such as **20** (Scheme 5).[22] Seco-acid **20** was planned to be accessed through a stereoselective glycolate aldol reaction with aldehyde **21**; the latter was to be obtained from aldehyde **22** and vinyl iodide **9**, in analogy to the formation of **7** from **9** and **10** (Scheme 2). Lastly, the THP-containing fragment **22** was to be accessed from homoallylic alcohol **23** and aldehyde **24**[23] via Prins reaction and subsequent functional group manipulations. The synthesis of



Scheme 5. Retrosynthesis of 7,8,9-trideoxy-peloruside A (**4**).



Scheme 6. a) **24** (2.4 equiv), SmI_2 (16 mol%), THF, −10°C, 1 h, 88% (d.r. 15:1); b) **26**, CH_2Cl_2, 0°C, 4 h 45 min, 88% (8:1 mixture of **27**/**28**); c) DIBALH, CH_2Cl_2, −100°C, 2.5 h, then pyridine, DMAP, Ac_2O, −100°C, 5 h, −78°C, 14 h, 82% (d.r. 5:3); d) $CeCl_3$, LiI, CH_2Cl_2, RT, 7 h 15 min, quant. (**30**/**31** 11:2); e) Pd/C, H_2 (atmospheric pressure), $NaHCO_3$, MeOH/AcOEt 4:1, RT, 2 h, 90%; f) DDQ, CH_2Cl_2/H_2O 10:1, 0°C, 50 min, 80%; g) DMP, CH_2Cl_2, 0°C, 4 h, 83%.

building block **23** had already been established as part of our work on analogue **2** (and involved the stereoselective allylation of aldehyde **11** with *ent*-**12**).[11]

As illustrated in Scheme 6, 1,3-reduction of **23** with aldehyde **24** under Evans–Tishchenko conditions[24] led to the required 1,3-*anti* product **25** in high yield (88%) and with excellent diastereoselectivity (d.r. 15:1). The predicted 1,3-*anti* relationship at C9/C11 was ascertained by the conversion of **25** into the corresponding diol and the derived acetonide; the analytical data for both compounds were in perfect agreement with those reported previously.[11] While TBS protection of **25** with TBSOTf and 2,6-lutidine resulted in extensive acyl migration (2:3 mixture of **27** and **28**; 75% yield), reaction with *N*-*tert*-butyldimethylsilylpyridinium triflate (**26**) led to a 8:1 mixture of the desired C11-TBS ether **27** and the undesired C9-TBS regioisomer **28** in a total yield of 88%; **27** and **28** proved to be chromatographically inseparable.

With ester **27** in hand we then turned our attention to the Rychnovsky segment coupling Prins cyclization.[25] To this end the mixture of **27**/**28** was treated with a slight excess of DIBALH in CH_2Cl_2 at −100°C to produce, after in situ acetylation of the ensuing aluminated hemiacetal with acetic anhydride in the presence of pyridine and DMAP,[25b] α-acetoxy ether **29** (Scheme 6). The latter was obtained in 82% yield as a 5:3 mixture of diastereoisomers at C5. Interestingly, the undesired regioisomer **28** did not react under these conditions and was recovered from the reaction mixture unchanged (although it was not separated from **29**). Initial attempts to perform the Lewis acid-promoted cyclization of **29** under standard conditions (e.g., with TMSI or $SnBr_4$)[26] resulted in decomposition (with TMSI) or the formation of only traces of the desired product (with $SnBr_4$). However, excellent results were obtained for the construction of the desired 2,6-*cis*-disubstituted-4-halotetrahydropyrans **30**/**31** by treatment of **29** with $CeCl_3$ and LiI as Lewis acids.[27] The reaction could be conducted at room temperature in CH_2Cl_2 and led to a 11:2 mixture of diastereoisomers **30** and **31** in quantitative yield (>95%; based on the amount of **29** in the **29**/**28** mixture). At this stage, **28** could be readily removed by FC.

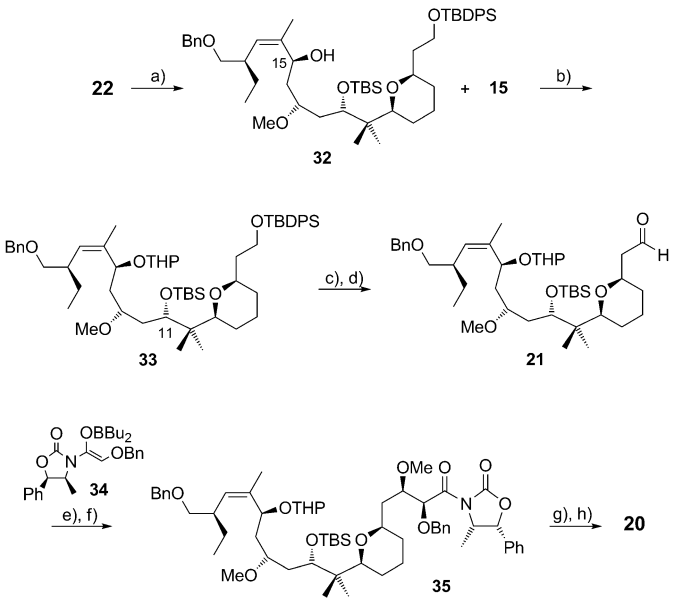
The expected *cis*-arrangement of the substituents at positions 2 and 6 of the THP ring in **30** and **31** was confirmed by NOE measurements.[28] A clear NOE was detectable between H5 and H9 for both isomers; in contrast, NOEs between H7 and H5/H9 were only observed for **31**, thus pointing to an equatorial orientation of the iodo substituent on the THP ring in this isomer. The axial selectivity of the Prins cyclization reaction, with **30** as the major isomer, is further supported by chemical shifts of $\delta = 4.87$ and 4.21 ppm for the H7 proton in **30** and **31**, respectively. These numbers are clearly indicative of an equatorial orientation of the H7 proton in **30**, while its orientation must be axial in **31**.[26]

The attempted reductive removal of the C7 iodo group by radical dehalogenation (Bu_3SnH/AIBN)[29] was associated with complete decomposition of starting material. In contrast, hydrodehalogenation[30] of the **30**/**31** mixture with Pd/C and H_2 led to the desired des-iodo-**30**/**31** as a single isomer in high yield (90%). For the reaction to proceed smoothly, ca. 5 equiv of $NaHCO_3$ had to be added to the reaction mixture, in order to trap hydroiodic acid and prevent TBS-ether cleavage. Finally, PMB-removal with DDQ followed by DMP oxidation of the resulting primary alcohol furnished

aldehyde **22** in 60% overall yield for the 3-step sequence from **30**/**31**.

Metalation of vinyl iodide **9** and subsequent addition of the resulting vinyllithium species to aldehyde **22** according to the protocol that had been employed for the preparation of **7** (Scheme 2) provided the desired 15*S*-allylic alcohol **32** as a single isomer in 65–73% yield (based on **22**) (Scheme 7). As for **7**, however, the product was again contaminated with methyl ketone **15**, which was obtained in 13% yield (based on **9**); **32** and **15** could not be separated and were carried into the next step as a mixture. Treatment of the **32**/**15** mixture with 3,4-dihydro-2*H*-pyran (DHP) and 20 mol% PPTS produced acetal **33** as a mixture of two diastereoisomers in 87% yield (based on the amount of **32** in the starting material) without affecting the secondary TBS-ether. The two THP isomers could be separated by FC; they were processed into seco-acid **20** either separately, in order to facilitate the interpretation of NMR spectra, or as the 1:1 mixture. No significant differences in yields were observed between reactions with single isomers and the 1:1 mixtures. The TBDPS group in **33** was then selectively removed with refluxing methanolic NaOH (10%) in 71–88% yield.[31] Subsequent oxidation of the liberated hydroxyl group with DMP gave aldehyde **21**, which was submitted to an Evans aldol reaction[32] with a 10-fold excess of the dibutylboron enolate **34** (derived from the corresponding glycolyl imide and Bu_2BOTf). This reaction afforded the desired aldol product as a single isomer in 88% yield. The use of a large excess of enolate **34** was found to be crucial for the effectiveness of the reaction, as lower amounts of **34** resulted in incomplete conversion of aldehyde **21**. Due to the large excess of **34**, the aldol product could only be obtained as a 1:9 mixture with the starting glycolyl imide; however, the latter could be readily removed by FC after methylation of the free hydroxyl group with Meerwein salt (Me_3OBF_4).[33] Selective cleavage of the THP-acetal with $MgBr_2$[34] followed by removal of the chiral auxiliary with $LiOH/H_2O_2$ then furnished seco-acid **20** in 51% overall yield for the 4-step sequence from aldehyde **21**.

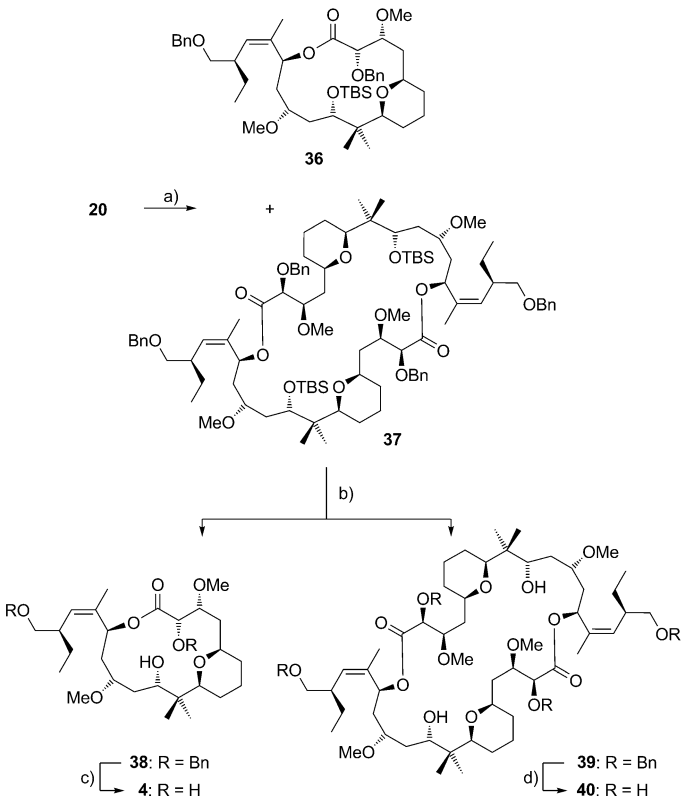
At this stage we were confident that the completion of the synthesis of **4** would be reasonably straightforward. However, very surprisingly, the macrolactonization of seco-acid **20** turned out to be highly challenging. Among the various cyclization methods investigated the Yamaguchi protocol[19] proved to be the most effective, even if the desired macrolactone **36** was obtained in only moderate yield (25%, 3.1 μmol) and the reaction produced an inseparable ca. 2:1 mixture (on a molar basis) of **36** and diolide **37** (25%, 1.5 μmol) (Scheme 8). Based on TLC, the starting material was completely consumed and, in addition to **36** and **37**, was converted into unidentified polar side products; the latter may be speculated to be non-cyclized oligomers.[35] Subsequent TBS-deprotection of the **36**/**37** mixture with HF·pyridine afforded partially deprotected macrolactones **38** and **39** as single compounds in 80 and 85% yield, respectively. Compound **38** and **39** showed dramatically different polarities and thus could be easily separated by FC on silica. Final



Scheme 7. a) 2.5 equiv **9**, 4.2 equiv *t*BuLi, Et_2O, −78 °C, 40 min, then 1.0 equiv **22**, −78 °C, 14 h, 65–73%; plus **15**, 13% (based on **9**); b) DHP, PPTS, CH_2Cl_2, RT, 6 h, 87%; c) NaOH (10%), MeOH/THF 10:1, reflux, 14 h, 71–88%; d) DMP, CH_2Cl_2, 0 °C, 90 min, 86–92%; e) **34**, CH_2Cl_2, −78 °C, 2.5 h, 88%; f) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 °C, 2 h, 91%; g) $MgBr_2 \cdot OEt_2$, Et_2O, RT, 1 h, 77%; h) LiOH, H_2O_2, THF/H_2O 4:1, 0 °C, 1 h 15 min, 83%.

deprotection of **38** and **39** with H_2 and Pd/C in ethanol provided the targeted bicyclic peloruside A analogue **4** and diolide **40** in 77 and 50% yield, respectively. No complications arose in this step from the presence of the olefinic double bond in the side chain.

Biological evaluation: The in vitro antiproliferative activity of desTHP-peloruside A (**3**) and 7,8,9-trideoxy-peloruside A (**4**) was evaluated in three human cancer cell lines and the results of these studies are summarized in Table 1. Diolide **40** did not show any appreciable antiproliferative activity (IC_{50} > 10 μM). Monocyclic peloruside A analogue **3** displayed single digit μM IC_{50} values against all three cell lines investigated. The compound, thus, is more potent in this cell line panel than its previously reported 7*S* isomer **2**,[11] although it still remains several-hundred fold less active than natural peloruside A (**1**). (IC_{50} values of 27 nM[7a] and 7-32 nM[2,7a,9] have been reported for **1** against 1A9 human ovarian carcinoma cells and HL-60 leukemia cells, respectively; the IC_{50} against the MCF-7 breast carcinoma cell line was 4.9 nM[36]). Importantly, bicyclic analogue **4** inhibits cancer cell proliferation with distinctly sub-μM activity, which makes it a significantly more potent cell growth inhibitor than either of the monocyclic analogues **2** or **3**. These findings clearly suggest a defining character of the bicyclic core structure of peloruside A (**1**) for potent cellular activity. At the same time it is clear, however, that the bicyclic system by itself is not sufficient for peloruside A-like antiproliferative activity, as **4** (with a "naked" THP ring) is still



Scheme 8. a) 2,4,6-Trichlorobenzoyl chloride, NEt_3, THF, 0 °C, 3 h; then dilution with toluene and addition of the mixed anhydride solution to a solution of DMAP in toluene (via syringe pump, over 28 h), RT, 15 h, 60 °C, 18 h, 50 %, 2:1 mixture of **36**/**37**; b) HF·py, THF, RT, 36 h, **38**: 80 %, **39**: 85 % (separable); c) Pd/C, H_2, EtOH, RT, 3 h 15 min, 77 %; d) Pd/C, H_2, EtOH, RT, 5 h, 50 %.

ca. 10-fold less potent than natural peloruside A (**1**) (based on the comparison with literature values). The relative importance of the individual oxygen substituents on the THP ring remains to be established; given the activity of **4**, however, it is well conceivable that not all of these groups are required for full activity.

Table 1. Antiproliferative activity of 7*S* desTHP-peloruside A (**2**), 7*R* desTHP-peloruside A (**3**), and 7,8,9-trideoxy-peloruside A (**4**) in three human cancer cell lines (IC_{50} values [nM]).[a]

Compound	A549 (lung)	MCF-7[b] (breast)	HCT116 (colon)
2[c]	16400	>20000	>20000
3	1390±180	2050±270	1170±100
4	124±12	247±8	163±15

[a] Cells were exposed to compounds for 72 h. [b] An IC_{50} value of 4.9± 1.2 nM against the MCF-7 cell line has been reported for peloruside A (**1**).[36] [c] Data from ref. [11].

Conclusion

The stereoselective synthesis of two new analogues of the potent mitosis inhibitor peloruside A (**1**) has been accomplished based on macrocyclization by RCM, in the case of monocyclic analogue **3**, or macrolactonization, in the case of bicyclic analogue **4**. RCM-mediated formation of the 14-membered ring in **3** was unproblematic; in contrast, macrolactone formation was surprisingly inefficient for the bicyclic system in analogue **4** and was accompanied by extensive cyclic dimer formation. Bicyclic analogue **4** inhibits cancer cell proliferation with distinctly higher potency than **3** (ca. one order of magnitude), which points to the bicyclic nature of the peloruside macrolactone core structure as a crucial determinant for sub-μM growth inhibitory activity. At the same time, trideoxy analogue **4** is still less potent than the parent natural product. It remains to be investigated if any single one of the oxygen substituents attached to the THP ring in peloruside A (**1**) may be omitted individually without an erosion of potency.

Experimental Section

For further details see Supporting Information.

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