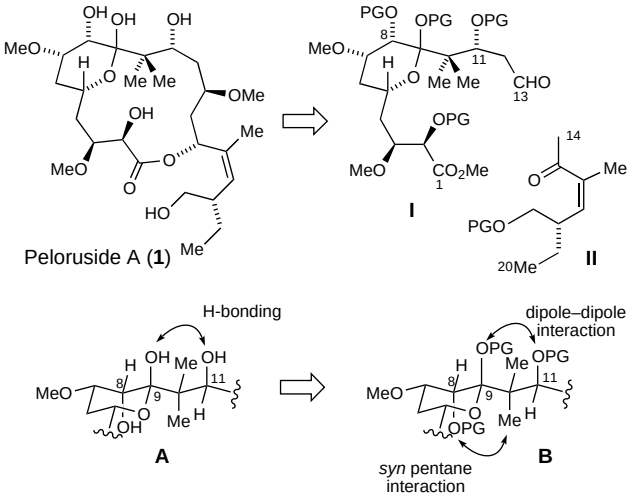

Scheme 1. Peloruside A (**1**): Structure and Strategy. PG = protecting group.

Macrolide Total Synthesis

Total Synthesis and Absolute Configuration of the Novel Microtubule-Stabilizing Agent Peloruside A**

*Xibin Liao, Yusheng Wu, and Jef K. De Brabander**

Recently, we became interested in peloruside A (**1**, Scheme 1), a marine metabolite isolated from sponge specimens of the species *Mycale* by Northcote and co-workers.[1] Peloruside A (**1**) is a potent cytotoxin and induces apoptosis in cultured mammalian cells.[2] Of potential clinical relevance is the recent observation that **1** affects microtubule dynamics in a manner similar to paclitaxel (Taxol).[2b] The relative stereochemistry of **1** was assigned based on extensive data gathered from a variety of high-field NMR experiments, although the absolute configuration remained to be solved. In addition to the presence of an array of ten stereogenic centers and a *Z*-configured trisubstituted olefin, we anticipated that one of the main challenges of a peloruside synthetic venture would be to find an efficient solution to the sterically crowded C8–C11 unit. In the solution-phase structure of **1**, this region adopts a conformation determined by optimal minimization of *syn* and *gauche* pentane interactions with potential intramolecular hydrogen bonding between the C9 and C11 hydroxy groups (**A**, Scheme 1). On a synthetic pathway, the introduction of the C8, C9, and C11 hydroxy functionality will by necessity introduce additional *syn* pentane and dipole–dipole interactions depending on the protection scheme used (**B**, Scheme 1). Herein, we communicate a solution to these synthetic challenges that culminates in the first total synthesis of (−)-peloruside A (**1**), and in doing so, document the absolute configuration of the natural isolate (opposite to the one shown in Scheme 1).[3]

Strategically, we opted for a late-stage aldol coupling between a fully functionalized aldehyde **I** with methyl ketone **II**. This approach is driven by the perception that access to diastereomeric seco-acids, through reduction of a common C15 ketone, will increase the odds for a successful macrocyclization by accessing two mechanistically distinct pathways, namely acylative or invertive macrolactonization. A concise, enantioselective synthesis of fragment **II** is outlined in Scheme 2. The known homoallylic alcohol **2**, prepared in enantiopure form according to an elegant procedure described by Hoveyda et al.,[4] was acylated with methacryloyl chloride followed by ring-closing olefin metathesis with Grubb's second generation catalyst **4**.[5] The resulting lactone **5** then provides a valuable entry to the *Z*-trisubstituted enone

[*] Prof. Dr. J. K. De Brabander, Dr. X. Liao, Dr. Y. Wu
Department of Biochemistry
University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Blvd, Dallas, TX 75390-9038 (USA)
Fax: (+1) 214-648-6455
E-mail: jdebra@biochem.swmed.edu

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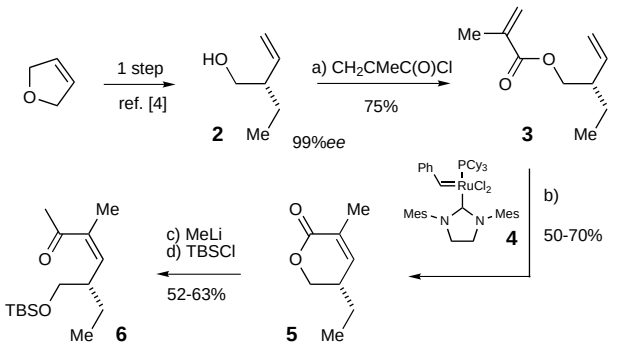
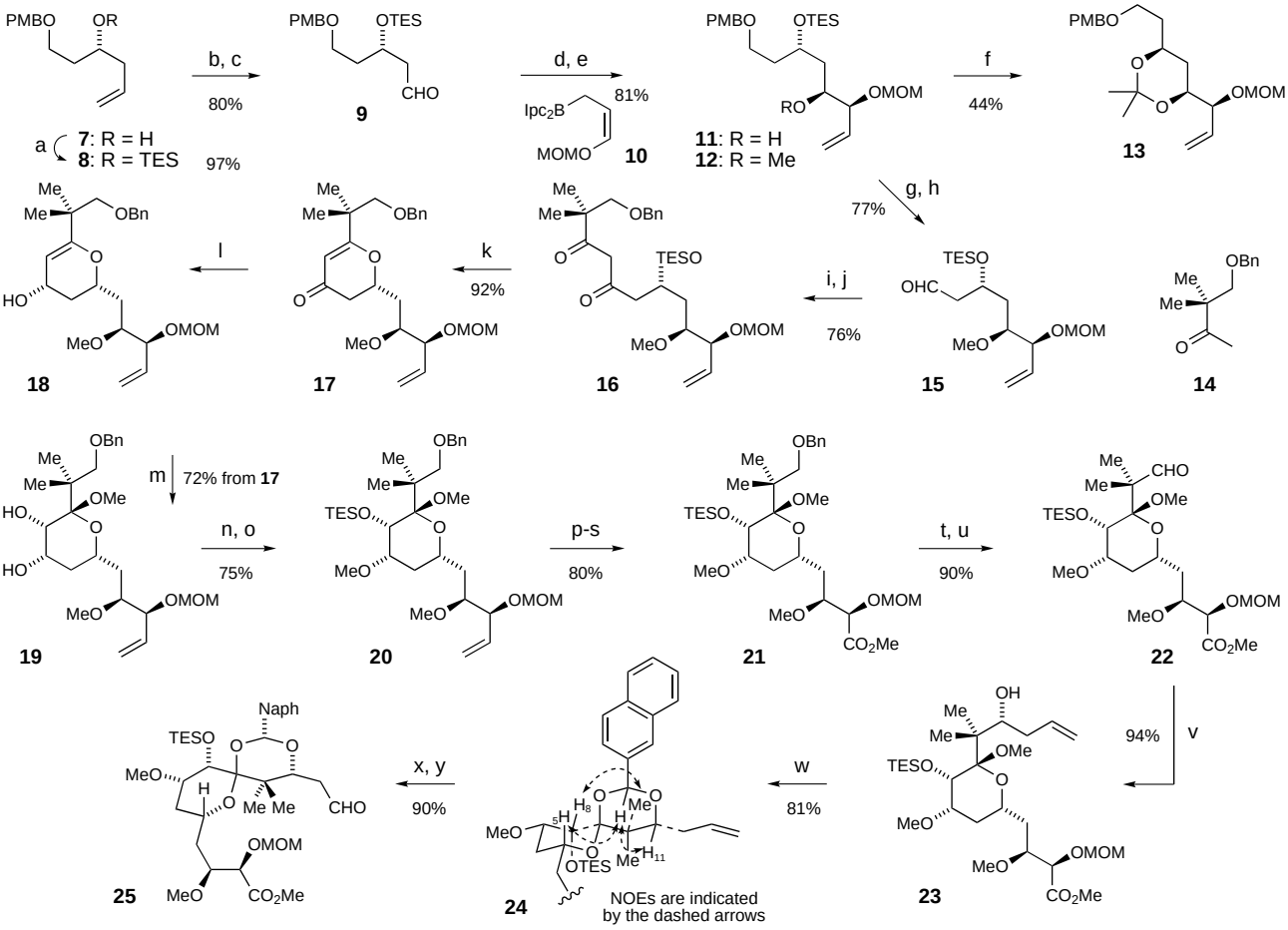


Scheme 2. a) $CH_2CMeC(O)Cl$, iPr_2NEt, DMAP, CH_2Cl_2 (75%); b) 10 mol% **4**, CH_2Cl_2 (0.0025 M), reflux, 17 h (50–70% + 20% dimer derived from **3**); c) MeLi, THF, −78 °C; or Me_3SiCH_2Li, pentane, −78 °C; d) TBSCl, imidazole, DMAP, DMF (52–63% from **5**). DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl.

6 by treatment with methyllithium and silylation of the primary alcohol.

Our approach towards the densely functionalized tetrahydropyranyl fragment is shown in Scheme 3. Addition of aldehyde **9** (derived from **7**[6] as shown) to (*Z*)-alkoxyallylborane **10** at low temperature produced the desired homoallylic alcohol diastereomer **11** (> 10:1).[7] The relative 1,3-*syn* stereochemical relationship was demonstrated by ^{13}C NMR analysis of the acetonide derivative **13** (resonances for the isopropylidene carbon atoms at $\delta = 20.0$, 30.3, and 98.8 ppm).[8] Compound **11** was advanced to aldehyde **15** by methylation (→**12**), oxidative debenzylation (DDQ), and oxidation of the resulting primary alcohol. Addition of aldehyde **15** to a cold solution of the lithium enolate derived from **14** and Dess–Martin oxidation[9] of the resulting aldol product fashioned β-diketone **16**. Transformation to dihydropyranone **17** ensued by stirring **16** in an acidic toluene



Scheme 3. a) TESOTf, 2,6-lutidine, CH_2Cl_2 (97%); b) cat. OsO_4, NMO, acetone/H_2O; c) $Pb(OAc)_4$, pyridine, CH_2Cl_2 (80% from **8**); d) **10**, *s*BuLi, THF, −78 °C, 15 min, then (+)-Ipc_2BOMe, −78 °C, 1 h, −78→0 °C, 1.5 h, then **9**, −95 °C, 3 h, slowly warm to RT; 30% H_2O_2, NaOH, 16 h (91%); e) NaH, MeI, DMF, −5 °C (89%); f) PTSA, MeOH, 20 min, remove solvent, then $Me_2C(OMe)_2$ (44%); g) DDQ, CH_2Cl_2/H_2O, 0 °C (88%); h) py·SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C (87%); i) **14**, LDA, THF, −78 °C, then **15**, −78 °C (94%); j) Dess–Martin periodinane, CH_2Cl_2, −10 °C (81% based on recovered starting material); k) PTSA, PhMe, RT (92%); l) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −30 °C; m) *m*CPBA, $NaHCO_3$, CH_2Cl_2/MeOH, 0 °C (72%, two steps); n) *t*BuOK, MeI, THF, 0 °C; o) TESOTf, 2,6-lutidine, CH_2Cl_2 (75% from **19**); p) cat. OsO_4, NMO, acetone/H_2O; q) $Pb(OAc)_4$, pyridine, CH_2Cl_2; r) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, *t*BuOH/H_2O; s) CH_2N_2, Et_2O, 0 °C (80% from **20**); t) H_2, Pd/C (10%), MeOH (quant.); u) py·SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C (90%); v) allylBEt_2, Et_2O, −10 °C (94%); w) TESOTf, 2-naphthaldehyde, −78 °C, then 2,6-lutidine, TESOTf, 0 °C (81%); x) cat. OsO_4, NMO, acetone/H_2O; y) $NaIO_4$ on silicagel, CH_2Cl_2 (90% from **24**). PMB = *p*-methoxybenzyl, TES = triethylsilyl, Tf = trifluoromethane sulfonate, NMO = 4-methylmorpholine-*N*-oxide, MOM = methoxymethyl, Ipc = isopinocampheyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LDA = lithium diisopropylamide, PTSA = *p*-toluenesulfonic acid, *m*CPBA = *m*-chloroperbenzoic acid.

solution. It proved critical to perform the subsequent Luche[10] reduction (→**18**) at −30 °C to prevent decomposition. Most satisfactorily, hydroxy-directed epoxidation of crude **18** followed by in situ methanolysis of the incipient glycal–epoxide produced one single glycoside, **19**, in high yield (72 % from **17**).[11] Sequential methylation (equatorial OH)/silylation (axial OH) of the α-diol (→**20**), oxidative transformation of the double bond to a C1 carboxylic acid, and diazomethane treatment furnished methyl ester **21**. Access to the aldehyde **22** by hydrogenolytic removal of the benzyl ether and oxidation set the stage for progression through C11–C12 bond formation. Concerns related to the feasibility of this critical event[12] seemed justified when various attempts to add carbon nucleophiles to the sterically demanding aldehyde **22** failed.[13] Ultimately, a highly efficient allyl transfer was achieved with allyldiethylborane. Remarkably, a single alcohol diastereomer, **23**, was produced with C11 configuration ascertained by NOE analysis of spirocyclic ketal **24** and advancement of **23** to peloruside A (see below).[14]

With fragments **6** and **25** (derived from **24** as shown) at hand, their union and completion of the peloruside macrocycle seemed an attainable goal, yet unexpected surprises lay ahead (Scheme 4). Mukaiyama-type aldol reaction of aldehyde **25** with the enol silane derived from methyl ketone **6** afforded almost exclusively (14:1) the compound that was assumed to be the expected 1,3-*anti* aldol product based on extensive literature precedent.[15] Evidence provided below, however, indicates that aldehyde **25** entered this reaction with an unprecedented bias for the formation of the 1,3-*syn* β-hydroxy ketone **26** instead (80 % yield). Initially unaware of this stereochemical outcome, we continued with methyl ether formation (→**27**), CBS reduction,[16] and ester hydrolysis to reach seco-acid **28**. Slow addition of this compound to a premixed solution of PPh_3 and diisopropylazodicarboxylate instigated formation of macrolactone **29** in 40–50 % yield.[17] We were able to deduce the stereochemistry of **29** based on a series of NOE correlations that locate H11, H13, and H15 on the same upper side of the macrolactone ring in agreement with the assigned C13(*S*) configuration (Figure 1). At this point, we were left with the obvious challenge of correcting the stereochemistry at C13. Various attempts to remove the (2-naphthyl)methylidene acetal failed.[18] Undeterred, we embraced the opportunity to explore a more attractive avenue that would eliminate this protecting group problem altogether, that is, we decided to advance materials with a free C11 alcohol through the remainder of the synthesis.

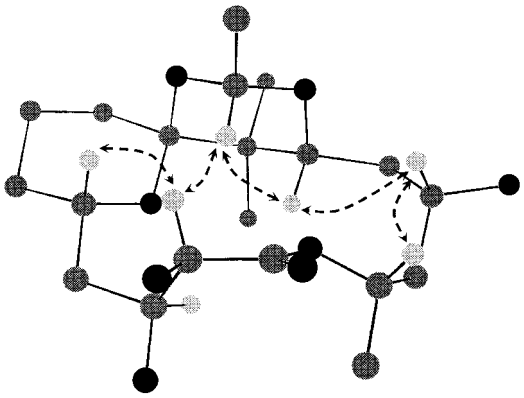
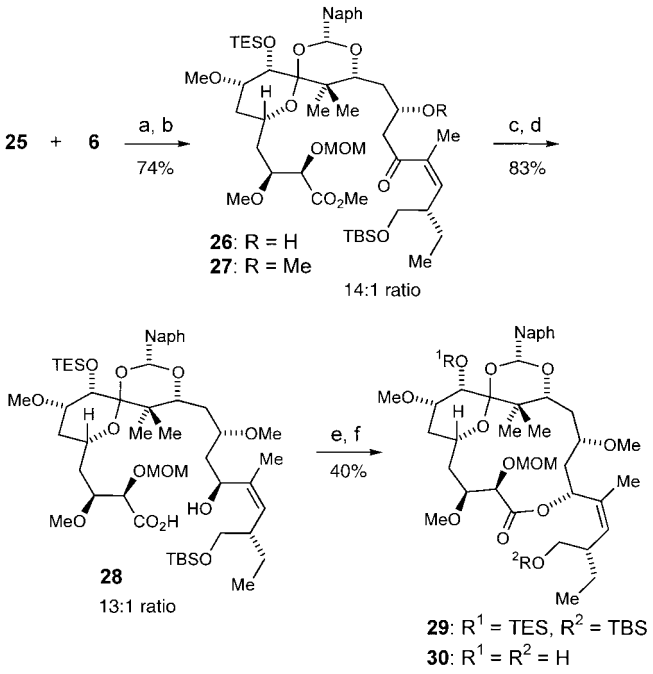
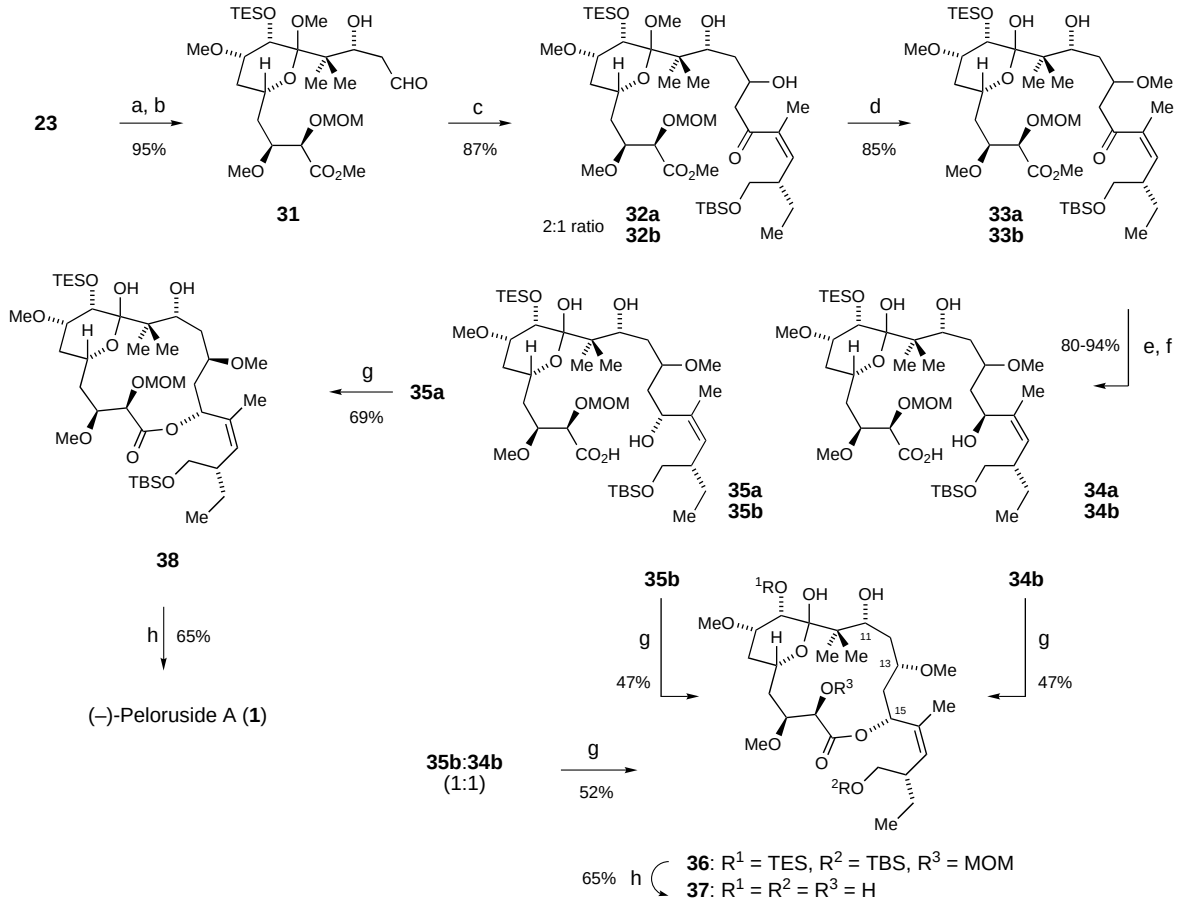


Figure 1. Chem3D representation of **29** (C in dark gray, H in light gray, and O in black). Important NOEs are illustrated with dashed arrows.



Scheme 4. a) Enolsilane derived from **6** (TMSOTf, Et_3N, CH_2Cl_2, −10 °C, 25 min, aqueous extraction), **25**, CH_2Cl_2, −78 °C, add $BF_3{\cdot}Et_2O$, 2 h (80 %, 14:1 ratio); b) Me_3OBF_4, 1,8-bis(dimethylamino)naphthalene, CH_2Cl_2, RT (92 %); c) (*S*)-*B*-Me-CBS (20 equiv), $BH_3{\cdot}SMe_2$ (7 equiv), CH_2Cl_2, −30 °C, 1 h, →RT (4 h), add MeOH (83 %, 13:1 ratio); d) 0.3 N aq. LiOH, THF, RT (quant.); e) PPh_3, DIAD, THF (0.05 M), RT, 15 min, add **28** (0.003 M in THF) through syringe pump over 2 h, 1 h at RT (40–50 %); f) 48 % aq. HF, $MeCN/H_2O$, RT, 20 h (88 %). TMS = trimethylsilyl, CBS = catalyst named after Corey, Bakshi, and Shibata, DIAD = diisopropylazodicarboxylate.

As illustrated in Scheme 5, β-hydroxy aldehyde **31** (derived from **23** as shown) was a viable partner for coupling with the enolborinate derived from **6**. Most gratifyingly, a separable 2:1 mixture of C13 epimers (**32a**/**32b**) was generated in 87 % yield. This rather unselective reaction was welcomed when contrasted with the situation described above (cf. **25** + **6** → **26**). At this stage, we left the stereochemical assignment unresolved, and advanced both isomers **32a**/**32b** individually. Surprisingly, methylation of these compounds occurred with concomitant hydrolysis to the C9 hemiketals **33a**/**33b**. We did not reprotect these materials but instead positioned ourselves to explore, in line with our original conception, two mechanistically distinct macrocyclization pathways. Intramolecular acylation through an active ester intermediate required access to the C15(*R*)-configured seco-acids **35a**/**35b**, while Mitsunobu-type lactonization would initiate from the C15-epimeric relatives **34a**/**34b**. These requirements were best fulfilled by asymmetric reduction of enones **33a**/**33b** by using (*S*)- or (*R*)-*B*-Me-CBS-oxazabor-



Scheme 5. a) Cat. OsO_4, NMO, acetone/H_2O; b) $Pb(OAc)_4$, pyridine, CH_2Cl_2 (95% from **23**); c) **6**, iPr_2NEt, Et_2BOTf, CH_2Cl_2, −78°C, 15 min, −30°C, 45 min, −78°C, add **31**, −78°C, 2 h (87%, 2:1 ratio); d) Me_3OBF_4 (20 equiv), 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, RT (85%); e) **33a** or **33b**, (*R*)- or (*S*)-*B*-Me-CBS (20 equiv), $BH_3{\cdot}SMe_2$ (7 equiv), CH_2Cl_2, −30°C, 1 h, →RT (4 h), add MeOH (**34a**: 80%, **34b**: 80%, **35a**: 94%, **35b**: 80%); f) 0.3 N aq. LiOH, THF, RT (quant.); g) PPh_3, DIAD, THF (0.05 M), RT, 15 min, add seco-acid (0.003 M in THF) through syringe pump over 2 h, then 1 h at 0°C (**36**: 47% from **34b** or **35b**, 52% from ≈1:1 mixture of **34b**:**35b**, **38**: 69% from **35a**); h) 4 N HCl, THF, RT, 3 h (**37**: 65%, **1**: 65%).

olidine and $H_3B{\cdot}SMe_2$ (80–94% yield, ratios $>12{:}1$).[16] Note that no concomitant reduction of the C9 hemiketal was observed under these conditions! The corresponding carboxylic acids **34a**,**b**/**35a**,**b** were liberated by saponification.[19]

Since the C15 configuration could not be unambiguously inferred from the Corey model,[16] we explored both epimers **34b** and **35b** as substrates for a Mitsunobu-type macrolactonization, Remarkably, the same lactone **36** was produced from either **34b**, **35b**, or an equimolar mixture of both.[20] This lactone was later shown to have a C13 epimeric relationship to peloruside A (see below).[21] To the best of our knowledge, this represents the first documented case of a configuration-dependent mechanistic switch for a Mitsunobu lactonization.[22] We speculate that geometrical/conformational constraints preclude the formation of C15 epimeric lactones[23] and enforce the cyclization of substrate **35b** via an acyloxyphosphonium intermediate (retention) and **34b** via the familiar alkoxyphosphonium intermediate (inversion).[24,25]

The structure of **36** was assigned retrospectively,[21] that is, after the completion of peloruside A (**1**) from precursor **35a**. Initial evidence for a C13 epimeric configuration surfaced, however, when the ^1H NMR data of the deprotected lactone **37** (aq. HCl/THF) did not match those reported for the natural product. By inference, we realized peloruside A would fortuitously derive from the major aldol diastereomer **32a**. In the event, Mitsunobu lactonization of **35a** (69%) followed by simultaneous cleavage of the MOM and silyl protecting groups in lactone **38** (65%), did produce a pure compound (**1**) with spectroscopic properties (^1H and ^{13}C NMR, IR, HRMS) identical to those of the natural isolate.[1] However, the optical rotation of synthetic peloruside A (**1**) was of opposite sign ($[\alpha]_D^{23} = -16$; $c = 0.12$ in CH_2Cl_2) to the one reported for the natural product ($[\alpha]_D^{20} = +16$; $c = 0.30$ in CH_2Cl_2).[1] Also, synthetic **1** (up to 10 μM) had no effect on the growth of cultured human tumor cell lines (SK-MEL-5, HeLa).[26] Based on these results, we assign the absolute configuration of natural (+)-peloruside A as 2*S*, 3*R*, 5*R*, 7*R*, 8*R*, 9*R*, 11*S*, 13*S*, 15*S*, 18*R*.

In summary, we accomplished the first total synthesis of (−)-peloruside A and documented the absolute configuration of the dextrorotatory natural product. The advancement of minimally protected intermediates merits recapitulation, and was key to a successful endgame. A particularly noteworthy configuration-dependent mechanistic switch was observed

when epimeric seco-acids **34b**/**35b** were subjected to typical Mitsunobu lactonization conditions. Current efforts focus on gaining additional insights into the mechanistic aspects of this reaction, and the synthesis of naturally configured peloruside and tailored derivatives for structure–function studies.

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Keywords: antitumor agents · configuration determination · cyclization · natural products · total synthesis

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[18] We have explored a variety of solvolytic (protic or Lewis acid mediated), oxidative, and reductive pathways. Other protecting group schemes (cyclic and acyclic) were briefly investigated with no indication for success. Details will be included in a later disclosure.

[19] Reesterification with CH_2N_2 demonstrated that no epimerization had occurred. The *Z* configuration of the double bond was maintained throughout the synthesis and verified by NOE interactions.

[20] No diastereomeric or transposed (allylic) macrolactones were detected by NMR analysis of the nonpurified mixture.

[21] Clues about the stereochemistry of **36** were provided at this point by virtue of mutual NOE enhancements between the H11–H13 and H13–H15 proton pairs (cf. **29**).

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[25] A referee rightfully pointed out that our observations could also be explained by invoking a diastereoselective S_N1 reaction mechanism for the Mitsunobu lactonization with allylic alcohols. We had tentatively ruled out this possibility because we have not been able to detect[20] any products expected to derive to some extent from allylic carbocation intermediates (allylic transposition, double bond isomerization, elimination). For a reference pertinent to this issue, see: B. K. Shull, T. Sakai, J. B. Nichols, M. Koreeda, *J. Org. Chem.* **1997**, *62*, 8294 – 8303, and references therein.

[26] We are grateful to Dr. Michael G. Roth and Maria G. Kosfiszer (UT Southwestern Medical Center) for assistance with the cell-based assays.

