Natural Products

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Total Synthesis of Peloruside A through Kinetic Lactonization and Relay Ring-Closing Metathesis Cyclization Reactions**

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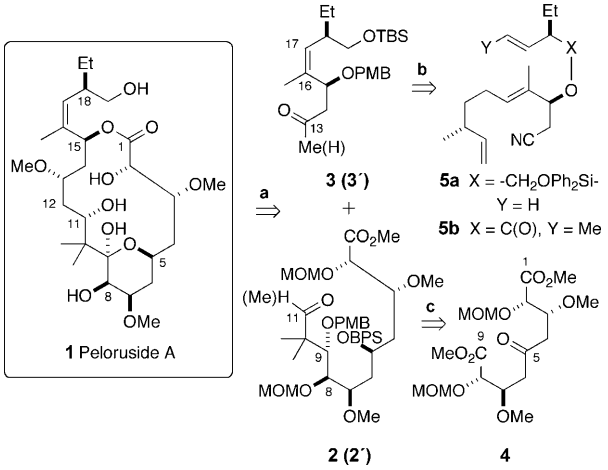
The highly cytotoxic marine macrolide (+)-peloruside A (**1**) was isolated from the New Zealand sponge *Mycale hentscheli* by Northcote and co-workers.[1] It showed LD_{50} values ranging from 6–18 nM toward H441, SH-SY5Y, and P388 cancer cell lines,[2] and has been additionally explored from a preclinical perspective. Like paclitaxel (Taxol), peloruside A is a microtubule stabilizer that arrests cells in the G2M phase of the cell cycle, but it targets a different tubulin binding site relative to paclitaxel.[3] As a consequence peloruside A (**1**) is a candidate for use against paclitaxel-resistant cell lines.[4] The therapeutic potential, low natural abundance (3 mg/170 g wet sponge), and architectural complexity have generated significant interest in the development of chemical syntheses of **1**. To date, four total syntheses of peloruside A have been reported by the research groups of De Brabander, Taylor, Ghosh, and Evans,[5–8] and related synthetic studies have been described.[9–11]

Our interest in peloruside A (**1**) as a target was greatly heightened when we identified a plan that seemed ideally matched with strategies and technologies developed earlier in our group. In particular, it was attractive to apply a diastereoselective kinetic lactonization of a pseudosymmetric azelaic acid derivative[12] and to capitalize on the versatility of relay ring-closing metathesis (RRCM)[13] reactions.

As summarized in Scheme 1 our plan for the synthesis was to effect a late-stage aldol coupling (path a) between the aldehyde acceptor **2** and methyl ketone donor **3** (or the complementary ketone/aldehyde pair **2′**/**3′**). We planned to install the *Z*-trisubstituted and doubly allylically branched $\Delta^{16,17}$-alkene in **3** (or its aldehyde analogue **3′**) through RRCM (path b) of the silaketal[14] **5a** or ester[15] **5b** (peloruside A skeleton numbering is used throughout). We envisioned the main aldehyde fragment **2** (or its ketone analogue **2′**) to arise from the C_2-symmetric azelaic ester precursor **4** (path c). As detailed below, reduction of the C5 ketone in **4** from either of its homotopic faces would give an alcohol that, through engagement of its pro-*S* rather than pro-*R* diastereotopic ester group, would selectively provide a valerolactone/monoester (i.e., **11** in Scheme 2).[16] Terminus differentiation and C9–C10 bond formation would then provide access to **2** (or **2′**).



Scheme 1. Retrosynthesis outline for accessing peloruside A (**1**). a) Aldol union of C11–C12 (or C12–C13). b) RRCM. c) Desymmetrizing kinetic resolution. BPS = *tert*-butyldiphenylsilyl, MOM = methoxymethyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

The synthesis of fragment **2** is presented in Scheme 2. The main features are: 1) synthesis of the C_2-symmetric ketodiester **4**, 2) diastereoselective conversion, by desymmetrizing kinetic lactonization, of the derived alcohol **9** into the δ-valerolactone **11**, and 3) chemoselective elaboration (including prenylation) of the lactone versus ester carbonyl groups (C9 versus C1) in **11** to give fragment **2**.

The tetrol **7** was prepared from the ethylene ketal of dimethyl acetone dicarboxylate (**6**)[17] by utilizing a one-pot DIBAL-H reduction of both esters to give the intermediate 1,5-dialdehyde, and subsequent in situ double Horner–Wadsworth–Emmons homologation with $(EtO)_2P(O)CH(Na)CO_2{}^nHex$.[18] The double Sharpless asymmetric dihydroxylation (SAD)[19] of the bis(methyl) ester analogue was initially studied,[16] but this transformation was plagued by incomplete conversion into the bis(methyl)ester variant of tetrol **7**. No-D (no deuterated solvent) ^1H NMR analysis[20] of the aqueous component of the biphasic mixture indicated the accumulation of the intermediate alkenediol. The polar nature of this half-oxidized intermediate likely led to its undesired partitioning into the aqueous layer and, consequently, away from the active hydroxylation species. The substantial water solubility of the desired tetrol was an additional complication. This prompted our selection and use

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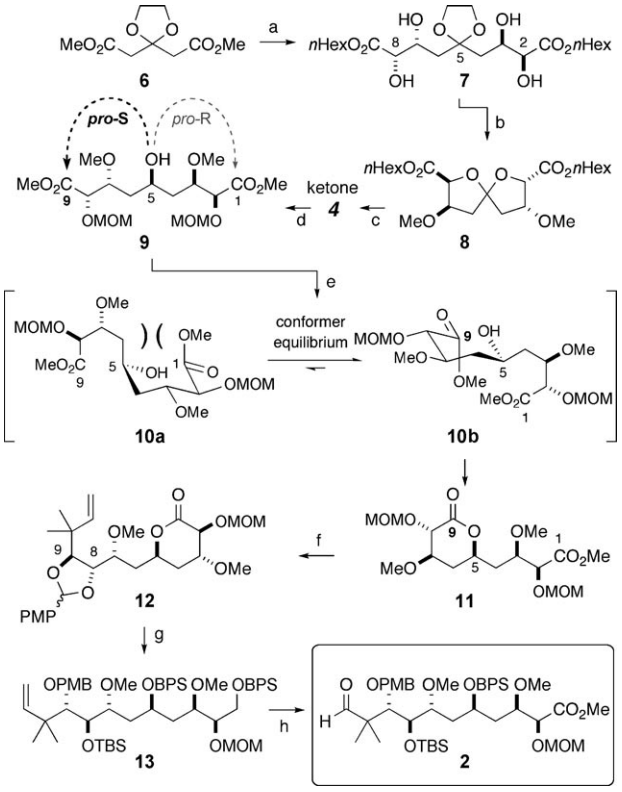


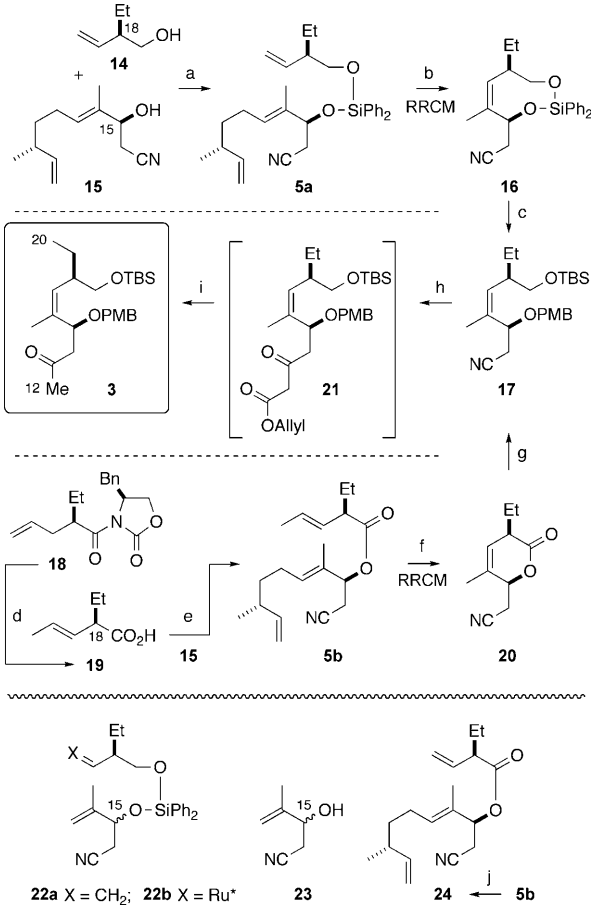
Scheme 2. Synthesis of main fragment **2** via the key diastereoselective lactonization of pseudosymmetric carbinol **9**. Reagents and conditions: a) 1. DIBAL-H, Et_2O, −78 °C; then $(EtO)_2P(O)CH(Na)CO_2nHex$, 80%; 2. SAD, 0 °C, 88%; b) 1. 30 mol% HI, THF, 0 °C, 83%; 2. Me_3OBF_4, proton sponge, 0 °C to RT, 84%; c) 1. 1,2-ethanedithiol, $BF_3{\cdot}OEt_2$, 0 °C; 2. MOMCl, iPr_2NEt, CH_2Cl_2, RT, 90% (2 steps); 3. I_2, $NaHCO_3$, acetone, H_2O, 0 °C, 91%; 4. Otera's catalyst,[22] MeOH, toluene, 90 °C, 77%; d) Raney nickel, H_2, EtOH, RT, 91%; e) TMG, C_6H_6, RT; then TFA, 98% (d.r. 12:1). f) L-Selectride, THF, −78 °C, 87%; 2. prenyl bromide, indium powder, DMF, 55 °C, 80%; 3. $AlCl_3$, NaI, CH_3CN, CH_2Cl_2, 0 °C, 92%; 4. (*p*-MeO)-PhCH(OMe)$_2$, CSA, CH_2Cl_2, M. S. (4 Å), 87%; 5. MOMCl, iPr_2NEt, CH_2Cl_2, RT, 99%; g) 1. LAH, THF, 0 °C, 96%; 2. BPSCl, ImH, DMAP, DMF, RT, 92%; 3. DIBAL-H, CH_2Cl_2, −78 °C, 95%; 4. DMP, $NaHCO_3$, CH_2Cl_2, RT; 5. $Zn(BH_4)_2$,[23] CH_2Cl_2, 0 °C (d.r. 3:1), 62% (2 steps); 6. TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 89%; h) 1. HF·pyridine, THF, pyridine, RT, 91%; 2. DMP, $NaHCO_3$, CH_2Cl_2, RT; 3. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, $Me_2C{=}CHMe$, RT; 4. CH_2N_2, RT, 87%, (3 steps); 5. O_3, pyridine, CH_2Cl_2, MeOH, −78 °C, 75%. CSA = camphorsulfonic acid, DMAP = 4-dimethylamino-pyridine, DMF = dimethylformamide, DMP = Dess–Martin periodinane, d.r. = diastereomeric ratio, ImH = imidazole, LAH = lithium aluminum hydride, M.S. = molecular sieves, OTf = triflate, SAD = Sharpless asymmetric dihydroxylation, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMG = tetramethylguanidine.

of the less polar and more well-behaved bis(*n*-hexyl)ester series, which allowed isolation of **7** in 88% yield. Exposure to a catalytic amount of aqueous hydriodic acid then promoted ketal metathesis by engagement (and protection) of the C2 and C8 hydroxy groups to give a spirocyclic ketal as a single diastereomer. Installation of the methyl ethers found at C3 and C7 in peloruside A (**1**) was achieved with Meerwein's salt to provide **8**. Transketalization of **8** with ethanedithiol ($BF_3{\cdot}OEt_2$),[21] MOM-ether protection of the C2/C8 diol, dithiolane removal (I_2, aq $NaHCO_3$), and transesterification with methanol (Otera's catalyst) smoothly gave **4** (see Scheme 1). The sequence from **6** to **4** proceeded in over 30% yield.

Although many reagents sufficed to chemoselectively reduce the C5 ketone in **4**, most were complicated by premature lactonization of the resulting hydroxy bis(ester) **9**, with not only modest but also irreproducible levels of diastereocontrol. Hence, neutral conditions for this reduction that also minimized handling of **9** were sought. Use of hydrogen gas over Raney nickel provided a convenient solution; simple filtration and solvent removal provided the C_1-symmetric alcohol **9** (91%), which contains the new nonstereogenic but chirotopic[24] C5-carbinol center. The key diastereoselective cyclization of this substrate[16] proceeded with preferential engagement of the pro-*S* ester group at C9 to give lactone **11** (98%, d.r. 12:1). Use of TMG (2.0 equiv) to promote this lactonization gave reproducibly high levels of diastereoselectivity. Interestingly, a labile adduct of TMG with the product **11**, perhaps involving a tetrahedral intermediate in which the lactone carbonyl group remained engaged with TMG, was generated. We found it best to cleave this adduct by treatment with anhydrous trifluoroacetic acid (NMR analysis) prior to aqueous workup. The sense of the kinetic diastereocontrol observed in this lactonization was anticipated[12] on the basis of conformational analysis; the equilibrium concentration of the reactive conformer **10a**, which could engage the C1 ester and lead to the minor (and undesired) C5 epimer of **11**, should be lower than that of the alternative reactive conformer **10b**, a necessary intermediate en route to **11**. Analogous considerations equally apply to the pair of tetrahedral intermediates derived from **10a** and **10b**, should it be the case that the rate-limiting step in the lactonization is not the initial closure implied by **10**. A distinguishing feature of this symmetry enabled approach is the rapidity and efficiency with which the C1–C9 portion of the peloruside skeleton was established.

Chemoselective reduction of the lactone rather than ester functional group in **11** was achieved with L-Selectride[25] to provide a lactol, which was treated with prenyl bromide/indium.[26] This sequence installed the gem-dimethylated C10 moiety, while simultaneously inducing relactonization, now of the C5–OH with the C1 ester.[25] Use of the prenyl unit was designed to permit potential access to either the aldehyde **2** or methyl ketone **2′**, but as things later developed, implementation in the former role proved more valuable. Removal of the two MOM groups ($AlCl_3$, NaI), PMP acetal formation, and reprotection of the C2–OH as a MOM ether gave **12** as a single epimer at C9 (assigned to be of *S* configuration,[27] consistent with α_{MOM}-chelation controlled addition). A series of functional/protecting group manipulations (see g); Scheme 2) served to carry **12** efficiently to **13**, the precursor to fragment **2**. Key among these was the oxidation/reduction of the C8 carbinol, which had just been revealed by a highly regioselective reductive cleavage by DIBAL-H of the PMP acetal, to effect the required inversion of configuration at C8. Finally, but again efficiently, the C1 methyl ester was reinstated and the C11 aldehyde generated by ozonolysis (see h; Scheme 2) to complete the synthesis of **2**.

To explore a metathesis-based synthesis of the hindered *Z* alkene in **3** (Scheme 3), we first prepared and examined the RCM reaction of the simple diene[14] **22a** (Scheme 3), which was an epimeric mixture at C15. This diene proved to be a poor RCM substrate (e.g., < 20% yield of **16** using 45 mol% of **G2**).[28] We turned to the RRCM substrate **5a**,[29] which was made by sequential loading of the alcohols **14**[13] and **15** onto Ph_2SiCl_2. RRCM proceeded to give **16** in 92% yield. For the preparation of **5a** as essentially one diastereomer, enantiomerically enriched β-hydroxynitrile **15** was accessed by addition of lithioacetonitrile to the enal derived from allylic oxidation (SeO_2) of (*R*)-citronellene, and subsequent enzymatic (kinetic) resolution of the resulting C15-epimeric carbinols (Novozyme 435).[13,30] An added advantage of adopting the RRCM strategy here was that the two epimeric carbinols (**15** and C15-*epi*-**15**) were easily discriminated by the lipase, thereby allowing efficient resolution; the alternative substrate **23**, the precursor to **22a**, has two nearly isosteric groups and was a poor substrate for lipase resolution.



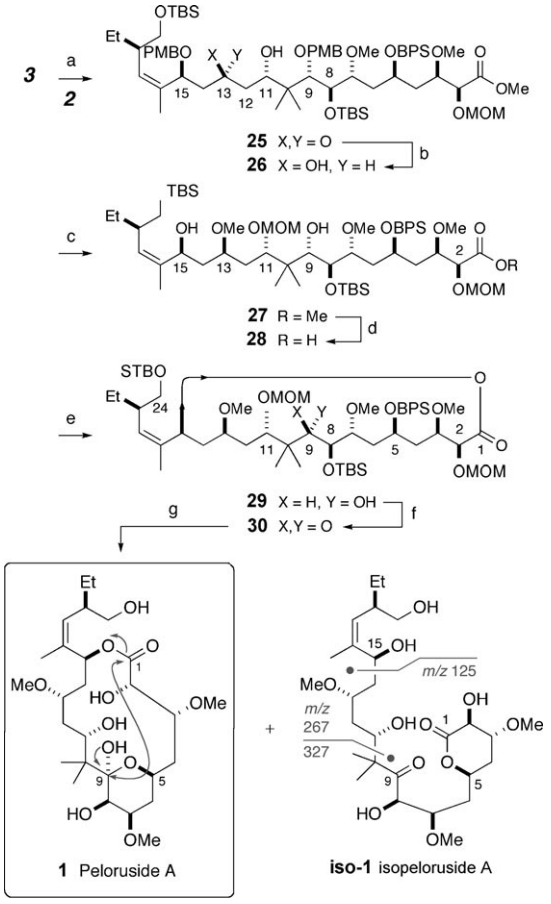
Scheme 3. Synthesis of fragment **3** through the relay ring-closing metathesis reactions of substrates **5a** and **5b**. Reagents and conditions: a) 1. **15**, Ph_2SiCl_2, pyridine, RT; 2. **14**, pyridine, 41%; b) **G2**, toluene, N_2, 65°C, 92%; c) 1. TBAF, THF, RT, 93%; 2. TBSCl, Et_3N, DMF, RT, 84%; 3. $Cl_3CC(=NH)OPMB$, CSA, CH_2Cl_2, RT, 76%; d) 1. $RhCl_3 \cdot 3H_2O$, EtOH/H_2O (10:1), 80°C, 98% (*E*/*Z* = 15:1); 2. LiOH, H_2O_2, THF/H_2O (3:1), 0°C, 99%; e) **15**, DCC, DMAP, CH_2Cl_2, 0°C to RT, 82%; f) **G2**, CH_2Cl_2, 45°C, 70%; g) 1. $NaBH_4$, AcOH, EtOH, 0°C to RT, 82%; 2. TBSCl, Et_3N, DMAP, CH_2Cl_2, RT, 99%; 3. $Cl_3CC(=NH)OPMB$, CSA, CH_2Cl_2, RT, 77%; h) 1. Zn^0, Cp_2TiCl_2, allyl 2-bromoacetate, THF, 60°C; 2. pH 3 buffer, *i*PrOH/H_2O/THF (4:1:2), RT; i) $[Pd(PPh_3)_4]$, HCO_2H, Et_3N, THF, RT, 61% (3 steps). j) $CH_2{=}CH_2$ (15 psi), **G2**, PhH, 65°C, quantitative. Cy = cyclohexyl, **G2** = second-generation Grubbs initiator, [Ru = CHPh(Cl)$_2$(PCy$_3$)(H$_2$IMes)], Ru* = [Ru(Cl)$_2$(H$_2$IMes)L$_n$], IMes = *N*,*N*′-bis(mesityl)imidazol-2-ylidene, TBAF = tetrabutylammonium fluoride, DCC = dicyclohexylcarbodiimide.

A complementary approach involving the ester **5b** and its RRCM product, the lactone **20**, was also studied. Preparation of **5b** is inherently easier than that of the silaketal **5a**, since it involves simple cross-coupling of two functional groups with complementary reactivity, namely the alcohol **15** with the acid **19**. Moreover, a sample of nonracemic **19** proved to be easier to access than one of **14**. The terminal alkene in the 2-propenylated compound **18**[31] was efficiently isomerized to the more stable, internal, 1-propenyl analogue using $RhCl_3$/EtOH;[32,33] there was no evidence of erosion of the high d.r. value, which implies that the branched α carbon effectively impedes additional isomerization by β-hydride elimination of the C_α-methine hydrogen atom. This sequential allylation/2- to 1-propenyl isomerization/ethylene cross-metathesis degradation[34] resulted in net vinylation of, in this instance, an Evans acyloxazolidinone auxiliary (i.e., **24**). We recommend consideration of this strategy in instances when ethenylation of carbanionic species is needed. Hydrolysis of the oxazolidinone **18** gave the acid **19**, which upon DCC activation was coupled with **15** to provide **5b**. This ester smoothly underwent RRCM to give lactone **20** in 70% yield.

Efficient elaboration of either **16** or **20** into the differentially protected diol derivative **17** was straightforward with either desilylation (of **16**) or reduction (of **20**) and sequential TBS and PMB installations on the promary and secondary hydroxy groups, respectively. The choice of sodium borohydride in acetic acid as the reagent for the reduction of **20** was dictated by its base lability, which otherwise led to epimeric mixtures of the reduced diol product. Base instability was an even bigger obstacle in the final conversion of the nitrile in **17** into the methyl ketone in fragment **3**. A solution emerged in the form of a modified Blaise reaction, wherein the reagent formed in situ from $BrCH_2CO_2allyl/Zn^0/Cp_2TiCl_2$[35] converted the nitrile into an intermediate β aminoenoate, the hydrolysis of which was carefully monitored at pH 3 (ca. 2 days) to afford the β-ketoester **21**. Attempts to effect hydrolysis or dealkylation and decarboxylation of the methyl ester analogue of **21** into **3** were compromised by competitive β elimination of PMB-OH. We solved this complication by use of the allyl ester **21**, which could be smoothly decarbalkoxylated with $[Pd(PPh_3)_4]$ (HCO_2H, Et_3N).[36] The non-basic conditions associated with this conversion of nitrile into methyl ketone render this strategy applicable to other base-sensitive nitrile substrates.

The final stage of the synthesis is presented in Scheme 4. The main features are 1) the Paterson boron aldol coupling[37] of fragments **2** and **3**, 2) the regioselective macrocyclization of the diol acid **28**, and 3) the removal of protecting groups from the penultimate intermediate **30**, including our observation of a by-product that we name here isopeloruside A (**iso-1**).

A number of model experiments designed to establish the feasibility of either the **2′**/**3′** or **3**/**2** aldol donor/acceptor



Scheme 4. Synthesis of peloruside A (**1**) by aldol coupling of fragments **2** and **3**, macrolactonization of seco-acid **28**, and deprotection. Reagents and conditions: a) *c*Hex_2BCl, Et_3N, **3**, Et_2O, −78 °C to −40 °C; then **2**, Et_2O, −78 °C to −20 °C, 64% (along with 34% of recovered **3**); b) $NMe_4BH(OAc)_3$, AcOH/MeCN (1:1), −30 °C, 95% (d.r. 95:5); c) 1. Me_3OBF_4, 2,6-di-*t*Bu-pyridine, CH_2Cl_2, 0 °C to RT, 82% (after two cycles); 2. MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0 °C to RT, 98%; 3. DDQ, CH_2Cl_2/pH 7 buffer (1:1), 0 °C to RT, 94% (after two cycles); d) LiOH, H_2O_2, THF/MeOH/H_2O (3:1.5:1), 0 °C to RT, ca. 100%; e) 2,4,6-trichlorobenzoyl chloride, *i*Pr_2NEt, toluene, 0 °C to RT; DMAP, $PhCH_3$, RT, 54%; f) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 83%; g) 1. HF·py, THF, py, RT to 60 °C; 2. HCl (4 N), THF, RT; 49% **1** and 5% **iso-1** (2 steps). py = pyridine.

pairing were carried out.[38] These eventually guided us to the use of the dicyclohexylboron enolate derived from ketone **3**, which added to the aldehyde **2** (1.0 equiv, −78 to −20 °C) to form the C11–C12 bond and produce the ketoalcohol **25** (64%) with essentially full control of the configuration at C11. Presumably, the 1,5-stereoinduction keyed by the β(C15) stereocenter in the ketone donor **3**[39] is enhanced by (i.e., matched with) that from the β(C9) stereocenter of the α,α-gem-dimethylated aldehyde acceptor **2**[40] to impart essentially perfect diastereoselection during this powerful cross-coupling reaction.[41] Reduction of the C13 ketone with $Me_4NBH(OAc)_3$ proceeded to give the 1,3-*anti*-diol **26** (d.r. 95:5). Methylation with Meerwein's salt proceeded with near perfect regioselectivity. Installation of a MOM ether at C11 and removal of both PMB ethers at C9 and C15 proceeded smoothly to complete the preparation of **27**.

Conversion of the methyl ester in **27** into the acid **28**, in preparation for the required macrolactonization, was very slow with LiOH (aq MeOH) and was complicated by partial epimerization at C2 when $KOSiMe_3$ (THF) was employed. These issues were solved by use of the more reactive and less basic LiOOH. Yamaguchi cyclization of the diol acid substrate **28** was uneventful; the free C9-hydoxy group gave no evidence of interference (lactonization substrates in all previous peloruside A syntheses and studies have had the ketone oxidation state at C9). Oxidation of **29** into the C9-ketone **30** was smoothly effected with the Dess–Martin periodinane.

The silyl ether and MOM ether protecting groups were sequentially removed by treatment first with HF·pyridine in THF, buffered by additional pyridine, and second with 4 N aqueous HCl in THF (room temperature). The first stage (removal of three silyl groups) was monitored by LC/MS analysis. The primary C24–OH was generated quickly at room temperature, the C5 *tert*-butyldiphenylsilyl ether (OBPS) was cleaved in about a day at 60 °C, and the hindered C8–OTBS required an additional day to completely release the C5/C8/C24 triol (having the C5–OH engaged to C9 as a hemiketal). Even though it required strongly acidic conditions (aq HCl, RT), the removal of the final MOM group was planned with confidence, given the precedent from the earlier total syntheses. Without additional purification, the C5/C8/C24 triol was treated with aq HCl at room temperature for 3 hours to deliver (+)-peloruside A (**1**) in 49% overall yield from **30** (over 2 steps). We also observed and isolated (by careful chromatography on SiO_2, $MeOH/CH_2Cl_2 = 5:95$) a minor (5%) and slightly more polar by-product formed during this experiment. We deduced its structure as that of the valerolactone derivative **iso-1** based on ^1H NMR and ESI MS/MS analyses. The masses of fragments observed from the latter (and indicated on the structure of **iso-1** in Scheme 4) were informative in suggesting the absence of a macrolactone in this new isomeric substance. In particular, the fragmentation of the C10–C11 bond through a retro-aldol reaction was evidenced by the complementary pair of sodiated ions at *m/z* 327 and 267 and additional cleavage of the C14–C15 bond in the latter gave the ion observed at *m/z* of 125. Additionally, ^1H NMR data of **iso-1** bore strong similarities with the earlier described valerolactone **12**. Isopeloruside A (**iso-1**) presumably arose from intramolecular translactonization within **1** by the C5-hydroxy group in the minor [and unobserved (^1H NMR)] open form of the C9 hemiketal to the C1-carbonyl group.

In conclusion this total synthesis of peloruside A (**1**) capitalizes on the kinetic lactonization reaction of the pseudosymmetric azelaic acid derivative **9** (to **11**, Scheme 2) and a relay ring-closing metathesis reaction to access the trisubstituted $\Delta^{16.17}$-alkene subunit (**5b** to **20**, Scheme 3). Modified Blaise and net enolate ethenylation sequences are also noteworthy. Formation of the isomeric valerolactone **iso-1** during final HCl-catalyzed removal of the MOM ethers at C2 and C11 was observed for the first time.

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[41] Interestingly, Evans et al. reported that the oxidation state of C9 strongly influenced the diastereoselectivity and yield of boron-mediated aldol coupling between substrates quite similar to acceptor aldehyde **2** and donor ketone **3**. "For example, the reaction does not proceed if the C9-carbonyl group is reduced and protected."[8] The contrasting behavior we observed in the successful aldol union of **2** with **3**, the former containing a PMB-protected hydroxy group at C9, points to additional, likely yet longer-range, structure–reactivity subtleties in the powerful aldol cross-coupling[35] strategy.

