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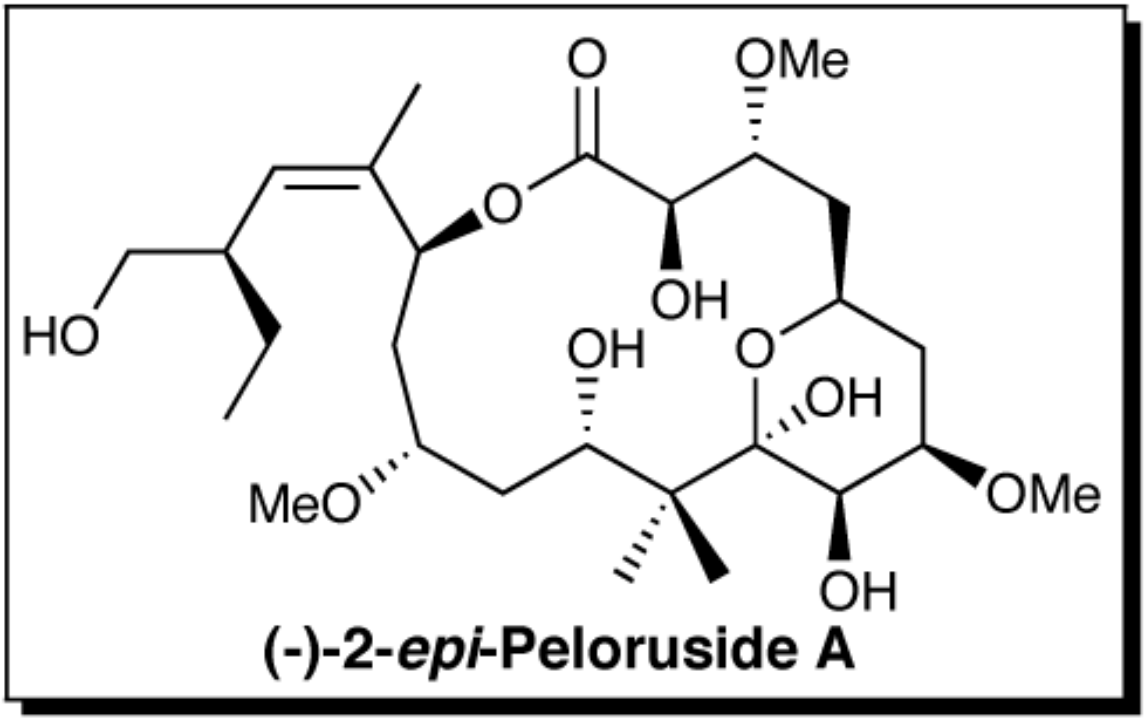
Total Synthesis of (-)-2-*Epi*-Peloruside A

Amos B. Smith III*, **Jason M. Cox**, **Noriyuki Furuichi**, **Craig S. Kenesky**, **Junying Zheng**, **Onur Atasoylu**, and **William M. Wuest**
Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania, 19104

Abstract



A convergent synthesis of (-)-2-*epi*-Peloruside A has been achieved. Highlights include implementation of multicomponent Type I Anion Relay Chemistry (ARC) to unite 2-TBS-1,3-dithiane with two epoxides to construct the eastern hemisphere, a late-stage dithiane union to secure the complete, fully functionalized carbon backbone, and Yamaguchi macrolactonization, which led to (-)-2-*epi*-peloruside A via an unexpected epimerization at C(2).

*E-mail: smithab@sas.upenn.edu.

Supporting Information Available Spectroscopic and analytical data for compounds **6-28** and selected experimental and computational procedures. This material is available free of charge via the internet at http://pubs.acs.org.

In 2000 Northcote and co-workers reported the isolation and relative stereochemistry of (+)-peloruside A (**1**),[1] an architecturally complex marine metabolite produced by the sponge *Mycale* (*Carmia*). Although a microtubule-stabilizing agent with potency similar to Taxol,[2] recent studies reveal that (+)-peloruside A competes competitively for the laulimalide binding site, at a newly discovered microtubule site.[3]

Our interest in (+)-peloruside A (**1**) emanated from the synthetic challenge, in conjunction with the opportunity to showcase the synthetic utility of dithiane linchpin tactics, in particular the use of the three-component union of trialkylsilyl dithianes with diverse electrophiles, a synthetic tactic we now recognize as Type I Anion Relay Chemistry (ARC).[4]

Structurally (+)-peloruside A (**1**) is comprised of 10-stereogenic centers, a *Z*-trisubstituted olefin, and a six-membered hemi-ketal ring, inscribed in a 16-membered macrolactone. Not surprisingly, the structural complexity, interesting biological activity, and scarcity, has led to considerable interest from both the chemical[5] and biological communities.[6]

In 2003, De Brabander and co-workers[7] achieved an elegant total synthesis of unnatural (−)-peloruside A, thus permitting assignment of the absolute configuration. Shortly thereafter (2005), the Taylor group[8] reported the first total synthesis of natural (+)-peloruside A, followed in 2008 by a second total synthesis from the Ghosh laboratory.[9] We report here completion of the total synthesis of (−)-2-*epi*-peluroside A (**28**, Scheme 5), the result of a surprising, late stage epimerization (*vide infra*) that procluded access to (+)-peloruside A (**1**).

Shortly after the report by Northcote and co-workers,[1] we initiated a synthetic venture directed toward the total synthesis of (+)-peloruside A (**1**).[10] Our endgame strategy called for formation of the inscribed tetrahydropyran ring after macrocyclization (Scheme 1). Central to this scenario was a flexible route that would permit either acid *or* alcohol activation to achieve macrolactonization. Taken together, (+)-peloruside A (**1**) was envisioned to arise from macrolide **2** upon removal of the dithiane and isopropylidene protecting groups. To construct the macrolactone precursor, we would employ union of a dithiane **3** with aldehyde **4**, followed by appropriate functional group adjustments.

Construction of dithiane (−)-**3** began with known homoallylic alcohol (+)-**5** (Scheme 2),[11] which was protected as the BPS-ether. Ozonolysis furnished aldehyde (+)-**6**. Installation of the trisubstituted *Z*-olefin was next achieved via a Still-Gennari modification of the Horner-Wadsworth-Emmons olefination[12] to yield ester (-)-**8** in 89% yield as a single diastereomer. Next, enal (-)-**9**, available by a two-step reduction/oxidation sequence, was subjected to a Brown asymmetric allylation[13] to generate alcohol (-)-**10** in a highly diastereoselective fashion (>20:1).[14,15] Protection of the resulting alcohol as the PMB ether, followed by selective dihydroxylation[16] of the terminal olefin and oxidative cleavage furnished (-)-**11**, the requisite aldehyde for the proposed Mukaiyama aldol.[17] Toward this end, reaction of (-)-**11** with the silyl-enol ether derived from ketone **12**[18] led to β-hydroxy ketone (-)-**13** with >20:1 diastereoselectivity at C(13).[14] Ketone (-)-**13** was then subjected to a SmI_2 promoted Evans-Tishchenko reduction[19] to generate (-)-**14**, possessing the correct stereochemistry at C(11).[14]

Completion of dithiane (-)-**3** entailed formation of the MOM-ether, reductive removal of the ethyl ester with DIBAL-H, and generation of the methyl ether. The overall sequence to (-)-**3**, the dithiane coupling partner, proved highly efficient, proceeding with a longest linear sequence of fourteen steps and in 21.4% overall yield from (+)-**5**.

Construction of aldehyde (+)-**4** was designed specifically to demonstrate the utility of our multicomponent Type I ARC protocol, employing epoxide (+)-**16**, readily prepared from known epoxide (-)-**15**[20] and epoxide (+)-**18**[21] (Scheme 3). Toward this end, addition of the lithium anion of TBS-1,3-dithiane (**17**) to epoxide (+)-**16**, followed by a solvent controlled

Brook rearrangement (HMPA) and addition of epoxide (+)-**18** furnished alcohol (+)-**19**[14] in 65% yield. Methyl ether formation, followed by removal of both the TBS and 1,3-dithiane moieties led to ketone (+)-**20**. We next called upon a hydroxyl directed 1,3-*syn* reduction,[22] followed in turn by acetonide formation[23] and removal of the benzyl ether via hydrogenolysis to generate alcohol (+)-**21**. Completion of (+)-**4**, the aldehyde coupling partner, was achieved in five steps. First, alcohol (+)-**21** was converted via a three-step sequence to the corresponding methyl ester, and then subjected to oxidative removal of the PMB moiety to provide (-)-**22**. Parikh-Doering oxidation[24] of the resultant terminal hydroxyl then furnished aldehyde **(+)-4** in 87 % yield. The synthesis of (+)-**4** also proved efficient, proceeding with a longest linear sequence of thirteen steps and in 12.9% overall yield from (-)-**15**.

With advanced coupling fragments (-)-**3** and (+)-**4** in hand, we turned to their union (Scheme 4). Reaction of the lithium anion derived from dithiane (-)-**3**, with aldehyde (+)-**4**, in the presence of HMPA, led to alcohol (-)-**23** as a mixture at C(8) favoring the desired isomer (ca. 9:1) presumably under Felkin-Anh control[25]. Importantly, union of (-)-**3** and (+)-**4** furnished the complete, stereochemically correct, carbon backbone of (+)-peloruside A. Formation of seco-acid (-)-**24** was next readily achieved, in two steps, by removal of the PMB ether (DDQ) and saponification of the methyl ester (LiOH). Unfortunately, all attempts to achieve macrolactonization[26] via the Mitsunobu protocol proved unsuccessful; only recovery of starting material or complete decomposition occurred.

Undeterred, and with acid activation for macrolactonization as a backup, we inverted the C (15) hydroxyl (Scheme 5). The inversion required three steps: deprotection of the PMB-ether, oxidation of the derived secondary hydroxyl, and CBS reduction[27] to provide the requisite C (15) stereogenicity. Saponification then furnished seco-acid (−)-**25**, setting the stage for macrolactonization. Here we encountered what proved to be an unexpected result. Execution of the Yamaguchi protocol[28] involving acid activation and cyclization generated a macrolide in 71% yield, albeit with *complete (!)* epimerization at C(2) to furnish (−)-**26**, a result that went undetected until after global deprotection.

To understand after the fact (vide infra) this surprising result, we initiated a series of computational studies of (-)-**26** and the corresponding desired C2-epimer. Initial conformational searches were preformed using Macromodel 7.2 software.[29] The resulting low energy conformers were then clustered according to the macrocyclic ring torsions with the representative structures subjected to full geometry optimization at the B3LYP/6-31G(d,p) level of theory. The undesired, albeit observed, epimer (-)-**26** was found to be more stable by 1.8 kcal/mol. Not surprisingly, the lowest energy conformations of the two compounds possess different macrocyclic ring conformations with the major torsional differences residing in the C1-C2 bond. As seen in Figure 1, the C2 hydrogen of (-)-**26** adopts a favorable eclipsed conformation with the C1 carbonyl due to A(1,3) strain,[30] while remainder of the macrocyclic ring does not show additional eclipsed interactions. The epimer, *epi*-**26**, on the other hand, takes up a bisected rather than an eclipsed conformation at C2, resulting in different C2-C3 and C5-C6 bond torsions around the protected 1,3-diol. In addition, the lowest energy macrocyclic ring conformer has one eclipsing interaction between the C7 methoxy and the C8 hydroxyl groups.

Unaware at the time of the the C(2) epimerization, treatment of macrolide (-)-**26** with the Stork reagent [$PhI(O_2CCF_3)_2$][31] resulted in concomitant hydrolysis of the 1,3-dithiane, removal of the isopropylidene protecting group, and hemi-ketal formation to yield (-)-**27**.[32] Selective methylation of the C(3) hydroxyl group with Meerwein's reagent (Me_3OBF_4),[33] followed by global deprotection employing 4N HCl in MeOH then delivered what was revealed by extensive 1-D and 2-D NMR analyses to be (-)-2-*epi*-peloruside A (**28)**.

In summary the synthesis of 2-*epi*-peloruside A (**28**) has been achieved with a longest linear sequence of 25 steps and in 0.56% overall yield. Pleasingly, this synthetic venture demonstrates the utility of both dithiane linchpins and the multicomponent Type I ARC tactic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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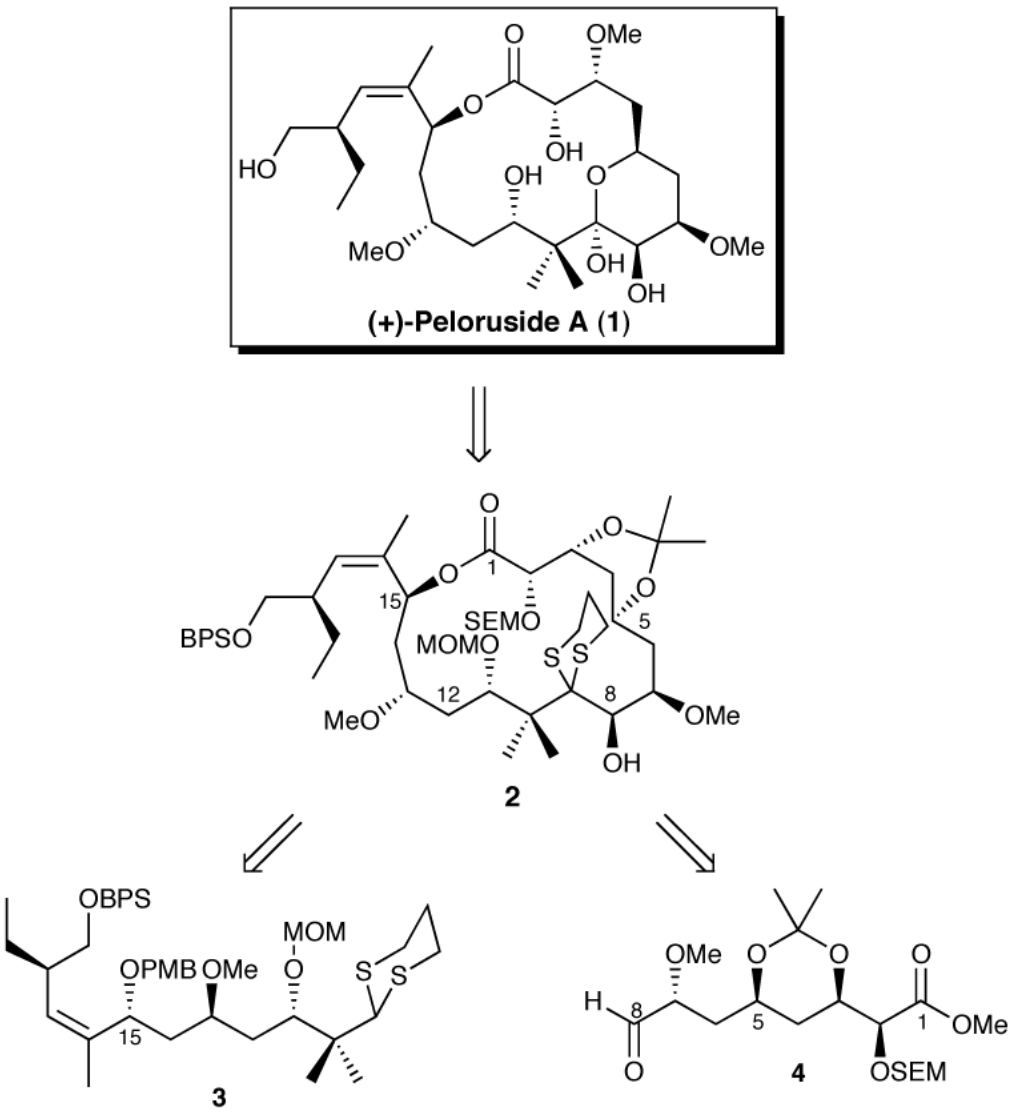
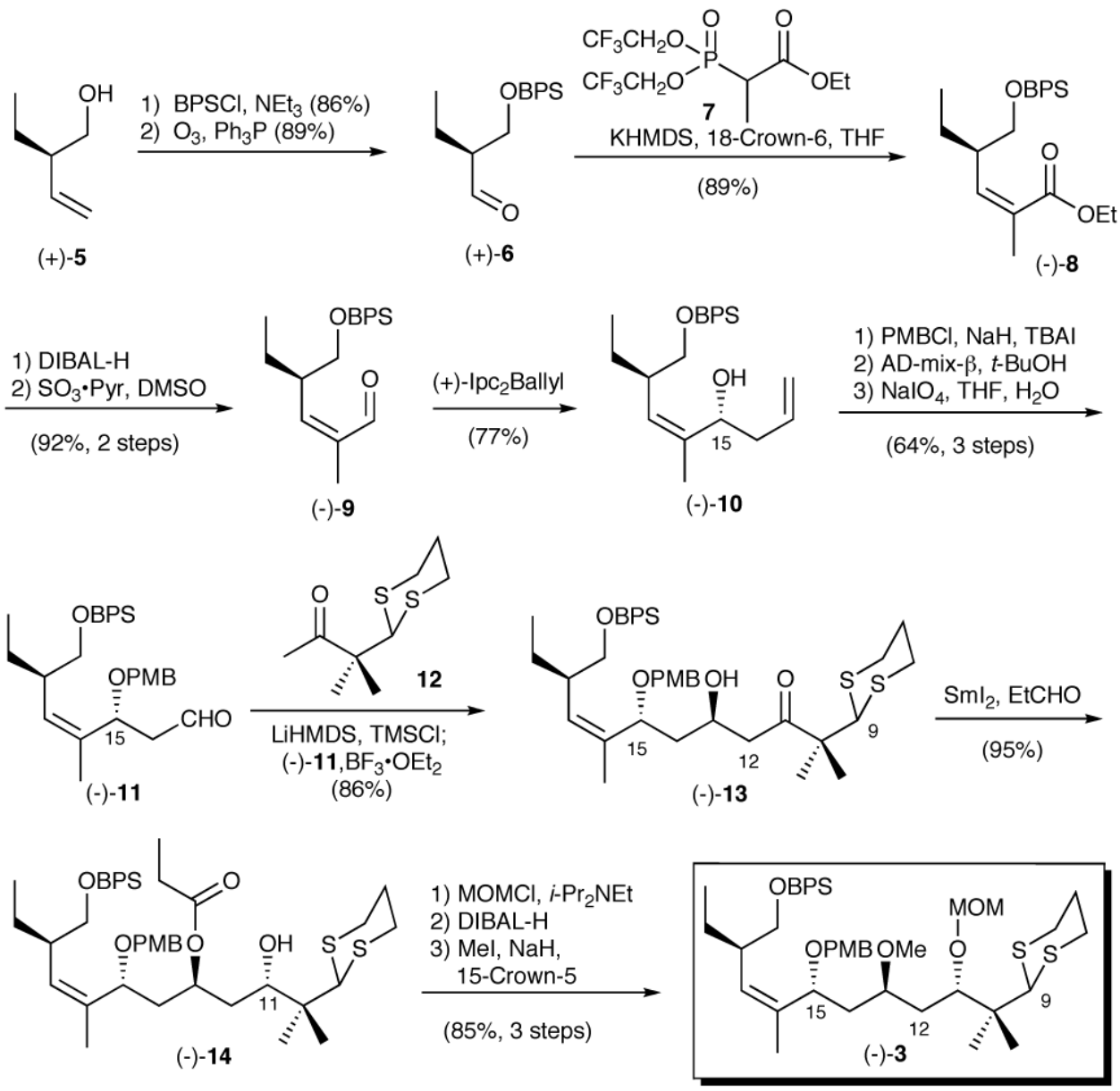
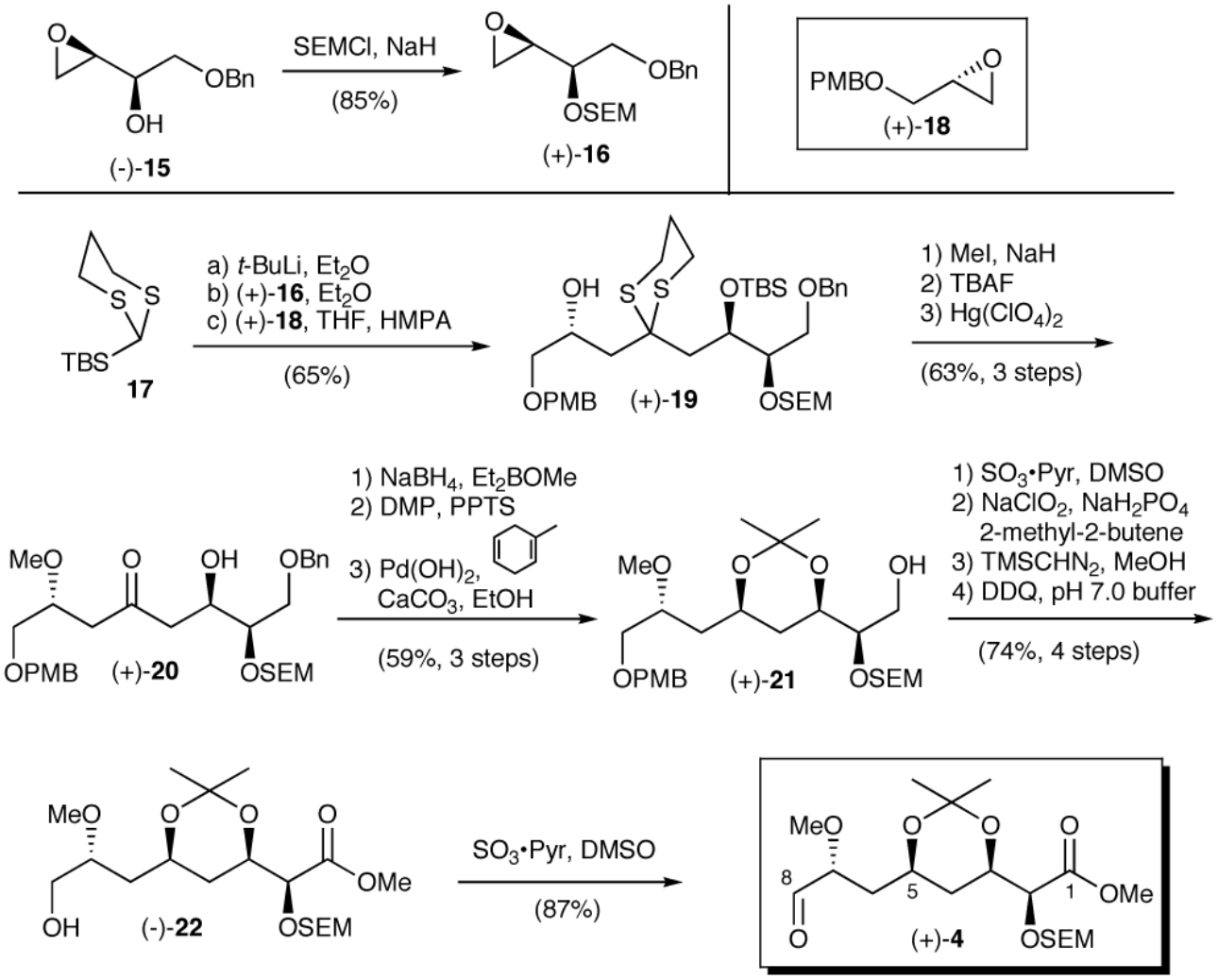


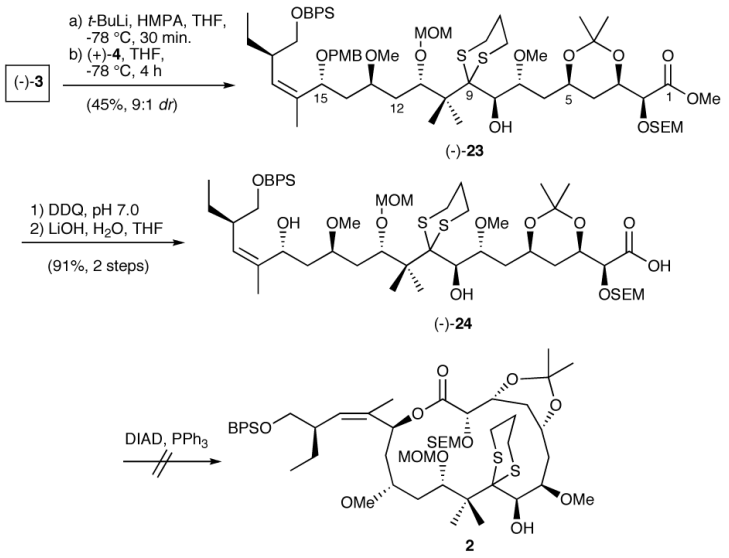
Scheme 1.
(+)-Peloruside A Retrosynthesis



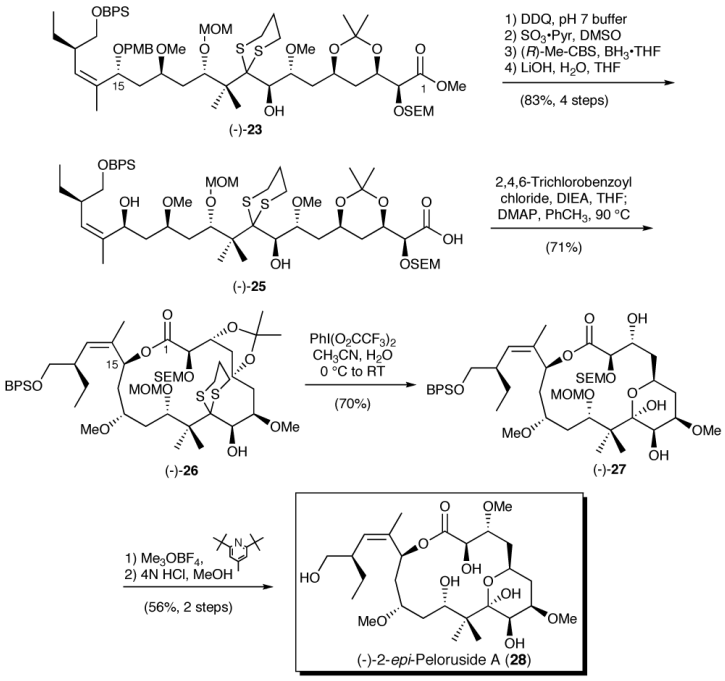
Scheme 2.
Synthesis of Dithiane (-)-**3**



Scheme 3.
Synthesis of Aldehyde (+)-**4**



Scheme 4.
Efforts Toward (+)-Peloruside A



Scheme 5.
Synthesis of (-)-2-*epi*-Peloruside A

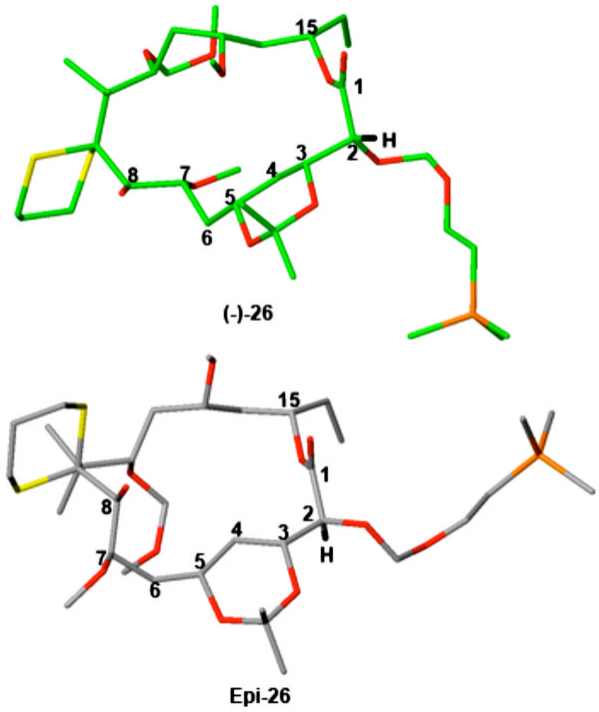


Figure 1.
The observed **(-)-26** epimer in green and the desired C2-epimer in grey, with the hydrogen at C2 shown in black. The C15 side chain has been omitted for better view.