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Synthesis of the C1–C9 Fragment of Callipeltoside-A†

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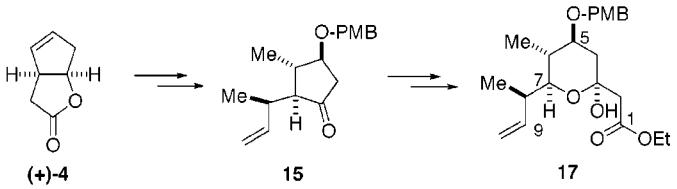
ABSTRACT



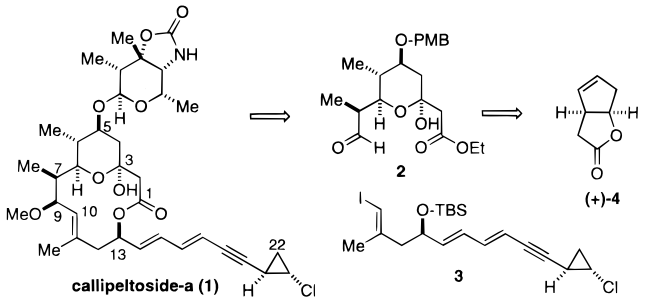
The C1–C9 fragment of callipeltoside (17) was prepared in 12 steps and 7.2% overall yield from bicyclic lactone (+)-4. Key steps include a stereoselective epoxidation and further regiocontrolled nucleophilic opening of the oxirane ring to install two vicinal stereocenters (C5 and C6), and the use of bis(trimethylsilyl) peroxide and a catalytic amount of Sn(IV) chloride for the chemoselective Baeyer–Villiger oxidation of unsaturated cyclopentanone 15.

Three macrocyclic lactones possessing the same aglycon skeleton and bearing different sugars, callipeltosides A−C, were isolated from the marine lithistid sponge *Callipelta* sp. by Minale and collaborators in 1996.[1] Callipeltoside A (**1**) was found to inhibit in vitro proliferation of KB and P388 cells and to protect cells infected with HIV virus. The relative configuration of this complex macrolactone containing a hemiketal ring and adorned with a unique dienyne-*trans*-chlorocyclopropyl side chain and a deoxyaminosugar moiety was deduced by extensive 2D NMR experiments (absolute stereochemistry not determined). We are engaged in an enantioselective synthesis of this molecule to confirm the relative configuration, determine the absolute stereochemistry, and provide sufficient amounts for further biological studies.

The complex structure of this natural product has already motivated some synthetic efforts. The synthesis of the aminosugar callipeltose was reported by Giuliano and coworkers.[2] Hoye and Zhao recently reported their attempts to cyclize the C1−C14-containing fragment of callipeltoside.[3]

In planning our synthesis of callipeltoside, we envision a convergent synthesis that leads to fragments **2** and **3** through cleavage of the macrolide linkage (C1-*O*-C13) and the C9−C10 vinylic bond (Scheme 1). In the synthetic direction,

Scheme 1



linkage of aldehyde **2** and vinyl iodide **3** will be accomplished via a Ni(II)/Cr(II)-mediated coupling reaction[4] followed by macrolactonization. We envisioned the construction of the hemiketal framework (C1−C9) of callipeltoside starting from bicyclic lactone (+)-**4**.

† Dedicated to Prof. Tomas Hudlicky on occasion of his 50th birthday.

(1) (a) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085−11088. (b) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C. *Tetrahedron* **1997**, *53*, 3243−3248.

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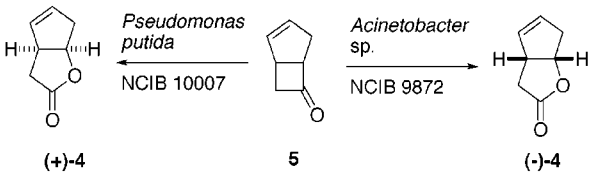
Bicyclic lactone **4** is readily available in multigram scale[5] and has been prepared enantioselectively using microbial Baeyer−Villiger oxidations[6] and by recrystallization of diasteromeric salts.[7] Interestingly, oxidation of bicyclo[3.2.0]-hept-5-en-2-one (**5**) with *Acinetobacter* sp. (NCIB 9872) produces the enantiomer (−)-**4**,[6b] while oxidation with *Pseudomonas putida* (NCIB 10007) produces the enantiomer (+)-**4**, Scheme 2.[6c] Lactone **4** has proved to be a useful

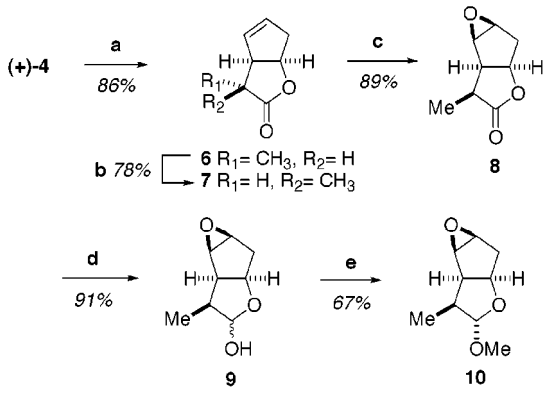
Scheme 2



intermediate for the synthesis of prostaglandins[8] and monoterpenes.[5a] Lactone **4** has also been used to prepare tetrasubstituted δ-lactones via oxidation of cyclopentanones with *m*-chloroperoxybenzoic acid (*m*-CPBA).[9] This strategy appears very attractive to prepare a large variety of substituted δ-lactones with a high degree of stereocontrol, but it is limited to compounds lacking unsaturations. To overcome this problem, we were interested in enlarging a cyclopentanone ring possessing an unsaturated substituent using a chemospecific Baeyer−Villiger oxidation.[10] We report in this letter a stereoselective synthesis of the C1−C9 fragment of callipeltoside from bicyclic lactone (+)-**4**.

Alkylation of lactone (+)-**4** with methyl iodide provided compound **6**, Scheme 3. Kinetic protonation of the lithium

Scheme 3[a]

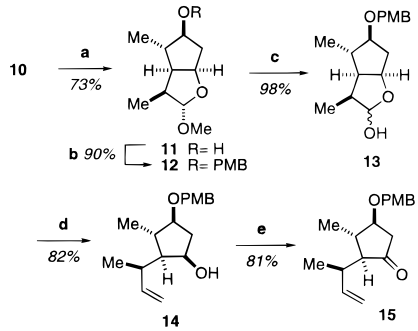


[a] (a) LHMDS, MeI, − 78 °C, THF, 1.5 h; (b) LHMDS, − 78 °C, 2 h; then aq NH_4Cl; (c) AcOOH (1.5 equiv), NaOAc (2.0 equiv), HOAc, rt, 48 h; (d) DIBAL-H, toluene−CH_2Cl_2, − 78 °C, 3 h; (e) MeOH, Dowex-50, rt, 4 h.

enolate of lactone **6** gave the thermodynamically unfavored methyl lactone **7**. We found that the workup procedure in the epimerization step was critical in the stereochemical outcome of the reaction.[11] Stereoselective epoxidation of unsaturated lactone **7** using peracetic acid in a mixture of sodium acetate−acetic acid gave preferentially the *endo*-epoxide **8**.[8a] Protection of the lactone moiety of compound **8** was required before the nucleophilic opening of the oxirane ring. Epoxylactol **9** was obtained as a mixture of stereoisomers, which were smoothly converted to the corresponding methyl acetal **10** when reacted with methanol in the presence of Dowex ion-exchange resin.[9]

Regioselective nucleophilic opening of the oxirane ring of compound **10** with Gilman's reagent at low temperature gave the desired alcohol **11** as the major product (16:1 ratio of regioisomers), Scheme 4. Protection of the hindered

Scheme 4[a]



[a] (a) MeLi, CuI, Et_2O, − 78 °C to − 30 °C, 5 h; (b) PMBCl, NaH, *n*-Bu_4NI, DMF−THF, rt, 40 h; (c) concd HCl, THF/H_2O (2:1), 40 °C, 2 h; (d) PPh_3=CH_2, 40 °C, THF, 12 h; (e) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 12 h.

hydroxyl group of compound **11** as its *p*-methoxybenzyl ether **12** was accomplished in high yield using *p*-methoxybenzyl chloride in the presence of tetrabutylammonium iodide. Deprotection of methyl acetal **12** under acidic conditions furnished lactol **13**. Olefination with methylenetriphenylphosphorane did not proceed at room temperature but required warming to 40 °C to deliver unsaturated alcohol **14**.

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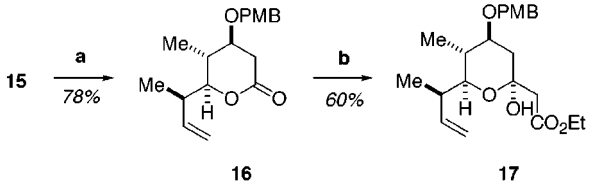
(10) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973.

(11) The epimerization step was previously reported to give isomers **6**:**7** in a 4.7: 1 ratio, 15% yield of **7**.[6b] We found that transferring the enolate solution into the organic phase to a 1:1 mixture of sat. solution of ammonium chloride−ether, and vigorous mixing leads to better yield (78%) and ratio of isomers **6**:**7** (1:17). See Supporting Information for a detailed procedure.

Oxidation of alcohol **14** with tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide yielded ketone **15**.[12]

Baeyer−Villiger oxidation of cyclopentanone **15** using hydrogen peroxide under acidic conditions gave the desired *δ*-lactone **16** in low yield (<30%) after 48 h. Oxidation of cyclopentanone **15** with *m*-CPBA gave also the desired *δ*-lactone **16** in 50−60% yield, 10−20% of starting material, and a small amount of mixture of epoxylactones.[13] Thus, we selected Shibasaki's protocol,[10] recently employed in his elegant synthesis of epothilone.[14] Oxidative ring expansion using bis(trimethylsilyl) peroxide (BTSP), a catalytic amount of Sn(IV) chloride, and *trans*-diaminocyclohexane gave the desired *δ*-lactone **16** in 78% yield, in which the terminal alkene remained intact (Scheme 5). Addition of the lithium

Scheme 5[a]



[a] (a) Bis(trimethylsilyl) peroxide, cat. $SnCl_4$, 4 Å molecular sieves, 1,2-diaminocyclohexane, CH_2Cl_2, 0 °C to room temperature, 48 h; (b) EtOAc, LHMDS, THF, − 78 °C to 0 °C, 2 h.

enolate of ethyl acetate to lactone **16** gave the desired hemiketal **17**.[15] Compound **17** is an advanced intermediate for the synthesis of callipeltoside, which contains four contiguous chiral centers and the hemiketal framework of the natural product.

In summary, we have prepared an advanced intermediate for the synthesis of the macrocyclic lactone of callipeltoside, starting from biocatalytically generated bicyclic lactone **4**. Gilman's reagent was highly regioselective and efficient in the nucleophilic opening of epoxide **10** to construct the vicinal stereocenters C5 and C6. The use of BTSP and Sn(IV) chloride proved to be an effective procedure to enlarge a functionalized cyclopentanone containing an unsaturation. The synthesis of the C10−C22 southern fragment **3** and the synthesis of **1** will be reported in due time.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for compounds **6**−**17**. This information is available free of charge via the Internet at http://pubs.acs.org.

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