Natural Products

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Convergent Total Syntheses of Callipeltosides A, B, and C**

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Marine sponges provide a rich diversity of structurally interesting natural products which often display a range of useful biological activities. As part of a sustained search to discover and identify new molecules with potential therapeutic benefit, Minale and co-workers isolated callipeltosides A, B and C (**1**–**3**) as minor metabolites from the shallow water lithistida marine sponge *Callipelta* sp.[1,2] At the time, these natural products represented a new class of polyketides that were later joined by new members; the phorbasides, aurisides, dolastatins and others.[3] The callipeltosides contain several interesting features which include: 14 stereocentres, an unusual *trans*-configured chlorocyclopropane ring conjugated to a di-ene-yne unit, and a 14-membered macrolactone ring incorporating a tetrasubstituted tetrahydropyran motif. All callipeltosides contain a common aglycon core, and differ only in the attached sugar unit (Figure 1), which is thought to

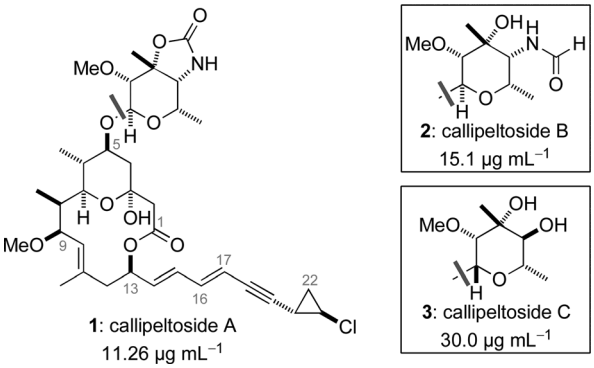

Figure 1. The callipeltoside family of natural products and corresponding IC_{50} values against the NSCLC-N6 cell line.

play an important role in moderating cytotoxic activity against human bronchopulmonary NSCLC-N6 (IC_{50} values detailed in Figure 1) and P388 cell lines.[1] These properties make these molecules attractive targets for synthesis.

Early efforts by the Trost[4] and Paterson[5] groups towards the synthesis of callipeltoside A defined the *trans*-configured chlorocyclopropane unit, the structure of the aglycon and the configuration of the sugar with respect to the natural product skeleton. These two groups as well as the laboratories of Evans,[6] Panek,[7] and Hoye[8] have since reported the synthesis of callipeltoside A.[9] Further work by MacMillan and co-workers culminated in the first synthesis of callipeltoside C resulting in a structural reassignment, meaning that the L-configured sugar moiety was present rather than the originally assigned D-configuration.[10] In spite of all these efforts, we believed that further work was still necessary to streamline the synthesis and complete the series by synthesizing callipeltoside B for the first time.

Our goal therefore was to devise a unified, efficient and convergent strategy to all three callipeltosides A, B and C and thereby also confirm the structure of B. While space here does not allow us to report on all of our routes to the various fragments of the callipeltosides, often using chemistries invented in our laboratories, we describe only the most successful sequence.[11]

Our analysis of the synthesis problem suggested starting from three equally-sized components: C1–C9 pyran **4**, C10–C22 vinyl iodide **5** and the relevant sugar moiety activated as the corresponding thioglycoside (callipeltoside A sugar **6** shown for clarity) (Figure 2). We expected that pyran **4** and vinyl iodide **5** could be joined by a diastereoselective alkenyl metal addition.[12] With the key C9 stereocenter in place, further manipulations followed by macrolactonization should provide the callipeltoside aglycon by the most convergent process reported to date. Pyran **4** could be accessed through the use of a catalytic $AuCl_3$-induced cyclization protocol previously developed by our group.[13]

Synthesis of the C1–C9 pyran fragment **4** commenced from known (*R*)-Roche ester-derived aldehyde **10** (Scheme 1). Crotylboration using the Roush procedure provided homoallylic alcohol **12** in good yield (70%) and diastereomeric ratio (d.r. 88:12).[14] Subsequent dihydroxylation followed by sodium periodate-mediated cleavage produced the required aldehyde for propargylzinc addition. This three-step procedure gave diol **13** in 72% overall yield, with diastereoselectivity of 85:15 at C5 in favor of the desired 1,3-*anti*-configuration; presumably by a chelation-controlled process.[10] Protection as the acetonide followed by ynoate formation gave pure **14** in good yield. At this juncture all minor diastereomers could be easily and conveniently removed by silica gel chromatography. The relative stereochemistry of **14** was confirmed by single-crystal X-ray diffraction. Removal of the acetonide provided diol **15** which, upon treatment with $AuCl_3$ in MeOH, smoothly cyclized to give desired pyran **16** as a single diastereomer in an excellent 96% yield. The low catalyst loading of this reaction is of interest, requiring just 2 mol% to deliver product **16**. Thereafter, protection of the secondary alcohol as its TBS ether, hydrogenolysis and oxidation gave **4** in 26%

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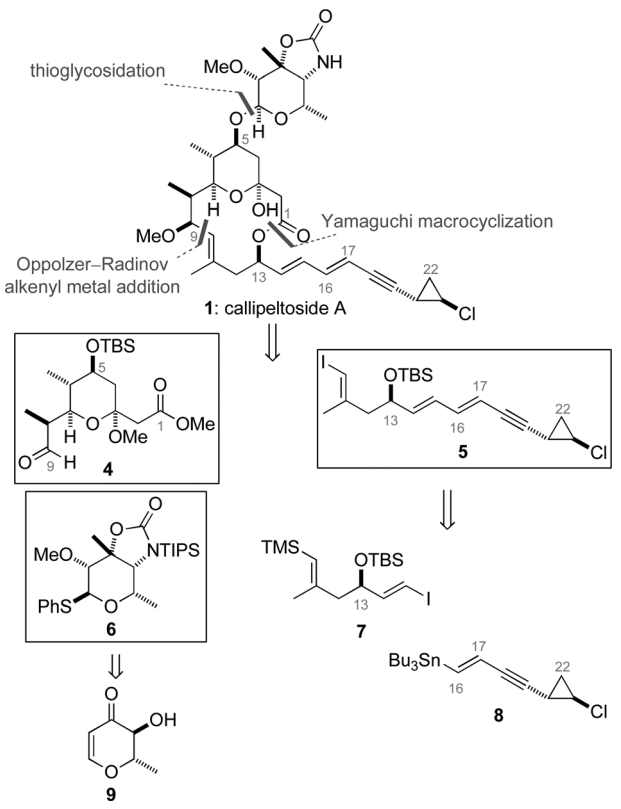
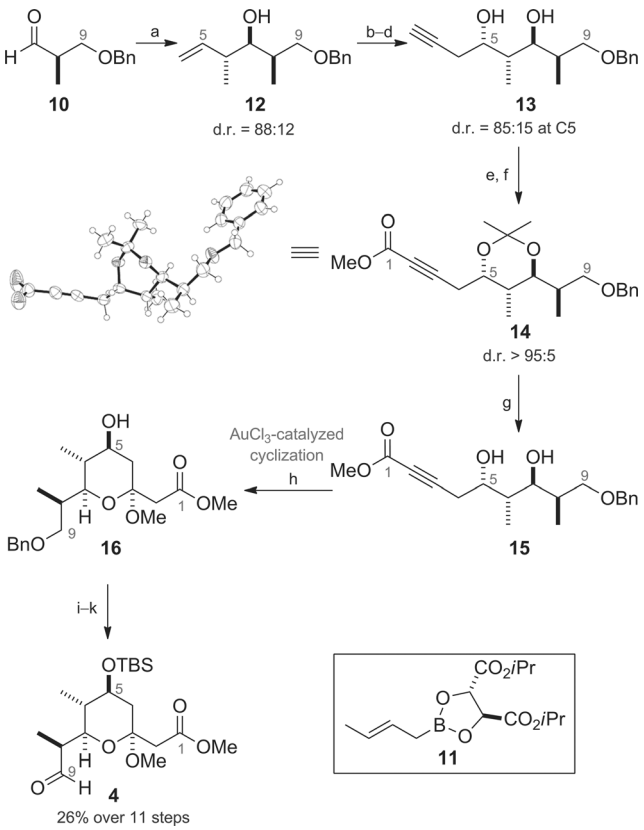


Figure 2. Retrosynthetic analysis of the callipeltoside family. Callipeltoside A shown for clarity.



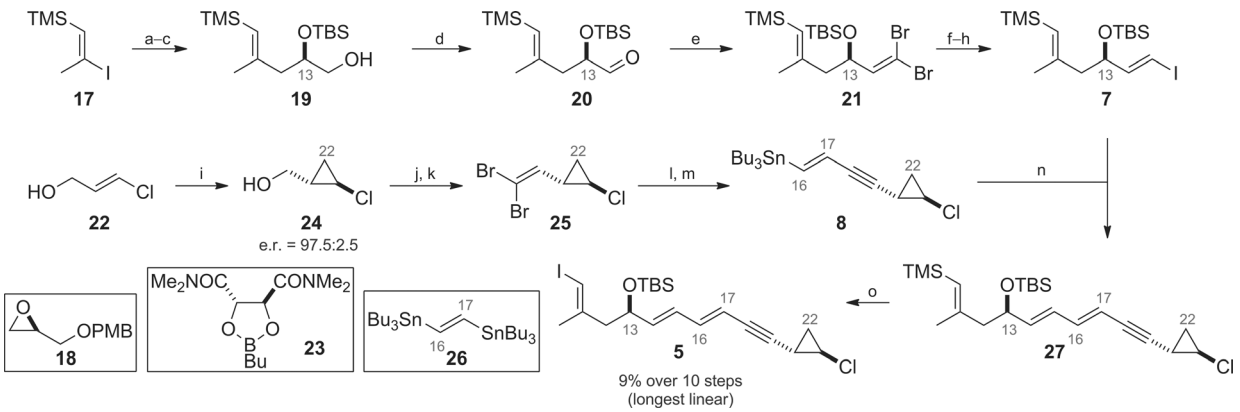
Scheme 1. Reagents and conditions: a) crotylborane **11**, 4 Å MS, PhMe, −78 °C, 70%; b) OsO_4, NMO, acetone/H_2O (2:1), RT; c) $NaIO_4$, THF/H_2O (10:1), 0 °C→RT; d) Zn, propargyl bromide, THF, 0→−100 °C, 72% over 3 steps; e) 2,2-dimethoxypropane, (±)-CSA, acetone, RT; f) *n*BuLi, THF, −40→−78 °C, then $ClCO_2Me$, 73% over 2 steps; g) QP-SA, MeOH, RT, 95%; h) $AuCl_3$ (2 mol%), MeOH, RT, 96%; i) 2,6-lutidine, TBSOTf, CH_2Cl_2, −78 °C, 91%; j) H_2, Pd/C (10% wt), EtOAc, RT, 96%; k) Dess–Martin periodinane, K_2CO_3, CH_2Cl_2, RT, 87%. NMO = *N*-methylmorpholine *N*-oxide; (±)-CSA = (±)-camphorsulfonic acid; QP-SA = Quadrapure sulfonic acid.

yield over 11 steps. This route is noteworthy for its minimal use of chromatography.

For the synthesis of C10–C22 vinyl iodide **5**, we required large amounts of known vinyl iodide precursor **17**, itself derived from TMS-propyne in two steps by Mo-catalyzed regioselective hydrostannylation followed by iodine exchange.[15] Halogen–lithium exchange with *t*BuLi in toluene at −78 °C followed by additon of PMB-protected epoxide (**18**) with $BF_3{\cdot}OEt_2$ proved to be the most effective means to the desired secondary alcohol.[16] Subsequent TBS-protection and PMB-deprotection gave primary alcohol **19**. Oxidation and Ramirez olefination[17] furnished **21** which, following Corey–Fuchs reaction, gave the corresponding terminal alkyne.[18] Pd-catalyzed hydrostannylation and subsequent tin–iodine exchange proceeded with high regioselectivity to give (*E*)-vinyl iodide **7** as a single diastereomer in 49% yield over 2 steps.[19] This completed the C10–C15 **7** fragment in 18% yield over 8 steps (Scheme 2).

The Stille coupling partner **8** was completed after considerable optimization by treatment of known dibromide **25**[7b,20] with TBAF to give the corresponding bromoalkyne, which was then coupled to bis-stannane **26** by a low-temperature (−10 °C) Stille reaction with Ag_2CO_3 as an additive.[21] This gave compound **8** exclusively, with no observation of biscoupled material. Fragments **7** and **8** were united by a second Stille reaction employing $[Pd(PFur_3)_2]Cl_2$ as the precatalyst[22] to yield **27** which, following treatment with NIS, provided **5** in a highly stereoselective fashion in 9% yield over 10 steps (longest linear sequence).

As discussed above, the three callipeltosides differ in the attached sugar unit which, on the basis of structural investigations by others,[4–10] has resulted in callipeltoside A and C being assigned with L-configured residues. It therefore seemed reasonable to us that the B sugar might also be L-configured. In an effort to synthesize appropriate carbohydrate coupling partners in an efficient manner, and thereby maximize convergency, we implemented a route to all three fragments from a common enantioenriched precursor **28**. Initial deacetylation of **28** followed by oxidation of the allylic alcohol efficiently provided pyranone **9** in 74% over 2 steps. Our approach to callipeltoside A and B thioglycosides **6** and **32**, respectively, began by nosylation of pyranone **9** and subsequent S_N2 displacement of the nosylate with nBu_4NN_3. Addition of MeLi at −100 °C gave **29** as a single diastereomer.[23] Having successfully installed the C4 stereocenter, epoxidation with *m*-CPBA and subsequent ring opening proceeded smoothly. Selective methylation of the secondary alcohol was achieved by careful control of the stoichiometry of freshly sublimed KO*t*Bu followed by addition of MeI to give key compound **30**, allowing diversification to both the

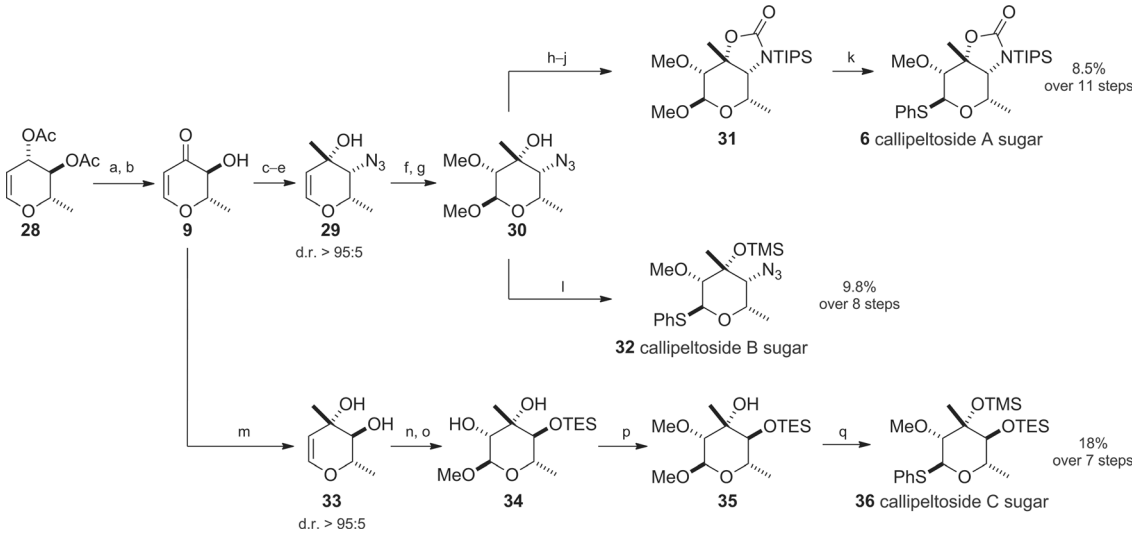


Scheme 2. Reagents and conditions: a) *t*BuLi, PhMe, −78 °C, then **18**, $BF_3{\cdot}OEt_2$, PhMe; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 53 % over 2 steps; c) DDQ, pH 7 phosphate buffer, CH_2Cl_2, 0 °C, 89 %; d) $SO_3{\cdot}Py$, Et_3N, DMSO, CH_2Cl_2, 0 °C→RT; e) PPh_3, CBr_4, CH_2Cl_2, then **20**, 2,6-lutidine, CH_2Cl_2, 0 °C, 89 % over 2 steps; f) *n*BuLi, THF, −78 °C, then H_2O, 85 %; g) $Pd(PPh_3)_2Cl_2$ (3 mol %), Bu_3SnH, THF, 0 °C; h) I_2, CH_2Cl_2, −78 °C, 49 % over 2 steps; i) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C, then **23**, **22**, CH_2Cl_2, 0 °C→RT, 74 %; j) PCC, celite, CH_2Cl_2, RT; k) PPh_3, CBr_4, CH_2Cl_2, 0 °C, then aldehyde, CH_2Cl_2, 0 °C→RT, 70 % over 2 steps; l) TBAF, DMF, 65 °C; m) Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), Ag_2CO_3 (1.0 equiv), THF, dark, −10 °C, then **26**, 45 % over 2 steps; n) $Pd(PFur_3)_2Cl_2$ (15 mol %), DMF, dark, RT, 63 %; o) NIS, MeCN, RT, 84 %. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; PCC = pyridinium chlorochromate; TBAF = tetrabutylammonium fluoride; NIS = *N*-iodosuccinimide.

callipeltoside A and B sugars.[7a,23] The callipeltoside A sugar methoxyacetal **31** was completed following reduction of the azide to the amine, formation of the cyclic carbamate and triisopropylsilyl (TIPS) protection.

This was successfully activated as the thioglycoside by use of thiophenol with $BF_3{\cdot}OEt_2$ to give **6** as the single α-anomer in 8.5 % over 11 steps.[6d] Azido sugar **30** was activated and protected in one step using TMSSPh, ZnI_2 and TBAI in DCE at 65 °C to provide α-configured sugar **32**, a precursor to the callipeltoside B sugar.[24] This approach meant that after attachment of sugar **32** to the callipeltoside aglycon further manipulation by means of azide reduction, formylation and deprotection would be necessary to deliver **2**.

With the callipeltoside A and B sugar precursors in hand, we focused on a separate synthesis of the activated callipeltoside C saccharide unit. This proceeded from the common pyranone **9**, through a complex-induced proximity-controlled nucleophilic addition to give **33** as a single diastereomer.[25] Selective TES-protection, epoxidation, ring-opening and methylation gave **35**. This was successfully converted to the anomeric thioglycoside **36** (Scheme 3). The preparative sequence to the callipeltoside C sugar **36** was efficient,



Scheme 3. Reagents and conditions: a) PS-Na_2CO_3, MeOH, RT; b) MnO_2, CH_2Cl_2, RT, 74 % over 2 steps; c) NsCl, Py, CH_2Cl_2, RT, 95 %; d) nBu_4NN_3, CH_2Cl_2, 0 °C, 72 %; e) MeLi, THF, −100 °C, 79 %; f) *m*-CPBA, MeOH, 0 °C→RT, 52 %; g) KO*t*Bu, MeI, THF, 0 °C, 79 %; h) H_2, $Pd(OH)_2$, EtOAc, RT, 93 %; i) triphosgene, Py, THF, −78 °C→RT, 72 %; j) TIPSOTf, 2,6-lutidine, CH_2Cl_2, RT, 97 %; k) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C→RT, 80 %; l) ZnI_2, TBAI, TMSSPh, DCE, 65 °C, 60 %; m) MeLi·LiBr, Et_2O, −78 °C, 78 %; n) TESCl, Py, DMAP, CH_2Cl_2, RT; o) *m*-CPBA, MeOH, 0 °C→RT, 45 % over 2 steps; p) KO*t*Bu, MeI, THF, 0 °C, 81 %; q) ZnI_2, TBAI, TMSSPh, DCE, 65 °C, 86 %. NsCl = 4-nitrobenzenesulfonyl chloride; *m*-CPBA = 3-chloroperbenzoic acid; TIPS = triisopropylsilyl; TMS = trimethylsilyl; TES = triethylsilyl; DMAP = 4-(*N*,*N*-dimethylamino)pyridine; TBAI = tetrabutylammonium iodide.

proceeding in 18% yield over 7 steps.[26] With all necessary fragments in hand, efforts to assemble the natural products began.

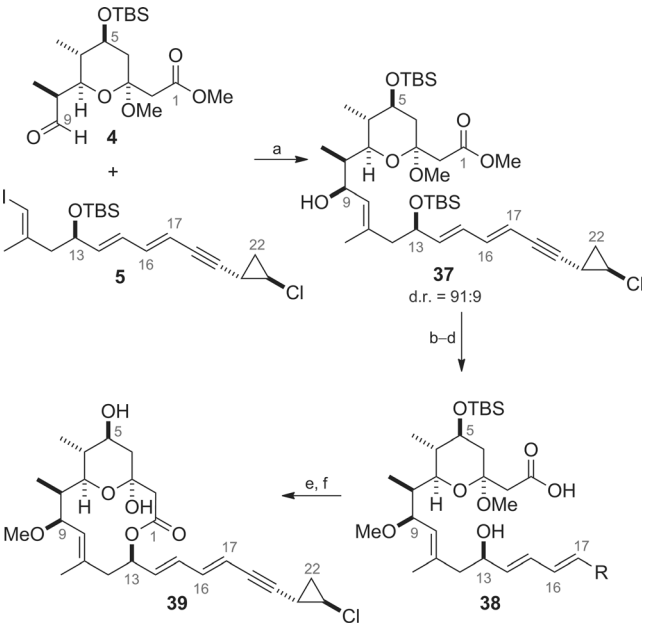
We first had to address the key convergent coupling of pyran **4** with fully assembled vinyl iodide fragment **5**. Initial investigations using the alkenylzinc nucleophile resulted in a successful union with d.r. = 1:1 at C9. Our attention then turned to the work of Oppolzer and Radinov,[12] and also the elegant studies of Marshall,[27] who demonstrated that the stereochemical information could be transferred through the ligand-directed use of *N*-methylephedrine derivatives. Inspection of the proposed model revealed that (1*R*,2*S*)-(−)-*N*-methylephedrine would be the reagent of choice; but in practise, disappointing diastereoselectivity was observed (34:66 at C9). However using the opposite enantiomer, (1*S*,2*R*)-(+)-*N*-methylephedrine gave greatly improved levels of diastereoselection (91:9). Subsequent methylation of both C9 epimeric products using MeOTf allowed for the interception of a known compound disclosed by MacMillan.[10] This allowed for the rapid and convenient determination of the stereochemical outcomes, with the major product of the (1*S*,2*R*)-(+)-*N*-methylephedrine reaction found to be the desired product. Hence, the desired transformation represents the matched case. This welcome but unexpected result is opposite to that predicted by Noyori's model.[28] We therefore suggest that this reaction involves a model similar to that proposed by Myers in the synthesis of the tetracycline antibiotics.[29] This reaction was optimized such that only a 0.3 equivalent excess of vinyl iodide **5** was required, allowing for maximum conversion of valuable advanced fragments.

Thereafter, selective removal of the C13 silyl ether with TBAF followed by saponification of the methyl ester gave seco-acid **38**. Yamaguchi macrolactonization[30] followed by treatment with TFA in THF/H_2O (5:1) installed the requisite hemiketal and removed the remaining secondary TBS group in a one-pot process to give the callipeltoside aglycon **39** in 58% over 2 steps (Scheme 4).

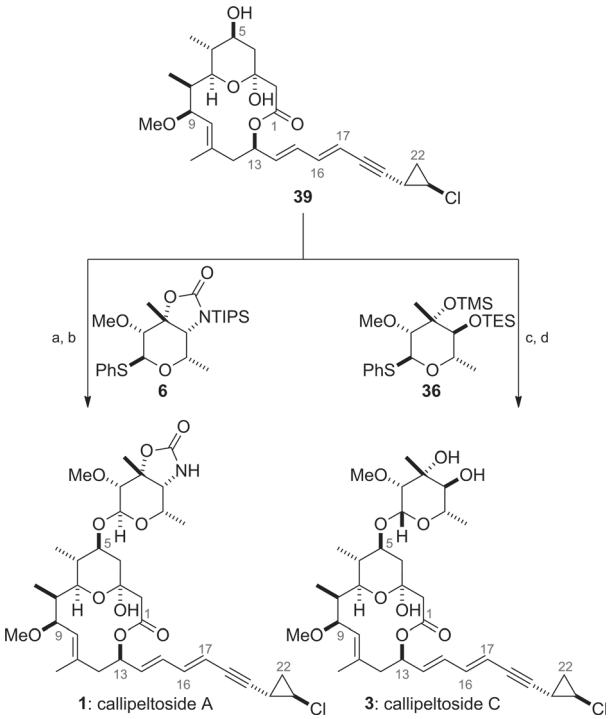
Attachment of the sugar **6** to aglycon **39** was successfully achieved using the protocol described by Evans,[6] which, after deprotection using TBAF furnished callipeltoside A (**1**). Application of the same glycosylation procedure provided protected callipeltoside C. Deprotection using TASF delivered callipeltoside C (**3**); identical to the natural product and that described by MacMillan (Scheme 5).[10]

With callipeltosides A and C in hand, our next concern was to address the synthesis of callipeltoside B. Following attachment using thioglycoside **32**, we faced the prospect of having to reduce the azide in the presence of multiple unsaturated functional groups. Pleasingly, this was achieved using 1,3-propanedithiol in aqueous pyridine/Et_3N.[31] Formylation using a large excess of reagent **40**,[32] and desilylation using TASF gave callipeltoside B (**2**) (Scheme 6) as a 4:1 mixture of formamide rotamers identical in all respects to the natural product. This therefore confirms that all members of the callipeltoside family contain L-configured sugars.[33]

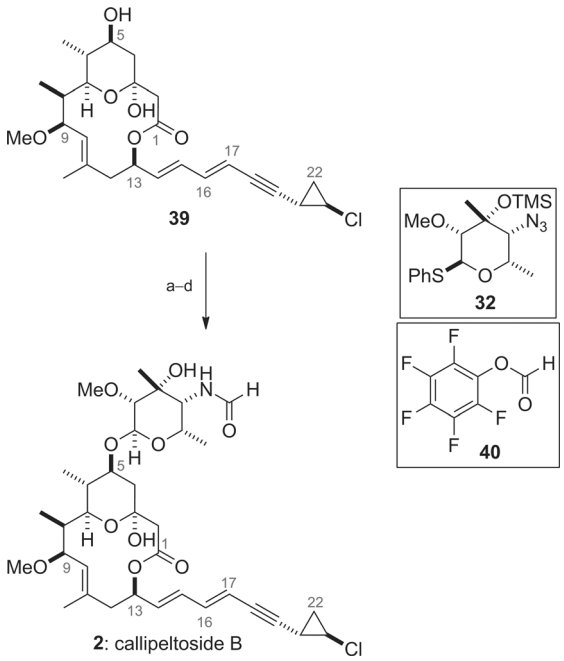
In conclusion, we have developed a highly convergent approach to the entire callipeltoside family, which has resulted in the first total synthesis of callipeltoside B (**2**).



Scheme 4. Reagents and conditions: a) **5**, (1.3 equiv), *t*BuLi, Et_2O, −78 °C; ii) $ZnBr_2$, Et_2O, −78→0 °C; iii) (1*S*,2*R*)-(+)-*N*-methylephedrine (1.1 equiv), *n*BuLi, PhMe, 0 °C; iv) **4**, PhMe, 0 °C, 48%; b) MeOTf, DTBP, CH_2Cl_2, RT, 73%; c) TBAF, THF, RT, 74%; d) $Ba(OH)_2{\cdot}8H_2O$, MeOH, RT, quant.; e) 2,4,6-trichlorobenzoyl chloride, Et_3N, RT, then addition to DMAP, PhMe, 80 °C; f) TFA, THF/H_2O (5:1), RT, 58% over 2 steps. DTBP = 2,6-di-*tert*-butylpyridine; TFA = trifluoroacetic acid.



Scheme 5. Reagents and conditions: a) **39**, **6**, 4 Å MS, CH_2Cl_2, DTBMP, RT, 50 min, then −15 °C, NIS, TfOH, −15 °C→RT; b) TBAF, THF, 83% over 2 steps; c) **39**, **36**, 4 Å MS, CH_2Cl_2, DTBMP, RT, 50 min, then −15 °C, NIS, TfOH, −15 °C→RT; d) TASF, DMF, 40 °C, 57% over 2 steps. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; TfOH = trifluoromethanesulfonic acid; TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.



Scheme 6. Reagents and conditions: a) **39**, **32**, 4 Å MS, CH_2Cl_2, DTBMP, RT, 50 min, then −15 °C, NIS, TfOH, −15 °C→RT, 56%; b) 1,3-propanedithiol, Et_3N, Py/H_2O (10:1), RT; c) **40**, $CHCl_3$, RT; d) TASF, DMF, 40 °C, 52% over 3 steps.

This has been achieved by 1) a high yielding approach to the pyran core **4**, which benefitted from our own $AuCl_3$-induced cyclization methodology[13] and required minimal chromatography; 2) formation of vinyl iodide **5** in a stereospecific manner by sequential Stille reactions; and 3) union of **4** and **5** by means of a highly convergent and diastereoselective Oppolzer–Radinov alkenylzinc addition. An extensive account of our efforts towards these targets will be presented in full at a later date.

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Keywords: callipeltoside · chlorocyclopropane · gold catalysis · Oppolzer–Radinov addition · Stille cross coupling

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[2] The depicted structures differ from those drawn in the original isolation paper and are the result of previous synthetic efforts and the work detailed in this Communication. Whilst the α-glycosidic linkage of callipeltoside A is well known, that of callipeltoside B and C has not been rigorously established. Despite the same method being used to unite each sugar fragment with the callipeltoside aglycon, analysis of NOESY data for callipeltosides B and C has led us to assign respective α- and β-configurations at the glycosidic linkage (see Schemes 5, 6 and the Supporting Information). At this stage it is not known why the opposite configurations are obtained.

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Communications

Natural Products

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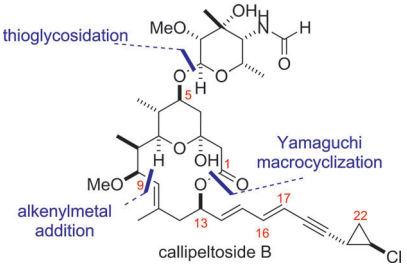
Convergent Total Syntheses of Callipeltosides A, B, and C



Going for the hat-trick: The synthesis of the entire callipeltoside family of natural products is described. Key to this synthesis was the coupling of the di-ene-yne and pyran fragments by a diastereoselective alkenylzinc addition allowing rapid access to the common aglycon. Attachment of each relevant L-configured sugar resulted in the first total synthesis of callipeltoside B (see scheme), and the syntheses of callipeltosides A and C.