

Total Synthesis of Callipeltoside A

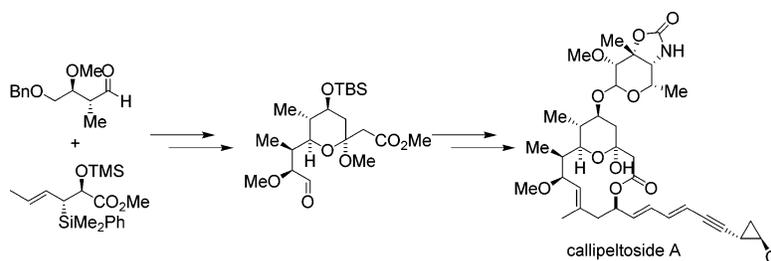
Hongbing Huang and James S. Panek*

Department of Chemistry and Center for Chemical Methodology and
Library Development, 590 Commonwealth Avenue, Boston University,
Boston, Massachusetts 02215

panek@chem.bu.edu

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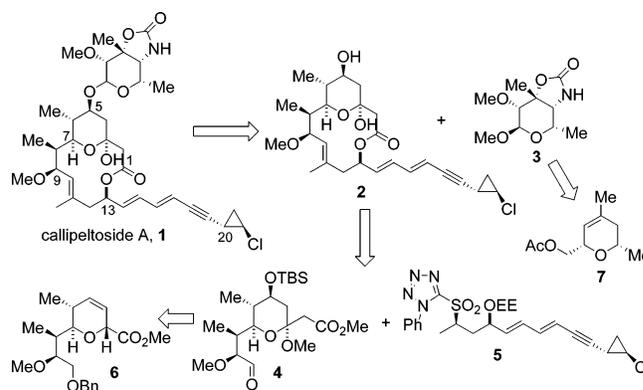
ABSTRACT



A convergent total synthesis of cytotoxic marine macrolide callipeltoside A is described. The synthesis highlights two stereoselective [4 + 2] annulations for the preparation of associated pyran rings.

Callipeltoside A is the first member of a family of novel glycosidic macrolides isolated in 1996 from the shallow water lithistid sponge, *Callipelta* sp., collected in the waters off the east coast of New Caledonia.¹ It is found to exhibit moderate cytotoxic activity against NSCLC-N6 and P388 cell lines.¹ Intriguing structural features of callipeltoside A include a hydroxylated hemiacetal pyran ring embedded in a 14-membered macrolactone, which is connected to a *trans*-chlorocyclopropane via a conjugated dienyne linkage. Attached to the macrolactone is a unique deoxyamino sugar callipeltose (Scheme 1). The initial structure assignment of callipeltoside A disclosed the relative stereochemical relationship of callipeltose to the macrolactone; however, the relative stereochemistry of the chlorocyclopropyl side chain to the rest of the molecule and the absolute stereochemistry of callipeltoside A remained unresolved. The novel structure of callipeltoside A, together with its stereochemical ambiguities and its intriguing biological activity, has prompted considerable interest from the synthetic community.² Recent

Scheme 1. Retrosynthetic Analysis of Callipeltoside A



total syntheses reported by Trost^{3a} and Evans^{3b} established the absolute configuration of natural callipeltoside A as illustrated in Scheme 1.³ In this communication, we report a convergent total synthesis of callipeltoside A based on the

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(2) For synthetic efforts towards callipeltoside aglycon, see: (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169–171. (b) Velazquez, F.; Olivo, H. F. *Org. Lett.* **2000**, *2*, 1931–1933. (c) Olivo, H. F.; Velazquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055–4058. (d) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603–607. (e) Romero-Ortega, M.; Colby, D. A.; Olivo, H. F. *Tetrahedron Lett.* **2002**, *43*, 6439–6441.

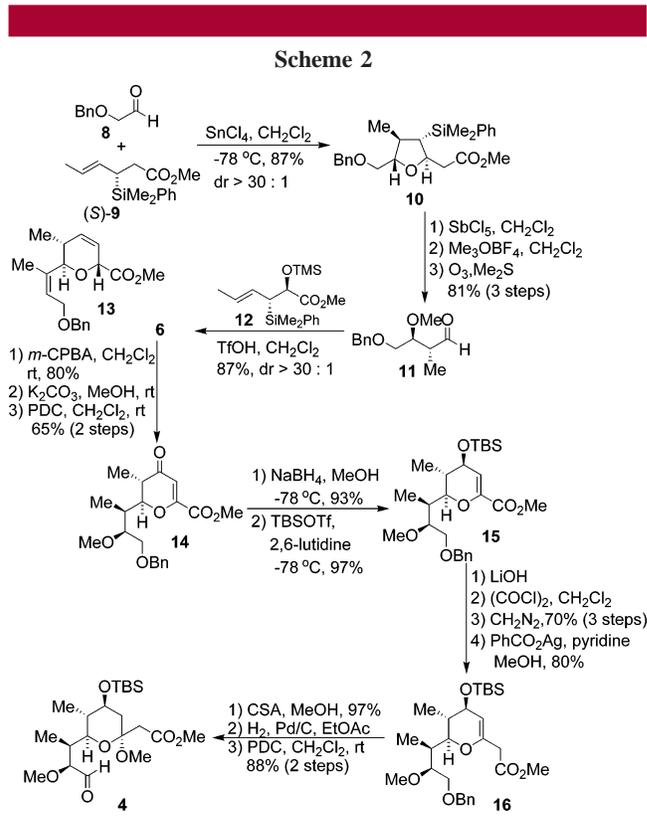
(3) Total synthesis: (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841–843. (b) Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654–5655. (c) Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477–4480.

use of chiral organosilane methodology developed in our laboratories.

Our retrosynthetic analysis of callipeltoside A led to three subunits 3–5. The tetrahydropyran-containing subunits 3 and 4 were thought to be obtained from dihydropyrans that were available from formal [4 + 2] annulations of chiral organosilanes recently reported from our laboratories.^{4a,b} In the synthetic direction, union of 4 and 5 via a Julia–Kocienski olefination⁵ precedes macrocyclization. It was envisioned that the anti stereochemical relationship at the C8 and C9 in 6 would be established utilizing a chelation-controlled anti crotylation, and the *trans*-chlorocyclopropane could be accessed by an asymmetric Simmons–Smith reaction.

Synthesis of intermediate 6 was initiated by an anti-selective condensation of the α -benzyloxyacetaldehyde 8 with silane (S)-9. In the presence of SnCl₄, the reaction provided tetrahydrofuran 10 in 87% yield (*trans/cis* >30:1).⁶ Upon treatment with SbCl₅, tetrahydrofuran 10 underwent E₂-type elimination, providing an anti homoallylic alcohol. This intermediate was converted to aldehyde 11 with a two-step sequence in 92% yield.

Under previously optimized conditions,^{4a} the annulation of 11 and organosilane 12 provided dihydropyran 6 with high diastereoselectivity; however, a significant amount of undesired dihydropyran 13 was also obtained. We suspected that the generation of 13 was associated with the β -elimination of aldehyde 11. Gratifyingly, the use of TFOH afforded 6 in 85% yield as a single diastereomer. Despite our previous success on the stereoselective epoxidation of a similar pyran system giving the epoxide *cis* to the adjacent methyl group,⁷ epoxidation of dihydropyran 6 under various conditions resulted in low selectivities that were circumvented by an oxidation/hydride reduction sequence. Epoxidation using *m*-CPBA was followed by epoxide ring opening (K₂CO₃/MeOH), and oxidation of the resulting alcohol (PDC) afforded enone 14. The C5 stereocenter was installed by 1,2-reduction of the enone under Luche's conditions.⁸ Protection of the emerging alcohol as a TBS ether was followed by one-carbon homologation of the methyl ester 15. In that regard, an Arndt–Eistert reaction provided the homologated methyl ester 16 in good yield. Debenzylation (H₂/Pd–C) and oxidation of the primary alcohol (PDC) completed the preparation of aldehyde 4. The synthesis of subunit 5 utilizes a stereoselective Horner–Emmons olefination and a Stille coupling reaction to install the (*E,E*)-dienyne moiety. The construction of 5 began with an asymmetric Simmons–Smith



reaction of allylic alcohol 17. The use of Charette's (*S,S*)-dioxoborolane ligand provided the cyclopropyl alcohol 18 in 97% ee.⁹ Oxidation to the aldehyde followed by dibromoolefination afforded vinyl dibromide 19. Stille coupling between 19 and vinylstannane 20 under conditions developed by Shen and Wang gave enyne 21 in moderate yield.¹⁰ The allylic alcohol was converted to phosphonate 22 in a straightforward manner. The Horner–Emmons reaction between phosphonate 22 and aldehyde 23 resulted in exclusive (*E*)-olefin formation providing (*E,E*)-dienyne 24 in 89% yield.¹¹ Deprotection of TBDPS silyl ether followed by a Mitsunobu reaction and oxidation of the intermediate sulfide gave sulfone 25. The preparation of 5 was completed after protecting group manipulation. With the synthesis of subunits 4 and 5 completed, conditions for their union were investigated. It was found that sulfone 5 was a very sensitive substrate in the Julia–Kocienski olefination. Reliable conditions were developed using THF as the solvent and LiHMDS as the base. The use of a more polar solvent (DME, DMF) and other bases (KHMDS, NaHMDS) led only to the decomposition of the sulfone. After deprotection of the ethoxyethyl ether (PPTS, MeOH), the alcohol 26 was obtained in 20% overall yield. After hydrolysis of the methyl ester to the seco acid, the crucial macrolactonization was undertaken using Yamaguchi conditions.¹² The reaction provided a 1:1 mixture of dihydropyran containing lactone 27 and the

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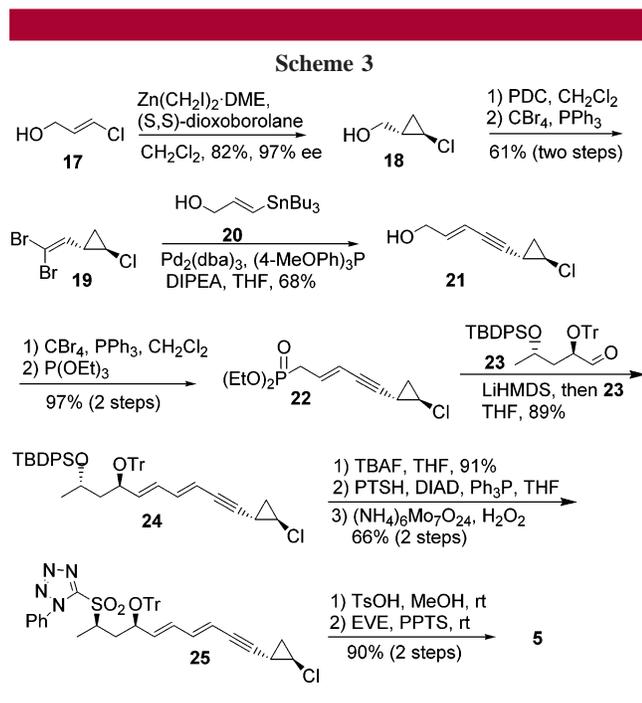
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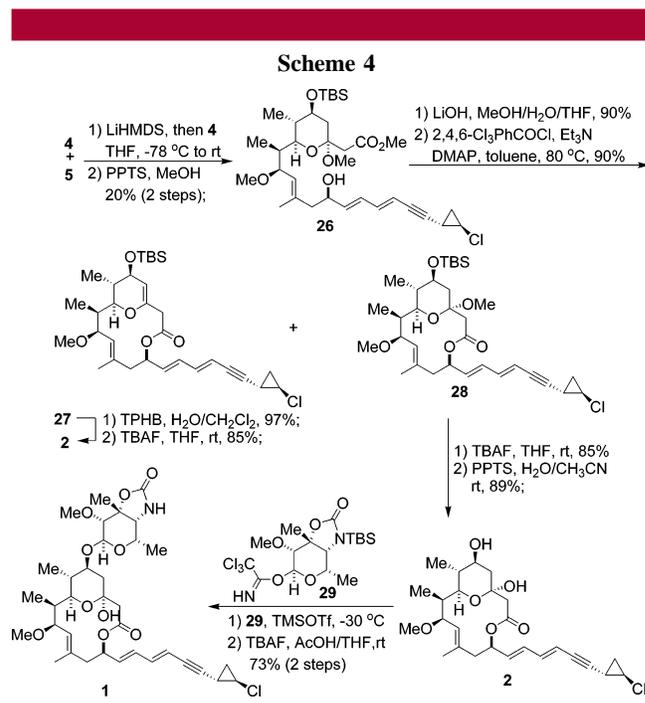
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desired lactone **28** in 90% yield. Gratifyingly, the dihydropyran **27** was converted to lactol in quantitative yield by treating with a catalytic amount of triphenylphosphine hydrogen bromide and water.¹³ The aglycon was obtained in 85% yield after deprotecting TBS silyl ether. Lactone **28** was also transformed to aglycon **2** by a two-step sequence: TBS deprotection (TBAF) and hydrolysis of the methyl lactol ether (cat. PPTS, H₂O/CH₃CN). The total synthesis of callipeltoside A was completed by a Schmidt glycosidation,^{4g,14} followed by deprotection (TBAF/AcOH) of N-TBS protecting group. The analytical data were fully consistent in all aspects with those reported for natural callipeltoside A. In conclusion, a convergent enantioselective synthesis of callipeltoside A has been completed with a longest linear sequence of 25 steps. Our approach highlights an enantioselective

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lective [4 + 2] annulation to assemble dihydropyrans suitably functionalized for complex molecule synthesis. Further experiments aimed at the development of the scope of the annulation are currently under investigation.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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