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Total Synthesis of Callipeltoside A

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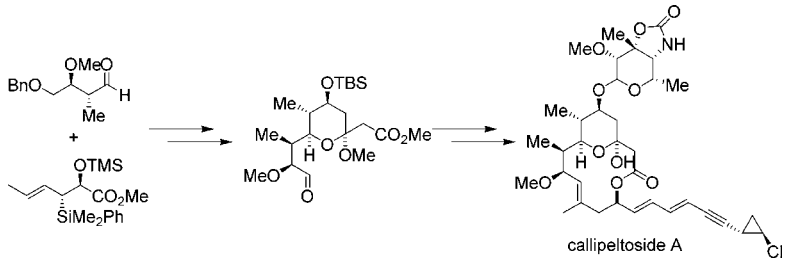
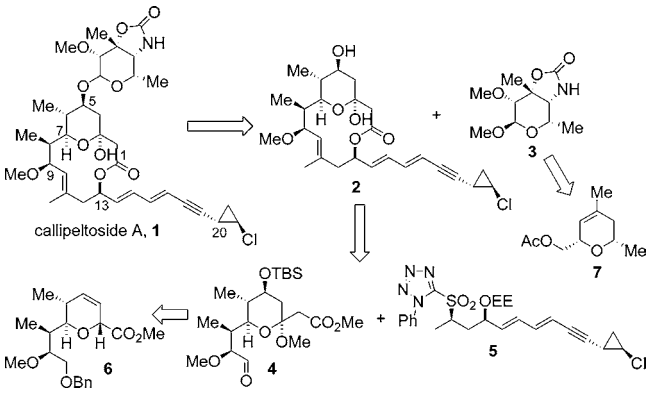
ABSTRACT



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

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

(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.

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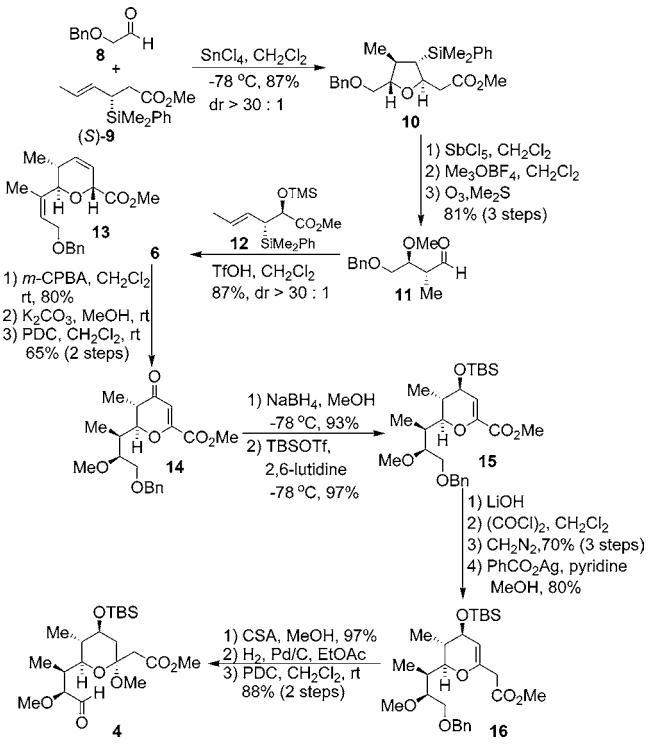
use of chiral organosilane methodology developed in our laboratories.

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 olefination[5] 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 $SnCl_4$, the reaction provided tetrahydrofuran **10** in 87% yield (*trans*/*cis* >30:1).[6] Upon treatment with $SbCl_5$, tetrahydrofuran **10** underwent E_2-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 (K_2CO_3/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 (H_2/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

Scheme 2



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 vinyldibromide **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−Kociensky 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

(4) (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836−9837. (b) We have reported the synthesis of methyl-L-callipeltose: Huang, H.; Panek, J. S. *Org. Lett.* **2003**, *5*, 1991−1993. For other syntheses of callipeltose, see: (c) Smith, G. R.; Finley, J. J., IV; Giuliano, R. M. *Carbohydr. Res*. **1998**, *308*, 223−237. (d) Gurjar, M. K.; Reddy, R. *Carbohydrate Lett*. **1998**, *3*, 169−172. (e) Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937−942. (f) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett*. **2001**, *3*, 3133−3136. (g) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc*. **2002**, *124*, 10396−10415.

(5) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.

(6) Panek, J. S.; Yang, M. *J. Am. Chem. Soc*. **1991**, *26*, 9868−9870.

(7) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693−1696.

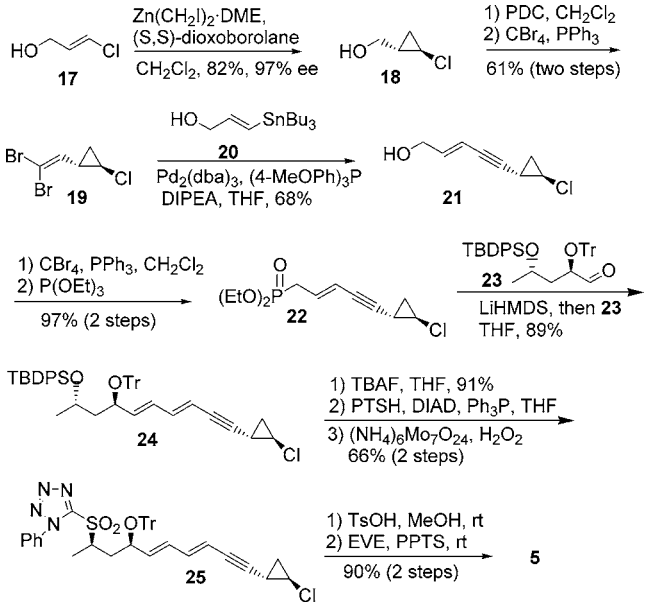
(8) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454−5459.

(9) (a) Charette A. B.; Juteau, H. *J. Am. Chem. Soc*. **1994**, *116*, 2651−2652. (b) Charette A. B.; Prescott, S.; Brochu, C. *J. Org. Chem*. **1995**, *60*, 1081−1083.

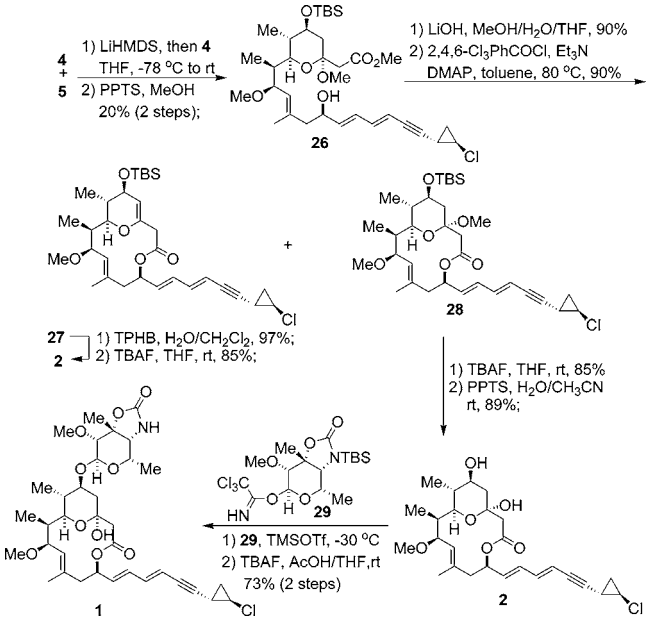
(10) Shen, W.; Wang, L. *J. Org. Chem*. **1999**, *64*, 8873−8879.

(11) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris B. D. *J. Am. Chem. Soc*. **1984**, *106*, 3548−3551.

Scheme 3



Scheme 4



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, H_2O/CH_3CN). 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 [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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(12) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(13) Bolitt, B.; Mioskowiski, C.; Lee, S.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812−5813.

(14) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731−732.