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Organosilanes in Synthesis: Application to an Enantioselective Synthesis of Methyl-L-callipeltose

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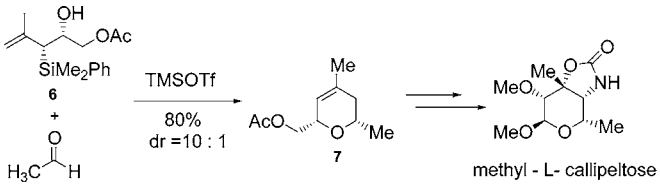
ABSTRACT



Methyl-L-callipeltose, the carbohydrate associated with callipeltoside A, has been synthesized in eight steps and 23% overall yield from enantioenriched allylsilane 6 and acetaldehyde. The key steps are a highly diastereoselective formal [4 + 2] annulation and a Cr(VI)-catalyzed oxidative C–C bond cleavage to produce lactone 11.

Callipeltosides A−C were isolated from the extracts of the shallow water lithistid sponge *Callipelta* sp.[1] and represent a class of novel cytotoxic glycoside macrolides. They were found to exhibit moderate cytotoxic activity against NSCLC-N6 and P388 cell lines. The structure of the callipeltosides features a hydroxylated hemiacetal oxane ring embedded in a 14-membered macrolactone, which is connected to a *trans*-chlorocyclopropane through a dienyne linkage. While callipeltoside C contains an evalose sugar moiety, callipeltosides A and B possess unprecedented deoxyamino sugars (Figure 1). The initial structure elucidation of callipeltoside A revealed the relative stereochemical relationships of callipeltose to the macrolactone. The relative stereochemistry of the chlorocyclopropyl side chain section of the molecule and the absolute stereochemistry of the callipeltoses remained unresolved at the time this project was initiated. Two recent total syntheses of callipeltoside A have established its absolute stereochemistry as illustrated (Figure 1).[2] In our approach to callipeltoside A, synthetic routes have been designed in order to access to both enantiomers of callipeltoside aglycon and callipeltose. Here, we describe an efficient asymmetric synthesis of methyl-L-callipeltose using a [4 + 2] dihydropyran construction.

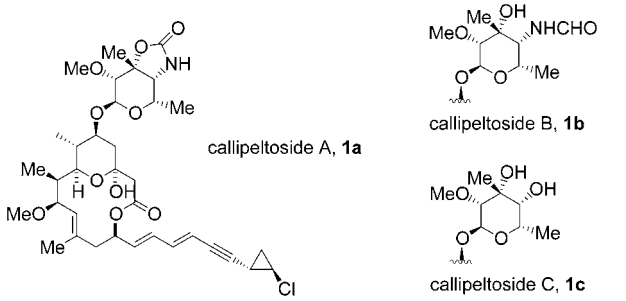


Figure 1. Proposed Structures of Callipeltosides A−C.

(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.; Roussakis, C. *Tetrahedron* **1997**, *53*, 3243−3248.

(2) (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841−843. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396−10415. (c) Evans, D. A.; Hu, E; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654−5655.

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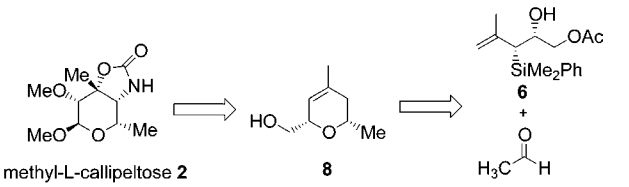
Recently, several syntheses of callipeltose have been reported exploiting starting materials obtained from the chiral pool, including rhamnose,[3] mannose,[4] D-glucal[5] and threonine.[6] Our approach is based on a stereoselective [4 + 2] annulation of chiral allylsilane **6** and illustrates the versatility of the silane reagent in accessing functionalized pyrans (Scheme 1).[7]

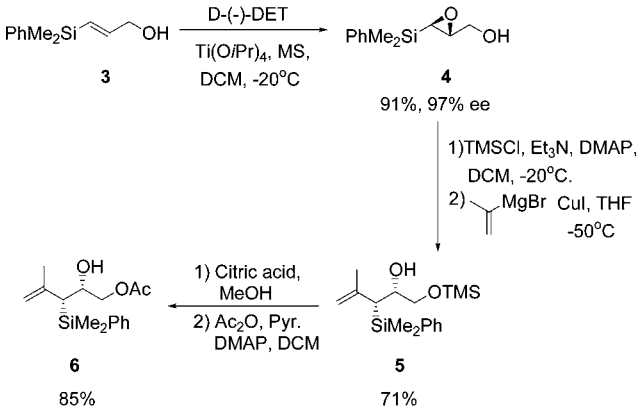
Scheme 1. Methyl-L-callipeltose Retrosynthetic Analysis



Given the ready availability of highly enantioenriched organosilanes, this annulation process would prove to be an efficient method for synthesizing functionalized dihydropyrans, useful intermediates for natural product synthesis.

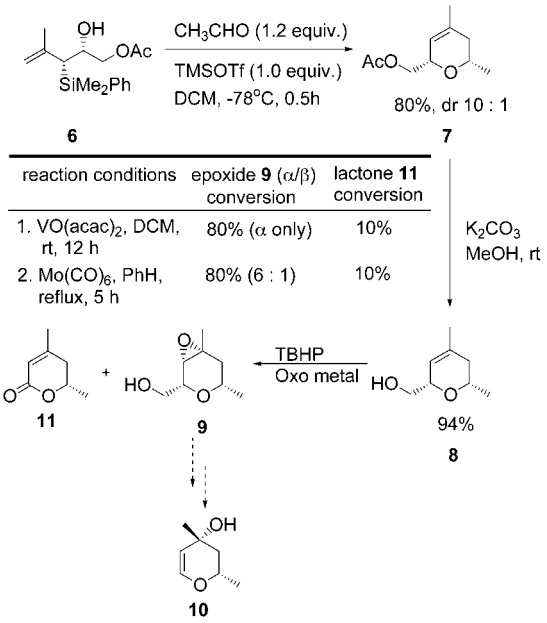
The chiral allylsilane **6** was prepared in high optical purity using a regioselective epoxide ring-opening as described by Chong and co-workers (Scheme 2).[8] Accordingly, the enantioenriched 3-silyl epoxy alcohol **4** was prepared from allylic alcohol **3** by a Sharpless asymmetric epoxidation[8,9] and was isolated in 91% yield and with high enantiomeric purity (ee = 97%).[10] The epoxide ring-opening reaction of **4** with 2-propenylmagnesium bromide proved to be sluggish and resulted in significant amounts of Peterson olefination product, which could not be suppressed even at low temperature (−78 °C).[11] However, the epoxide opening of the TMS ether of **4** provided allylsilane **5** as a single regioisomer in good yield (71%). This reaction has been routinely scaled up to 10 g. After exchanging trimethylsilyl ether to an acetate, allylsilane **6** was obtained in 85% yield.

Scheme 2. Synthesis of Chiral Allylsilane



The annulation of allysilane **6** with acetaldehyde proceeded to give dihydropyran **7** in 80% yield (dr = 10:1).[12] Methanolysis of acetate **7** gave pyran alcohol **8** in quantitative yield. Our initial synthetic plan called for the synthesis of **9** by a directed epoxidation,[13] which would then be converted to alcohol **10**, a key intermediate to callipeltose (Scheme 3).[2b]

Scheme 3. Substrate-Directed Stereoselective Epoxidation

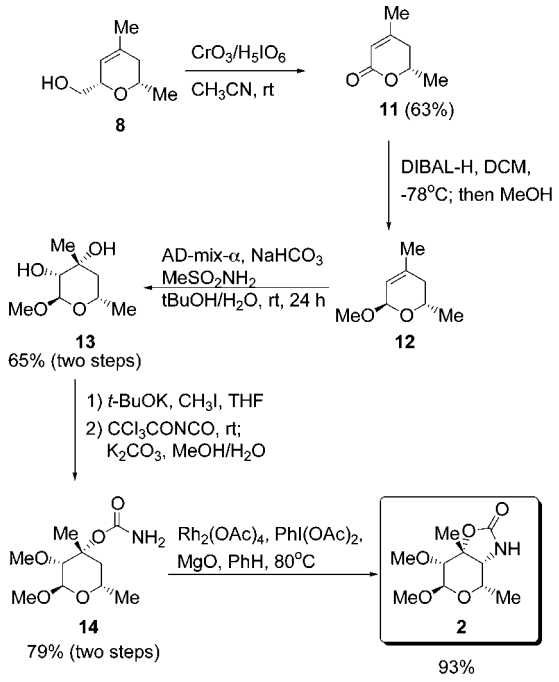


Though the $VO(acac)_2$-catalyzed epoxidation provided the desired epoxide **9** as a single isomer, an unexpected side product lactone **11** (~10%) was observed by examination of ^1H NMR of the crude reaction mixture. Epoxidation using $Mo(CO)_6$ gave **9** with lower diastereoselectivity, but still equal amounts of **11** could be detected by NMR. Initially produced as a byproduct, we envisioned that lactone **11** could be a useful intermediate en route to callipletose and may have been generated by a transition metal-catalyzed oxidation with C−C bond cleavage. Encouraged by reports concerning C−H oxidation promoted by Cr[VI],[14] several combinations

(3) Smith, G. R.; Finley, J. J., IV; Giuliano, R. M. *Carbohydr. Res*. **1998**, *308*, 223−237.
(4) Gurjar, M. K.; Reddy, R. *Carbohydr. Lett*. **1998**, *3*, 169−172.
(5) Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937−942.
(6) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett*. **2001**, *3*, 3133−3136. For a racemic synthesis of methyl callipeltose, see 2b.
(7) (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc*. **2000**, *122*, 9836−9837. (b) Huang, H.; Panek, J. S. *Org. Lett*. **2001**, *3*, 1693−1696.
(8) Chauret, D. C.; Chong, J. M.; Ye Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3601−3614.
(9) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(10) Enantiomeric excess (ee) analysis was conducted by chiral HPLC analysis.
(11) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784.
(12) Stereochemistry of **8** was determined by NOE experiment. The cis stereoselectivity is consistent with our previous reported observations. For a discussion of the related transition state, see ref 7.
(13) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc*. **1973**, *95*, 6136−6137.

of oxidants with Cr[VI] complexes were evaluated: the combination of catalytic amounts of CrO_3 with H_5IO_6 provided the unsaturated lactone **11** in good yield. Although this reagent combination has been used to oxidize primary alcohols to carboxylic acids,[15] no reports of an oxidative C−C bond cleavage had been documented (Scheme 4).[16]

Scheme 4. Sythesis of Methyl-L-callipeltose



Due to the electron-deficient nature of the unsaturated lactone **11**, the standard Sharpless asymmetric dihydroxylation (SAD) was ineffective.[17a] Treatment of lactone **11** with DIBAL-H followed by workup with MeOH provided methyl glycoside **12** as a single anomer. This material was used without further purification. The standard SAD of **12** gave diol **13** in low conversion (30%) even after prolonged reaction periods (24 h), along with free lactol and lactone **11**. However, **12** could be cleanly oxidized to the diol **13** as a single diastereomer after addition of $NaHCO_3$ (2 equiv) to buffer the reaction mixture, using commercially available AD-mix-α.[17] The selective methylation of the secondary hydroxyl of **13** (tBuOK/MeI) afforded the intermediate tertiary alcohol, which was converted to the carbamate **14** upon reaction with $CCl_3C(O)NCO$ followed by K_2CO_3/MeOH. The final stage of the callipeltose synthesis was based on a Rh(I)-catalyzed oxidative insertion of a carbamate NH to afford the oxazolidin-2-one.[18] As reported by Trost and co-workers, the insertion reaction proceeded to approximately 70% conversion in refluxing CH_2Cl_2 when 10 mol % rhodium acetate was employed.[2b] Complete conversion could be achieved by increasing catalyst loading to 20 mol %. However, when this reaction was carried out in refluxing benzene, complete conversion to callipeltose **2** was achieved, using only 10 mol % catalyst (93%). The analytical data and optical rotation values are fully consistent with those reported.[2, 6]

In summary, an asymmetric synthesis of methyl-L-callipeltose has been accomplished in eight steps and 23% overall yield from silane **6**. A transition metal-catalyzed oxidative C−C bond cleavage was employed for the production of the key intermediate **11**. The synthesis of the callipeltose aglyon and of callipeltoside A will be reported in due course.

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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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(15) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323−5326.

(16) Study on the mechanism, scope, and limitation of this novel reaction will be reported elsewhere. For a leading reference on Cr(VI)-catalyzed oxidation of the C−H bond, see: Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978−13979.

(17) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Stereochemistry of **13** was determined by NOE experiment, see Supporting Information for detail.

(18) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.