Total Synthesis of Deschlorocallipeltoside A

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Callipeltoside A (**1**) is a recently isolated cytotoxic agent from a marine lithistida sponge (*Callipelta sp.*) with excellent prospects for the study and treatment of cancer.[1] It was found to inhibit in vitro proliferation of NSCLC-N6 human bronchopulmonary nonsmall-cell-lung carcinoma (11.26 μg/mL) and P388 (15.26 μg/mL) cells. To study this fascinating molecule and its biological activity, an efficient synthesis is required.[2] Furthermore, there are several unresolved stereochemical issues: (1) the relative configuration of C-21 with respect to the macrolide and (2) the absolute configuration of the natural product. Furthermore, the relative configuration of the sugar with respect to the macrolide rests only on two nOe's.[1a] In this communication, we disclose a facile synthesis of deschlorocallipeltoside (**2**) allowing for a general entry to this structural type.

Figure 1 illustrates a simplification of the synthetic target to three building blocks: the core **3**, the side chain **4**, and the sugar **5**. The three bond disconnections depicted facilitate the synthesis of the core **3**. The stereocenter at C-13 is envisioned to derive from a palladium-catalyzed allylic alkylation and that at C-9 by a diastereoselective reduction. The stereocenters at C-5, C-6, and C-7 were conceived to derive from diastereoselective aldol-type processes. The remaining stereocenter at C-8 came from the chiral pool and thus was purchased.

Scheme 1 begins the journey with the synthesis of the C-7 to C-11 fragment starting with the commerically available methyl *S*-3-hydroxy-2-methylpropionate. The Weinreb amide **8** was made by the Merck method[3] using a magnesium reagent (98%) rather than the more common aluminum reagents (best yield 65%). Diastereoselective reduction of ketone **9** with achiral reducing agents proved disappointing with threo:erythro ratios ranging from 0.5:1.0 to 1.8:1.0. Using 2-methyl (*S*)-CBS-oxazaborolidine, borane reduction gave an excellent result.[4]

The extension of the C-7 to C-11 fragment to C-14 is outlined in Scheme 2. The formation of the trisubstituted alkene requires a regioselective Alder ene-type reaction. In the ideal situation, the alcohol would already be activated for the subsequent allylic alkylation. Neither of these two aspects had previously been explored. Gratifyingly, this chain extension to form **12** proceeded without any complications under our standard conditions for the ruthenium-catalyzed alkene−alkyne coupling[5] in 85% yield. The use of chiral ligands was anticipated to control the regio- and diastereoselectivity to set the C-13 stereocenter.[6] Using the *R,R*-ligand, ent-**13**, gave a matched pair to produce a 19:1 dr and a 3.0:1 branched-to-linear regioselectivity but with the configuration opposite that of the natural product. Although this stereocenter could subsequently be inverted by a Mitsunobu protocol, the additional steps made that sequence unattractive. The *S,S*-ligand **13** provides a 20:1 dr and a somewhat reduced branched-to-linear 2:1 regioselectivity favoring the correct diastereomer which allowed it to be isolated pure in 51% yield.

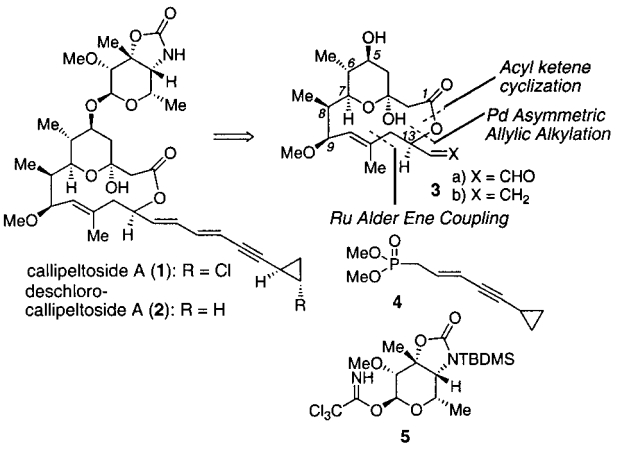
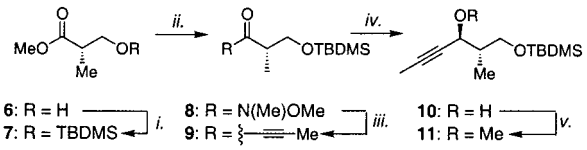


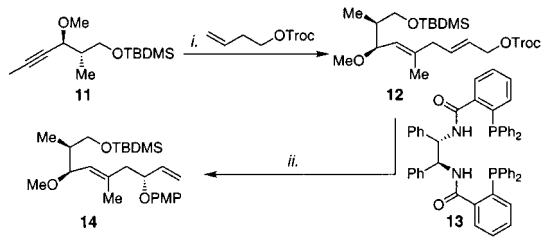
Figure 1. Structure of callipeltoside A **1** and **2**.

Scheme 1[a]



[a] Reagents and conditions: i.) TBDMSCl, imidazole, CH_2Cl_2, rt, 2h, 99%; ii.) MeNHOMe·HCl, *i*-PrMgCl, THF, −20 °C, 1 h, 98%; iii.) 1-propynylmagnesium bromide, THF, 0 °C, 89%; iv.) 2-methyl (*S*)-CBS-oxazaborolidine, BH_3·SMe_2, THF, −30 °C, 1 h, 10:1 dr, 99%; v.) MeI, Ag_2 O, Et_2O, rt, 4 h, 92%.

Scheme 2[a]



[a] Reagents and conditions: i.) $CpRu(CH_3CN)_3PF_6$ (5 mol %), acetone, rt, 20 min, 85%; ii.) *p*-methoxyphenol, **13** (7.5 mol %), Pd_2dba_3·$CHCl_3$ (2.5 mol %), tetrabutylammonium chloride, CH_2Cl_2, 20:1 dr, 2:1 regioselectivity (2°:1°), 79%.

The completion of the synthesis of the core (**23**) of callipeltoside A is displayed in Scheme 3. The kinetically formed *E* lithium enolate of *tert*-butyl thiopropionate adds to aldehyde **16** to provide the Cram-type addition product **17** with 5:1 diastereoselectivity.[7] Felkin−Ahn type addition to aldehyde **18** of the dienyl silyl ether **19**[8] produced a single diastereomer **20** whose silyl ether **21** was subjected to CAN to liberate the C-13 hydroxyl group (**22**) for macrocyclization. The Boeckman thermal protocol proceeded smoothly (82% yield) at high dilution to form the 14-membered macrolide **23**.[9] The synthesis of the macrolide required 16 steps from commercially available **6** and proceeded in 11% overall yield.

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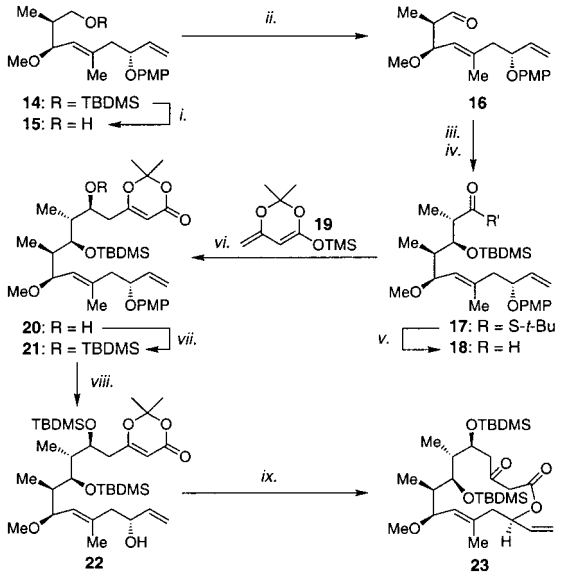
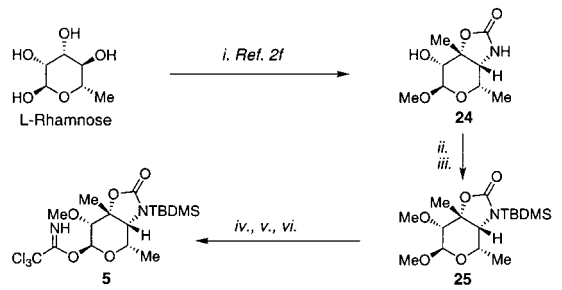
Scheme 3[a]



[a] Reagents and conditions: i.) TBAF, THF, rt, 12 h, 96%; ii.) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 84%; iii.) *tert*-butylthiopropionate, LDA, THF, −108 °C, 3 h, 5:1 dr, 82%; iv.) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 86%; v.) DIBAL, toluene, −78 °C, 3 h, 79%; vi.) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 45 min, 94%; vii.) TBDMSOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C, 1 h, 95%; viii.) CAN, acetone:H_2O (4:1), 0 °C, 5 min, 82%; ix.) 0.5 mM in toluene, 110 °C, 1 h, 82%.

Scheme 4[a]

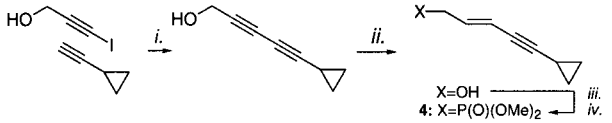


[a] Reagents and conditions: i.) ref 2f; ii.) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 55%; iii.) MeI, Ag_2O, DMF, rt, 12 h, 69%, iv.) H_2SO_4, PPTS, acetic anhydride, rt, 2 h, 81%; v.) K_2CO_3, MeOH, rt, 5 min, 89%; vi.) Cl_3CCN, NaH, CH_2Cl_2, rt, 10 min, 86%.

The timing for installation of the side chain was dictated by the nature of the two-step oxidative cleavage of the alkene and the Emmons−Wadsworth−Horner reaction. Best yields were obtained by performing these transformations at the stage of the macrolide **23**. Scheme 4 outlines the synthesis of the trichloroacetimidate of the *N*-silyl derivative of callipeltose (**15**). Methyl callipeltose (**24**) was synthesized starting from rhamnose as previously reported.[2f] In our hands, the *O*-methylation was best accomplished on the silylated oxazolidin-2-one. Scheme 5 provides a straightforward four-step approach to the deschloro side chain.

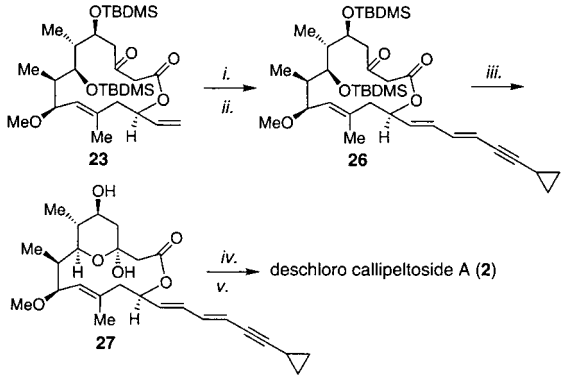
Scheme 6 depicts the completion of the synthesis. Chemoselective cleavage was best accomplished by sequential dihydroxylation followed by periodate cleavage. Emmons-−Wadsworth−Horner olefination produces a 4:1 *E:Z* mixture with the lithium salt at −78 °C.[10] Changing metal counterions to sodium or potassium or performing the reaction at higher temperature erodes the geometrical selectivity. Desilylation is accomplished by cyclization to form the aglycone **27**. Comparison of the ^1H and ^{13}C NMR spectra of **27** to those reported by Paterson for the chloro analogues[2e] showed a great likeness except for those regions associated with the chloro side chain. The glycosylation proceeded excellently to give a single diastereomer **2**. Again, comparison of the spectral data for **2** was virtually identical to that for callipeltoside A (**1**) except in those regions associated with the different side chains. The issue of the absolute configuration of the natural product is unresolved. Unfortunately, Paterson's data indicates the chloro substituent can have an immense impact on the sign of the rotation. Thus, although the sign of our rotation, $[\alpha]_D = +45.0$, is opposite that of the natural product,[1a] $[\alpha]_D = -17.6$, it is still not possible to assign the absolute stereochemistry. The excellent agreement of our NMR spectra to that of the natural product reinforces the correctness of the relative configuration of the sugar with respect to the macrolide.

Scheme 5[a]



[a] Reagents and conditions: i.) CuI, pyrrolidine, THF, 0 °C to rt, 2 h, 38%; ii.) Red Al, THF, 0 °C, 1 h, 96%; iii: PPh_3, CBr_4, CH_2Cl_2, −40 °C, 1 h, 95%; iv.) $P(OMe)_3$, 100 °C, 6 h, 97%.

Scheme 6[a]



[a] Reagents and conditions i.) OsO_4, NMO, THF:H_2O (4:1), 0 °C, 4 h; $NaIO_4$, THF:H_2O, rt, 3 h, 80%; ii.) **4**, LiHMDS, THF, −78 °C, 3 h, 4:1 (*E*:*Z*), 40%; iii.) HF·pyr, MeOH, rt, 3 h; ppts, H_2O, MeCN, rt, 1 h, 60%; iv.) **5** , TMSOTf, dichloroethane, 4 Å MS, dichloroethane, rt, 30 min, 80%; v.) TBAF, acetic acid, THF, rt, 5 min, 95%.

This concise synthesis of deschloro callipeltoside is comprised of 22 steps for the longest linear sequence with an additional five steps for the enyne and 14 steps for the sugar, all starting with commercially available materials. Either enantiomer of the core macrolide can be readily accessed since it emanates from two events: (1) the stereochemistry of methyl 3-hydroxy-2-methylpropionate (both enantiomers are commercially available) and (2) the Pd AAA which can provide either epimer simply by choice of ligand. Variation of the side chain including the naturally occurring chloro analogues may also be accessed. Our route highlights a new synthesis of geometrically defined trisubstituted alkenes using Ru catalysis and regio- as well as diastereoselective synthesis of an allyl ether via Pd AAA reactions that could not be easily accomplished otherwise.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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