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Asymmetric Synthesis of the Chlorocyclopropane-Containing Callipeltoside A Side Chain

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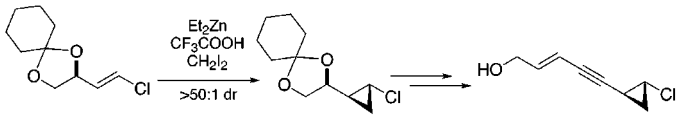
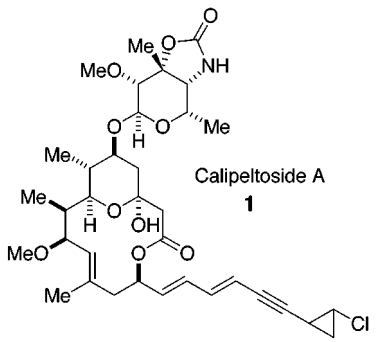
ABSTRACT



The callipeltoside A chlorocyclopropyl-containing dienyne side chain has been synthesized in nine steps and 33% overall yield from commercially available 1,2,5,6-*O*-dicyclohexylidene-D-mannitol. The key steps in the synthesis are a highly diastereoselective cyclopropanation of a vinyl chloride allylic ether and a Suzuki cross-coupling to complete the carbon framework.

During the course of screening marine organisms for the identification of new antitumor and antiviral agents, Minale and co-workers isolated the active constituent, callipeltoside A (**1**, Figure 1), from the marine sponge *Callipelta* sp. This new macrolide was found to display antitumor activity, as well as in vitro protection of HIV infected cells.[1] Callipeltoside A contains a highly functionalized deoxyamino sugar (callipeltose) and a dienyne-*trans*-chlorocyclopropane side chain appended to a polyketide-derived 14-membered macrolactone. The stereochemical assignment of **1** was made on the basis of extensive NMR spectroscopic studies. At the present time, the principal stereochemical ambiguity yet to be addressed is associated with the absolute stereochemical relationships associated with the pendant cyclopropane ring. The unique structure and biological activity of callipeltoside A has stimulated efforts directed toward a synthesis and ultimate stereochemical assignment of this natural product.[2] In this Letter we describe a practical asymmetric synthesis of the chlorocyclopropane-containing dienyne side chain.



Calipeltoside A
1

Figure 1.

Scheme 1 illustrates the general synthetic strategy that is being pursued in the assemblage of callipeltoside A. Because of the stereochemical ambiguity associated with the dienyne side chain, our objectives are to be able to readily access either C15−C22 side chain enantiomer which might be appended to the glycosylated macrolactone through an (*E*)-selective Horner−Emmons coupling of phosphonate **4** with the lactone subunit **3**.[3] Dibromoolefin **5** serves as a suitable precursor to phosphonate **4** using either a Stille[4] or a Suzuki[5] coupling/elimination sequence. The chlorocyclopropane **5**

(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. *Tetrahedron* **1997**, *53*, 3243−3248.

(2) (a) Smith, G. R.; Finley, J. J.; IV.; Giuliano, R. M. *Carbohydr. Res.* **1998**, *308*, 223−227. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169−171. (c) Velázquez, F.; Olivo, H. F. *Org. Lett.* **2000**, *2*, 1931−1933. (d) Olivo, H. F.; Velázquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055−4058.

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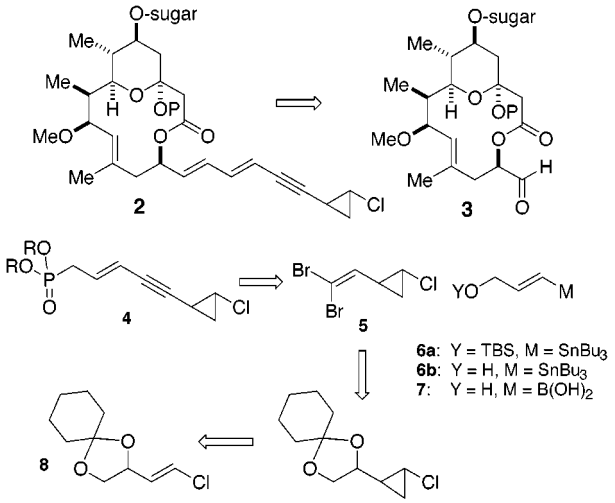
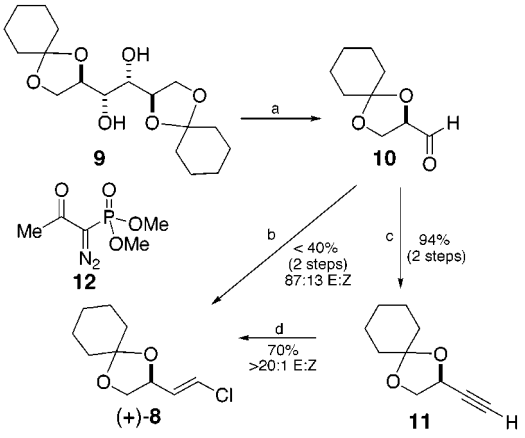
Scheme 1



would arise from a diastereoselective cyclopropanation of vinyl chloride **8**.

While the Takai reaction[6] of glyceraldehyde cyclohexylidene ketal **10**[7] was initially investigated to afford vinyl chloride (+)-**8**, the reaction exhibited modest selectivity (87:13) and yields (Scheme 2). Significantly, the olefin isomers

Scheme 2

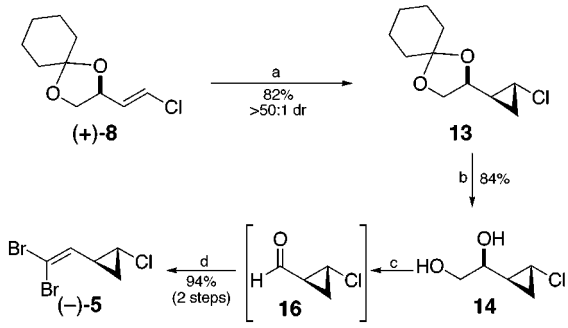


Reaction conditions: (a) KIO_4, $KHCO_3$, THF/H_2O, rt; (b) $CrCl_2$, $CHCl_3$, THF, 70 °C; (c) **12**, K_2CO_3, MeOH, rt; (d) (i) $Thexyl_2BH$, −15 to 0 °C, THF, (ii) $CuCl_2$, H_2O, HMPA, THF, 0 to 70 °C.

were not readily separated by chromatography. As an alternative, an improved two-step stereospecific route was adopted. Homologation of unpurified **10** using Ohira's reagent **12**[8] yielded alkyne **11** in 94% yield. The one-pot hydroboration/chlorination sequence developed by Masuda[9] was then employed to afford vinyl chloride (+)-**8** in 70% yield as a single olefin isomer (>20:1).

Vinyl chloride (+)-**8** proved resistant to Simmons−Smith cyclopropanation. Less than 15% conversion was observed using either the Furukawa[10] or Denmark[11] reaction variants. These failures prompted investigation of the highly activated conditions developed by Shi, in which Et_2Zn is premixed with 1 equiv of trifluoroacetic acid prior to the addition of 1 equiv of CH_2I_2.[12] This dramatically enhanced carbenoid delivered chlorocyclopropane **13** as a single diastereomer (>50:1)[13] in 82% yield (Scheme 3). This result illustrates

Scheme 3



Reaction conditions: (a) Et_2Zn, CF_3COOH, CH_2I_2, CH_2Cl_2, rt; (b) Dowex resin, MeOH, rt; (c) $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, rt; (d) PPh_3, CBr_4, CH_2Cl_2, rt.

that the Shi conditions can be used for directed cyclopropanations of electron-deficient olefins.

Removal of the cyclohexylidene protecting group initially proved difficult due to reketalization during in vacuo concentration. However, washing the methanolic reaction solution with hexanes prior to concentration removed the cyclohexanone dimethyl ketal and allowed the isolation of diol **14** in 84% yield (Scheme 3). Diol **14** was converted to the desired dibromide (−)-**5** in two steps (Scheme 3). Diol cleavage with potassium carbonate-buffered lead tetraacetate afforded the volatile aldehyde **16** which was treated with 5 equiv of the Corey−Fuchs reagent[14] without purification to

(3) (a) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548−3551. (b) Nicolaou, K. C.; Chung, Y. S.; Hernandez, P. E.; Taffer, I. M.; Zipkin, R. E. *Tetrahedron Lett.* **1986**, *27*, 1881−1882. (c) Nicolaou K. C.; Webber, S. E. *Chem. Commun.* **1986**, 1816−1817.

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

(5) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509−6512. (b) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691−2694.

(6) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(7) Aldehyde **10** was prepared by the method of: Schmid, C.; Bradley, D. A. *Synthesis* **1992**, 587−590.

(8) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

(9) Masuda, Y.; Hoshi, M.; Arase, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2725−2726.

(10) Furukawa, J.; Kawabata, N.; Nishimura. J. *Tetrahedron* **1968**, *24*, 53−58.

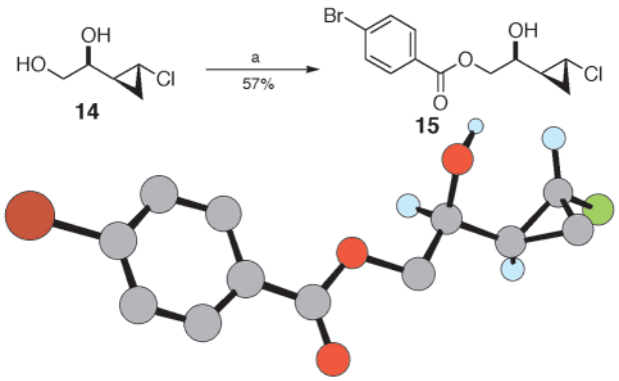
(11) Denmark, S.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390−3401.

(12) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621−8624.

(13) The diastereoselectivity was verified by independent synthesis of a mixture of cyclopropane diastereomers, which were distinguishable by gas chromatography (see Supporting Information).

(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *23*, 3769−3772.

Scheme 4



Reaction conditions: (a) *p*-BrC_6H_4COCl, pyr, CH_2Cl_2, 0 °C.

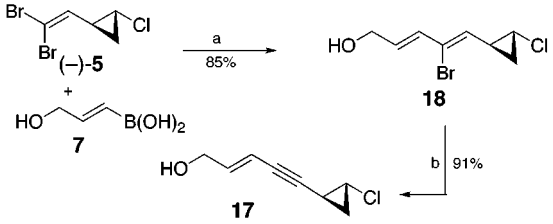
afford (−)-**5** in 94% overall yield. The relative and absolute stereochemistry of the cyclopropane was verified by single-crystal X-ray crystallographic analysis of the derived *p*-bromobenzoate **15** (Scheme 4).

Conversion of dibromide (−)-**5** to the desired enyne alcohol **17** using the Stille coupling/elimination conditions developed by Shen[4] was initially attempted with vinylstannanes **6a** and **6b**. This sequence produced the desired enynes in low yield (<50%), and chromatographic removal of tin byproducts proved problematic. A sequential coupling and elimination using the Roush modification of the Suzuki coupling[5] was pursued as an alternate coupling strategy. Coupling of dibromide (−)-**5** with vinylboronic acid **7**[15] in the presence of $Pd(PPh_3)_4$ and thallium ethoxide afforded the dienol **18** in 85% yield (Scheme 5). The side chain synthesis was completed using a DBU-induced elimination[16] to produce enyne alcohol **17** in 91% yield.

(15) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989−8992. The authors thank Prof. William Roush and Dr. Scott Frank for providing the experimental details for the preparation of **7**.

(16) Nakamura, T.; Namiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635−2645.

Scheme 5



Reaction conditions: (a) $Pd(PPh_3)_4$, TlOEt, THF/H_2O, rt; (b) DBU, MePh, 110 °C.

In summary, a highly stereoselective synthesis of the enantiopure side chain of callipeltoside A has been completed in nine steps and 33% overall yield from commercially available 1,2,5,6-di-*O*-cyclohexylidene-D-mannitol. This synthesis is amenable to the preparation of both enantiomers of the side chain, using *ent*-**10**, which is available by periodate cleavage of 5,6-*O*-cyclohexylidene-L-gulono-1,4-lactone.[17] The total synthesis of callipeltoside A will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of compounds (−)-**5**, (+)-**8**, **11**, **13**, **14**, **17**, and **18**; synthesis and GC separation of a diastereomeric mixture of **13**; X-ray crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The conversion of 5,6-*O*-pentylidene-L-gulono-1,4-lactone to L-glyceraldehyde pentylidene ketal is known; see ref 7.