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Synthetic Studies on the *trans*-Chlorocyclopropane Dienyne Side Chain of Callipeltoside A

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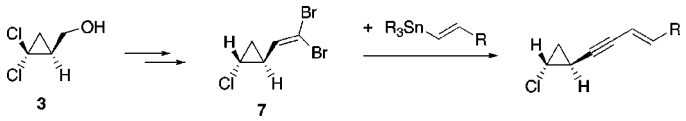
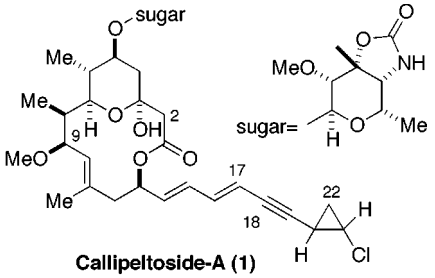
ABSTRACT



Enantiomerically enriched *trans*-chlorocyclopropanemethanol was obtained by lipase kinetic resolution of dichlorocyclopropanemethanol 3, followed by reduction. The sp–sp^2 bond of the *trans*-chlorocyclopropane dienyne side chain of callipeltoside A was constructed via a Stille coupling reaction of 1,1-dibromo-1-alkene 7 and a vinylstannane in a highly dipolar solvent capable of promoting HBr elimination to give internal alkynes.

Callipeltoside A (**1**, Scheme 1), a macrolactone isolated in small amount from the marine sponge *Callipelta* sp. in 1996,

Scheme 1



was found to exhibit moderate antitumor activity and to protect cells infected with HIV virus.[1] The relative configuration of this complex macrolactone, adorned with a deoxyamino sugar (callipeltose) and a dienyne side chain bearing a unique *trans*-chlorocyclopropane ring, was deduced by extensive NMR experiments. However, the relative configuration of the *trans*-chlorocyclopropane motif was not determined because connectivities "through space" between the protons of the cyclopropane ring and the rest of the molecule could not be observed.[1]

Synthetic efforts toward the synthesis of this natural product have led to the publication of a few reports, but no total synthesis has been reported to date. Hoye and Zhao reported their attempts to cyclize the C1−C14-containing fragment of callipeltoside A via ring closing metathesis.[2] The synthesis of the deoxyamino sugar callipeltose, from L-rhamnose, was reported by Giuliano and co-workers.[3] We recently reported the enantioselective synthesis of the C1−C9 fragment of callipeltoside, where the hemiketal framework was synthesized by means of a regiocontrolled epoxide-opening reaction to set two vicinal stereocenters and a chemospecific metal-catalyzed Baeyer−Villiger reaction to construct a δ-lactone precursor of the hemiketal ring.[4] In this Letter, we report our synthetic studies on the construction

(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) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169−171.

(3) Smith, G. R.; Finley IV, J.; Giuliano, R. M. *Carbohydr. Res.* **1998**, *308*, 223−227.

(4) Velázquez, F.; Olivo, H. F. *Org. Lett.* **2000**, *2*, 1931−1933.

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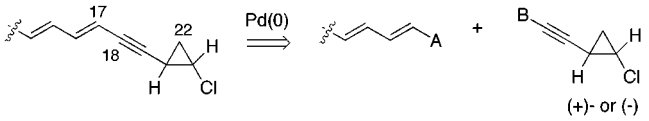
of the dienyne side chain and the enantioselective synthesis of the *trans*-chlorocyclopropane ring.

In our synthetic strategy of callipeltoside A, we envision the construction of the sp−sp^2 bond of the dienyne side chain (C17−C18) late in the synthesis (Scheme 2). Installation of

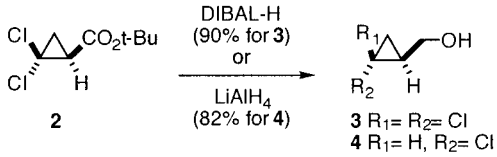
Scheme 2



either (+)- or (−)-enantiomers of *trans*-chlorocyclopropane acetylene to the terminal diene will allow us to prepare both possible diasteromeric structures of callipeltoside A to solve the relative configuration problem. Initially, we decided to investigate the construction of the dienyne side chain to pave the way to secure a total synthesis.

Diisobutylaluminum hydride (DIBAL-H) reduction of *tert*-butyldichlorocyclopropane carboxylate (**2**)[5] in dichloromethane furnished dichlorocyclopropanemethanol (**3**) when the reaction was carried out at 0 °C for 4 h (Scheme 3). The major

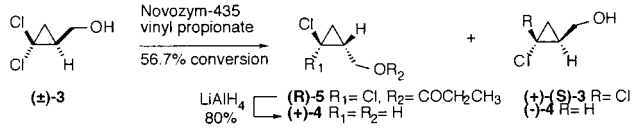
Scheme 3



product of the reduction of ester **2** was the *trans*-chlorocyclopropanemethanol (**4**) when the reaction was carried out with lithium aluminum hydride in diethyl ether at 40 °C for several days.[6]

Biocatalysis has proved to be a powerful tool in asymmetric synthesis.[7] Our laboratory has reported the application of biocatalysis in the synthesis of alkaloids and medicinally important compounds.[8] We decided to use a lipase kinetic resolution for the preparation of enantiomerically enriched *trans*-chlorocyclopropane methanol (**4**). However, lipase kinetic resolution of monochloro alcohol **4** was disappointing (E < 10)[9] after screening 20 different commercially available lipases. It has been suggested that increasing the size of the large substituent on the stereocenter of the primary alcohol can help to increase the enantiomeric discrimination.[10] To take advantage of this consideration, we turned our attention to dichloro alcohol **3**, in which the chiral center has a larger substituent than the initially studied monochloro alcohol **4** (Scheme 4). After some optimization of the enzymatic

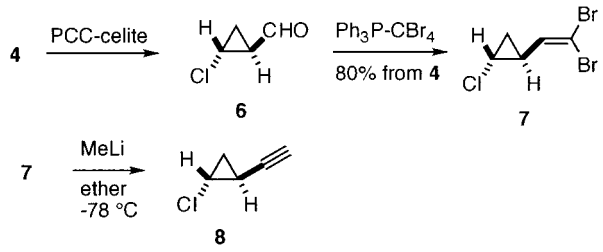
Scheme 4



transesterification conditions using immobilized enzyme Novozym-435 and vinyl propionate, we were delighted to obtain unreacted dichloro alcohol (+)-**3** with >97% ee[11,12] and propionate ester **5** with 74% ee (E = 27.2). Separation of ester **5** and alcohol **3** in gram scale was possible using extractive techniques. Lipase hydrolysis of enantioenriched ester **5** using the same immobilized enzyme in an acetone−aqueous buffer mixture gave dichloro alcohol (−)-**3** with > 97% ee. The absolute stereochemistry of the resolution product was determined applying Kazlauskas' empirical rule,[13] which predicts the enantiomer that reacts faster in reactions catalyzed by lipases on the basis of the sizes of the substituents at the stereocenter. Lithium aluminum hydride reduction of both enantioenriched dichloro alcohols (+)- and (−)-**3** gave the monochloro alcohols (−)- and (+)-**4**, respectively.[14]

Having the two enantioenriched alcohols of **4** in hand, we proceeded to homologate the molecule to the corresponding acetylene, Scheme 5.[15] Alcohol **4** was readily oxidized using

Scheme 5



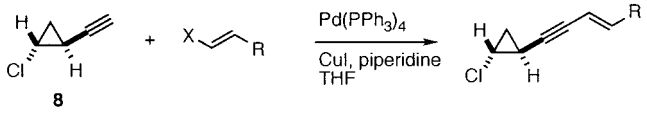
PCC−Celite to aldehyde **6**.[16] Aldehyde **6** was immediately

(5) Fedorynski, M.; Ziolkowska, W.; Jonczyk, A. *J. Org. Chem.* **1993**, *58*, 6120−6121.
(6) Nadim, A. M.; Romashin, Y. N.; Kulinkovich, O. G. *J. Org. Chem. (USSR)* **1992**, 1419−1422.
(7) Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, 1995.
(8) (a) Hemenway, M. S.; Olivo, H. F. *J. Org. Chem.* **1999**, *64*, 8968−8969. (b) Olivo, H. F.; Yu, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 391−392.
(9) The E value is the *enantiomeric ratio* as defined in the following: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.
(10) Bornscheuer, U. T.; Kazlauskas, R. J. In *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999.
(11) Enantiomeric ratios were determined by gas chromatography, using a Chiraldex G-TA capillary column.
(12) Dichlorocyclopropylmethanol (*S*)-**3**: $[\alpha]^{27}_D$ +4.0 (*c* 1.0, $CHCl_3$).
(13) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959−6969.
(14) Reduction of dichloro alcohol (+)-(*S*)-**3** gave monochloro alcohol (−)-**4**: $[\alpha]^{27}_D$ −68 (*c* 1.0, $CHCl_3$). Reduction of dichloro alcohol (−)-(*R*)-**3** gave monochloro alcohol (+)-**4**: $[\alpha]^{27}_D$ +68 (*c* 1.0, $CHCl_3$).
(15) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−72.
(16) Baldwin, J. E.; Villarica, K. A. *J. Org. Chem.* **1995**, *60*, 186−190.

reacted with triphenylphosphine−carbon tetrabromide to obtain dibromoolefin **7**. Treatment of dibromoolefin **7** with methyllithium gave the desired alkyne **8** in low yield presumably due to volatility and purification problems. The crude alkyne **8** was used without purification in palladium cross coupling reactions in an effort to solve the isolation problem.

Our first choice to form the sp−sp^2 bond was the Sonagashira coupling.[17] It was recently demonstrated that palladium(0)-catalyzed coupling of a vinyl halide with a terminal alkyne in the presence of CuI and base is a valuable procedure to prepare stereochemically well-defined enynes and dienynes.[18] Sonagashira coupling of acetylene **8**, prepared without purification from dibromoolefin **7**, with different vinyl halides (**9**−**11**) gave the desired enynes (**12**−**14**), albeit in less than satisfactory yields (Table 1). A

Table 1. Synthesis of Enynes via Sonagashira Coupling



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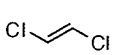
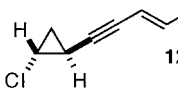
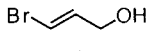
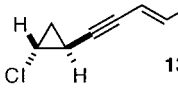
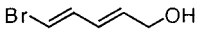
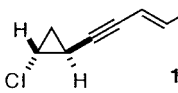
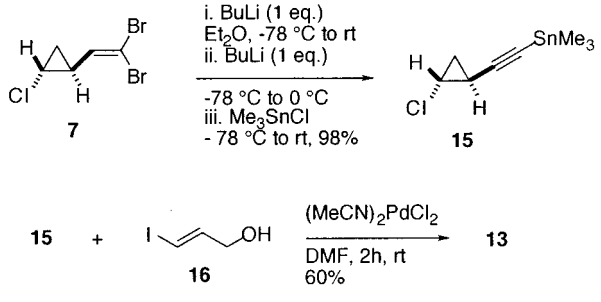
entry	vinyl halide	product (yield, %)
1	 **9**	 **12** (37%)
2	 **10**	 **13** (24%)
3	 **11**	 **14** (25-40%)

possible explanation is that impurities in the crude acetylene **8** may be responsible for the low yields. Thus, we elected to prepare a heavier alkyne derivative which could facilitate the purification process.

Using a modified Corey−Fuchs homologation procedure, alkyne stannane **15** was prepared in excellent yield from dibromoolefin **7** (Scheme 6). Purification of the trimethylstannane **15** was accomplished by bulb to bulb distillation without observing any decomposition. Palladium-catalyzed

Scheme 6

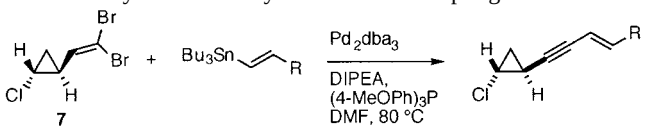


7 **15** **16** **13**

coupling of alkyne stannane **15** and vinylic iodide **16** in DMF at room temperature gave enyne **13** in good yield.[19]

Shen and Wang reported recently an elegant and detailed account on the chemistry of 1,1-dibromo-1-alkenes.[20] It was found that palladium-catalyzed cross coupling of 1,1-dibromoolefins with vinyl- or arylstannanes can be controlled by the kind of ligand and solvent employed to give (*Z*)-bromoalkenes, trisubstituted alkenes, and more importantly internal alkynes. This novel methodology appeared suitable to synthesize the dienyne fragment of callipeltoside A. Indeed, when dibromoolefin **7** was treated with vinylstannane **17**[21] in the presence of tris(dibenzylideneacetone)-dipalladium(0) (Pd_2dba_3) as the palladium source, an electron rich and highly coordinating ligand (tris(4-methoxyphenyl)-phosphine), and diisopropylethylamine (DIPEA) in a highly dipolar solvent (DMF), enyne **13** was obtained in good yield (Table 2). Furthermore, better yields were obtained when

Table 2. Synthesis of Enynes via Stille Coupling



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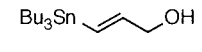
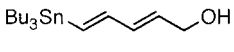
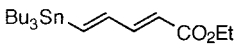
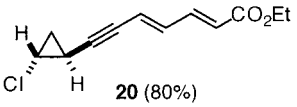
entry	vinyl stannane	product (yield, %)
1	 **17**	**13** (65%)
2	 **18**	**14** (95%)
3	 **19**	 **20** (80%)

diene stannanes **18** and **19** were employed in the coupling reaction with dibromoolefin **7**.[22] The application of this methodology to the synthesis of the dienyne side chain of callipeltoside A appears more advantageous than the other methods employed previously because it avoids the preparation of fragile intermediates and it gives direct access to the desired dienyne side chain.

In summary, we prepared both enantiomeric forms of *trans*-chlorocyclopropane methanol (**4**), valuable chiral intermediates for the total synthesis of callipeltoside A. Furthermore, we found that 1,1-dibromoolefin **7** can be used as an excellent alkyne equivalent in a Stille coupling to construct the dienyne side chain of callipeltoside A (C13−C22 fragment). Further studies of subunits synthesis leading to the total synthesis of callipeltoside A are currently in progress.

(17) Sonagashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 521−549.
(18) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, 65, 616−620.
(19) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.
(20) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873−8879.
(21) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854.
(22) Diene ester **19** was prepared from vinyl iodide **17** by one-pot oxidation−Wittig olefination.[18] Reduction of diene ester **19** with Dibal-H furnished alcohol **18**.

Acknowledgment. This work was supported by a grant from the National Science Foundation (MRPG, CHE-9974384). We thank Consejo Nacional de Ciencia y Tecnología (CONACyT, México) for a predoctoral fellowship to F.V., Fundação de Amparo a Pesquisa do Estado de São Paulo for a fellowship to H.C.T., and Amano Lipases and EnzyMed for the lipases used in this study.

Supporting Information Available: Experimental procedures for the lipase-catalyzed resolution and the Stille coupling, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra of compounds **2**−**7**, **12**−**15**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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