ORGANIC LETTERS

2009
Vol. 11, No. 23
5382−5385

Synthesis of (*S*)-Jamaicamide C Carboxylic Acid

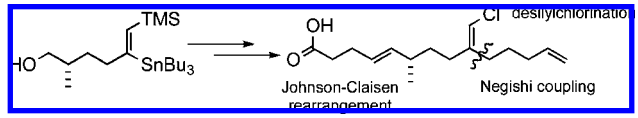
Kristin M. Graf,[†] Martin G. Tabor,[‡] Milton L. Brown,[‡] and Mikell Paige*[,‡]

Drug Discovery Program, Georgetown University Medical Center, 3970 Reservoir RD, NW, NRB EP15A, Washington D.C., 20057, and Department of Chemistry, University of Virginia, McCormick Road, Charlottesville, Virginia 22901

map65@georgetown.edu

Received September 14, 2009

ABSTRACT



The jamaicamides are natural product sodium channel blockers derived from the cyanobacterium *Lyngbya majuscula*. The carboxylic acid fragment of jamaicamide C contains a methyl stereocenter and a trisubstituted *E* chloroolefin. Herein, we present the nonracemic synthesis of the aliphatic chain of jamaicamide C. The methyl stereocenter was installed using Evans' oxazolidinone methodology, and the trisubstituted chloroolefin was set by silylstannylation of a triple bond.

Jamaicamides A, B, and C make up a family of lipopeptidic natural products isolated from a dark green strain of *Lyngbya majuscula*, a cyanobacterium from Hector's bay, Jamaica. The jamaicamides differ in structure only at the terminal end of their polyketide aliphatic chain (Figure 1).[1] Jamaicamides were found to block the sodium channel in a cell-based screen developed by Manger and co-workers, which involved measuring the end point of mitochondrial dehydrogenase activity in neuroblastoma cells.[2]

Sodium channel blockers are an important class of drugs,[3] and novel molecules that block this channel may provide new structures with clinical potential. To date, the jamaicamides and kalkitoxin are the only polyketide-peptides reported to be sodium channel blockers and, as such, represent a new template for the design of novel sodium channel ligands. Kalkitoxin was synthesized by White's group in 2003;[4] this was followed by a second total synthesis by the Shioiri group in 2004.[5] However, to the best of our knowledge, the total synthesis of jamaicamide has not been accomplished.

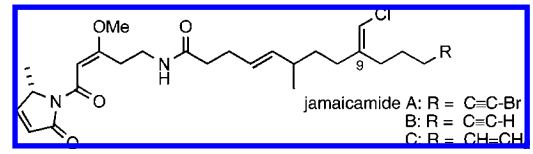


Figure 1. Structure of jamaicamides A, B, and C.

In our efforts toward the total synthesis of jamaicamide C, construction of the appended vinyl chloride substituent at C-9 proved to be a considerable synthetic challenge. In this report, we describe a strategy to stereoselectively set this *E* trisubstituted olefin, which led to the nonracemic synthesis of the polyketide aliphatic chain of jamaicamide C.

Initially, we envisioned setting the trisubstituted chloroolefin by suitable functionalization of a terminal acetylene, chlorination, and alkyl homologation, which together would

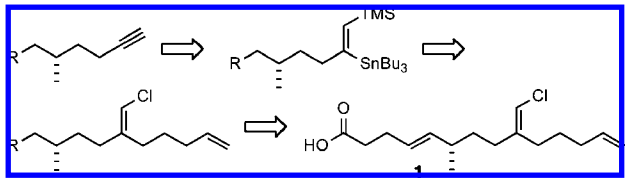
[†] University of Virginia.
[‡] Georgetown University.

(1) Edwards, D. J.; Marquez, B. L.; Nogle, L. M.; McPhail, K.; Goeger, D. E.; Roberts, M. A.; Gerwick, W. H. *Chem. Biol.* **2004**, *11*, 817–833.
(2) Manger, R. L.; Leja, L. S.; Lee, S. Y.; Hungerford, J. M.; Hokama, Y.; Dickey, R. W.; Granade, H. R.; Lewis, R.; Yasumoto, T.; Wekell, M. M. *J. AOAC Int.* **1995**, *78*, 521–527.
(3) Anger, T.; Madge, D. J.; Mulla, M.; Riddall, D. *J. Med. Chem.* **2001**, *44*, 115–137.
(4) White, J. D.; Lee, C.-S.; Xu, Q. *Chem. Commun.* **2003**, 2012–2013.
(5) Yokokawa, F.; Asano, T.; Okino, T.; Gerwick, W. H.; Shioiri, T. *Tetrahedron* **2004**, *60*, 6859–6880.

10.1021/ol9021222 CCC: $xxxx
Published on Web 11/11/2009

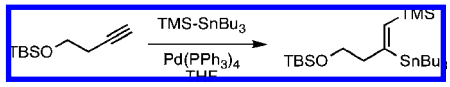
give a general route to unsymmetrical bisalkyl vinyl chlorides. Silylstannylation of terminal acetylenes is a convenient way of accessing a dimetalated olefin of defined stereochemistry and differential reactivity. We therefore decided to incorporate such a reaction in our strategy for the synthesis of the carboxylic acid polyketide of jamaicamide C as shown in Scheme 1.

Scheme 1. Strategy for Polyketide **1**



We began our studies with TBS-protected butyn-1-ol as our model substrate. As outlined in Table 1, treatment with trimethylsilyltributylstannane under conditions reported by Mitchell and co-workers[6] provided the silylstannylated product as a single isomer. Optimization of the silylstannylation reaction was accomplished under microwave conditions to give the product in 1 h as compared to 15 h at reflux in THF (Table 1, entries 3 and 1, respectively). Increasing catalyst loading resulted in a modest increase in yield. Although the yields for the thermally induced reactions were comparable to those obtained by microwave irradiation, the product obtained under microwave conditions was formed more rapidly and was more readily purified.

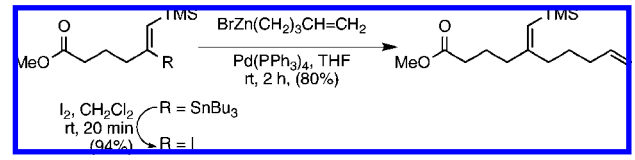
Table 1. Optimization of the Silylstannylation Reaction



entry	conditions	time	yield (%)
1	reflux, 2 mol % $Pd(PPh_3)_4$	15 h	64%
2	reflux, 4 mol % $Pd(PPh_3)_4$	24 h	71%
3	microwave 150 W, 95 °C, 2 mol % $Pd(PPh_3)_4$	1 h	61%
4	microwave 150 W, 95 °C, 4 mol % $Pd(PPh_3)_4$	1 h	75%

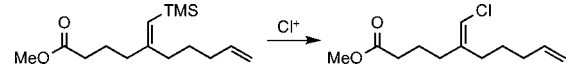
The silylstannylated product of methyl 5-hexynoate was synthesized as a model substrate for elaboration to the terminal end of jamaicamide C. Selective conversion of the tributylstannane group to the vinyl iodide followed by subsequent Negishi coupling to append the 5-pentenyl group was accomplished in high yield as outlined in Scheme 2.

Scheme 2. Iodination Followed by Negishi Coupling



Desilylchlorination was required to install the trisubstituted vinyl chloride motif. As outlined in Table 2, a series of conditions were screened to convert the trimethylsilyl group to a chloride.[7] The optimized conditions resulted from the use of 2 equiv of NCS in DMF for 72 h at 50 °C (Table 2, entry 7).

Table 2. Optimization of the Desilylchlorination Reaction[a]



entry	solvent	time	temp.	Cl^+	results
1	DMSO	24 h	50 °C	2 equiv NCS	desilylation
2	DMF	24 h	50 °C	2 equiv NCS	incomplete conv.
3	DMF	24 h	50 °C	5 equiv NCS	incomplete conv.
4	DMF	5 h	75 °C	2 equiv NCS	decomposition
5	DMF	2 h	50 °C	2 equiv HxC[b]	multiple impurities
6	CH_3CN	24 h	50 °C	2 equiv NCS	multiple impurities
7	DMF	72 h	50 °C	2 equiv NCS	complete, 80% yield

[a] Yields determined by GCMS. [b] HxC = 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one.

With the synthetic conditions devised for our model trisubstituted chloroolefin system, we commenced our synthesis of the polyketide region of the jamaicamides as shown in Scheme 3. From the known amide **2**,[8] lithium amidoborane reduction of the chiral auxiliary provided the primary alcohol **3**. TPAP-catalyzed oxidation of alcohol **3** to the aldehyde followed by treatment with vinylmagnesium bromide gave allylic alcohol **4** as a mixture of diastereomers (~1:1 mixture). Johnson−Claisen rearrangement to enoate **5** was followed by TBAF-mediated deprotection of the DPS protecting group and oxidation of the resulting alcohol to aldehyde **6**. One-carbon alkynylation was accomplished under Ohira−Bestmann conditions to yield the target alkyne **7**.

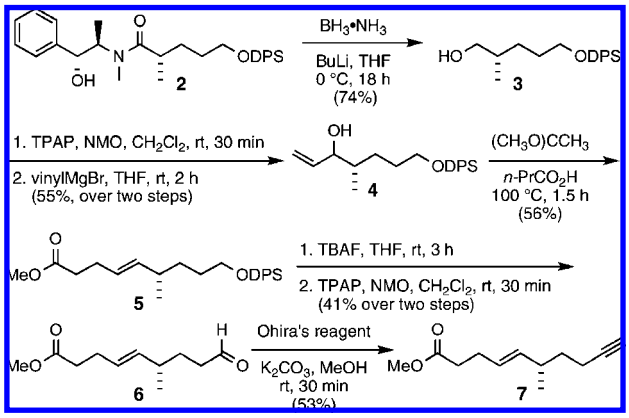
Silylstannylation of alkyne **7** produced the functionalized olefin **8** as expected. However, elaboration of stannane **8** to the vinyl iodide under the conditions worked out in Scheme 2 resulted in desilylated vinyl iodide **9a**. Buffering the reaction with triethylamine allowed for synthesis of vinyl iodide **9b** with the silyl group intact. Unfortunately, Negishi coupling under the conditions devised for our model system

(6) Mitchell, T. N.; Killing, H.; Dicke, R.; Wickenkamp, R. *Chem. Commun.* **1985**, 354–355.

(7) Initial conditions were derived from Kigoshi's synthesis of haterumalide NA, which contains a trisubstituted chloroolefin with a different substitution pattern than found in the jamaicamides. See: Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957–960.

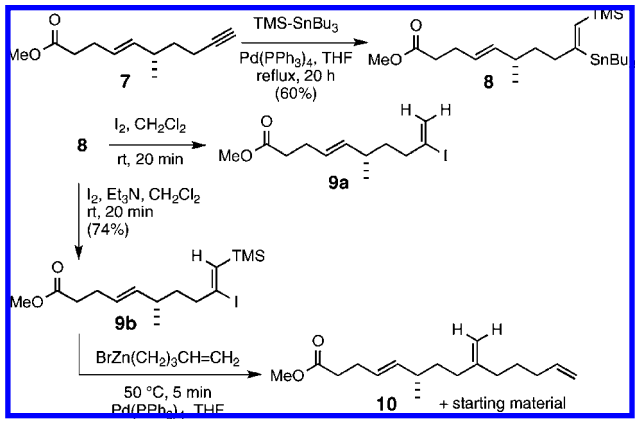
(8) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.

Scheme 3. Synthesis of Alkyne **7**



resulted in desilylation. The homologated substrate **10** was isolated with a considerable amount of starting material (Scheme 4).

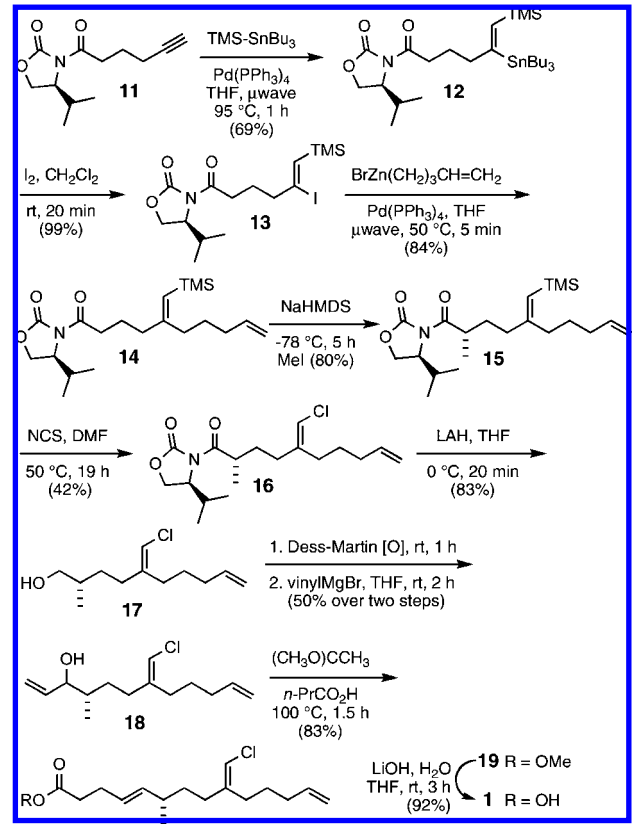
Scheme 4. Failed Approach to Jamaicamide C Carboxylic Acid



The reasons for the problems faced with the iodination followed by Negishi coupling of substrate **8** are not clear. The main difference between substrate **8** and the model system is a methyl stereocenter and the presence of an ester with a carbon−carbon double bond. Danishefsky reported a remote olefin-directed aldol facial selectivity presumably due to electron donation of the olefin into a carbonyl group.[9] Smith reported that the acidity of a dithiane was reduced due to $\pi \rightarrow \sigma^*$ donation of a remote olefin into an unfilled orbital on the dithiane sulfur atom.[10] It remains unclear whether a $\pi \rightarrow \pi^*$ event between the remote olefin and the silylstannylated olefin plays a role in the facile desilylation of our substrate.

On the basis of our hypothesis that the remote double bond is problematic for the Negishi coupling, we developed a revised route that involves installation of the internal *E* olefin late in the synthesis as outlined in Scheme 5.

Scheme 5. Synthesis of Carboxylic Acid **1**



Palladium-mediated silylstannylation of oxazolidinone **11** under microwave irradiation conditions provided vinylstannane **12** in 69% yield. Iodination gave vinyl iodide **13** in 99% yield, which then underwent Negishi coupling to give the homologated product **14** in 84% yield. Generation of the enolate of oxazolidinone **14** followed by methylation resulted in compound **15** in 80% yield as a single product.[11] Conversion of the vinylsilane to the vinyl chloride was accomplished by treatment with NCS in DMF to give the product in 42% yield. Removal of the oxazolidinone was accomplished by treatment with lithium aluminum hydride and gave alcohol **17**. Oxidation to the aldehyde under Dess−Martin conditions followed by addition of vinylmagnesium bromide afforded allylic alcohol **18** in 50% yield over the two steps as a mixture of diastereomers (∼1:1 mixture). Johnson−Claisen rearrangement gave methyl ester **19** in 83% yield, which was saponified to give the nonracemic jamaicamide C carboxylic acid (**1**) in 11 steps from commercially available 5-hexynoic acid.

According to Tamao and co-workers, vinylsilanes react with electrophilic halides to give a stabilized carbocation β

(9) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 2267–2270.

(10) Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468–10477.

(11) Kalesse, M.; Quitschalle, M.; Claus, E.; Gerlach, K.; Pahl, A.; Meyer, H. H. *Eur. J. Org. Chem.* **1999**, 2817–2833.

to the silyl group.[12] For *E* disubstituted vinylsilanes, inversion of configuration with respect to the position of the starting silane was observed when the reaction was carried out in DMF. Following Tamao's analysis, conditions for conversion of our trisubstituted vinylsilane to the vinyl chloride in DMF were predicted to give inversion of configuration. However, Chou and co-workers reported the conversion of a trisubstituted vinylsilane (with a similar substitution pattern to ours) to the corresponding vinyl halide with retention of configuration.[13] In Chou's case, (*E*)-2-ethyl-1-(trimethylsilyl)-1-hexene was treated with iodine monochloride in carbon tetrachloride to give the corresponding (*E*)-vinyl iodide. On the basis of these reports, it was necessary for us to determine whether our reaction resulted in inversion or retention of configuration (Figure 2).

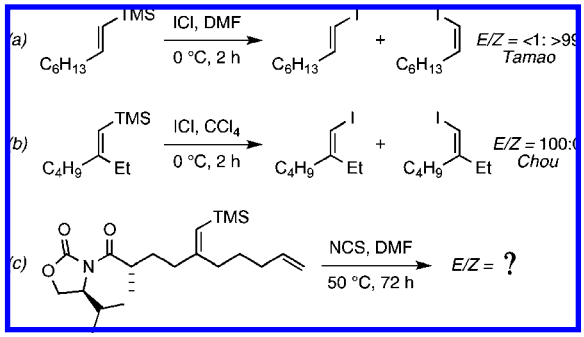


Figure 2. Stereochemical results of desilylhalogenation reactions.

For the structure elucidation of the jamaicamides, the configuration of the chloroolefin was determined by HSQMBC experiment, which allowed for measurement of the coupling constants between the chloroolefin vinylic proton and each adjacent allylic carbon atom.[1,14] We employed 400 MHz 2D-NOESY analysis to determine the configuration of the chloroolefin. As shown in Figure 3, there was an intense NOE signal between δ 5.77 and δ 2.00 ppm suggesting that the configuration of the double bond was *E*.

In summary, the synthetic sequence presented above is an efficient route for the synthesis of the polyketide fragment

(12) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100–1106.
(13) Chou, S. -S. P.; Kuo, H.-L.; Wang, C.-J.; Tsai, C.-Y.; Sun, C.H-M. *J. Org. Chem.* **1989**, *54*, 868–872.
(14) Williamson, R. T.; Marquez, B. L.; Gerwick, W. H.; Kover, K. E. *Magn. Reson. Chem.* **2000**, *38*, 265–273.

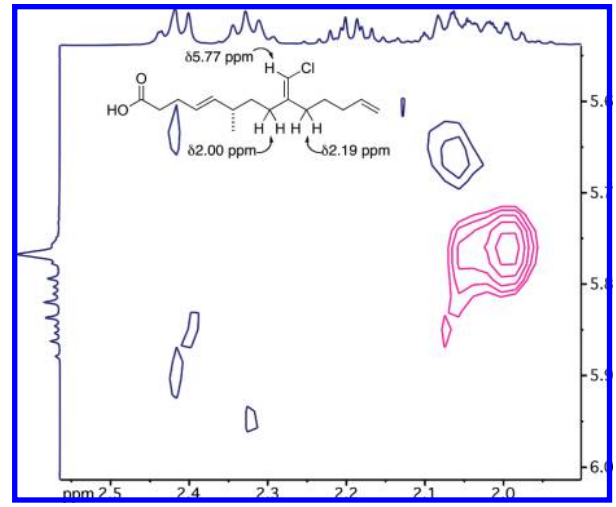


Figure 3. 400 MHz 2D-NOESY of jamaicamide C carboxylic acid ($CDCl_3$).

of jamaicamide C that can be applied toward the total synthesis of the jamaicamide family of natural products. We have also reported a new strategy for setting unsymmetrical trisubstituted chloroolefins with complete stereocontrol. Also noteworthy are optimization of the silylstannylation reaction and the Negishi coupling under microwave irradiation. Finally, we report optimized conditions for the conversion of a vinylsilane to the chloroolefin and show by 2D-NOESY NMR experiments that the reaction gives retention of configuration.

Acknowledgment. We would like to thank the Georgetown University Drug Discovery Program and the Lombardi Comprehensive Cancer Center (LCCC) for support. We thank Dr. James A. Marshall at the University of Virginia for suggesting a thorough analysis of the stereochemistry of the desilylchlorination reaction, and we acknowledge LCCC Proteomics & Metabolomics Shared Resource (PMSR) for mass spectrometry analysis.

Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9021222