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Synthesis of the C20–C26 Building Block of Halichondrins via a Regiospecific and Stereoselective S_N2' Reaction

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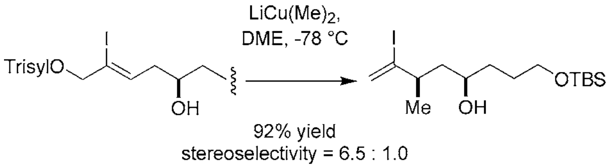
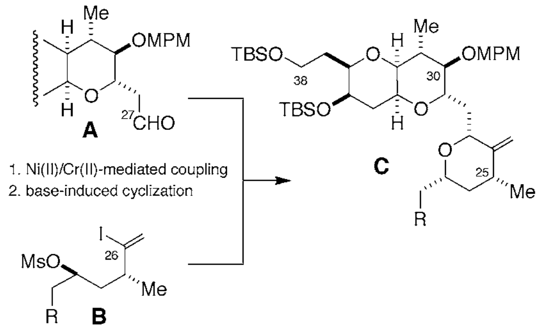
ABSTRACT



A regiospecific and stereoselective S_N2' reaction to convert the trisylate into the vinyl iodide is presented. The homoallylic alcohol is used to direct the delivery of $LiCu(Me)_2$.

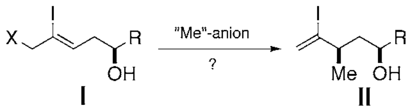
In earlier work, we demonstrated that the C26−C27 bond of the halichondrins can effectively be formed via Ni(II)/Cr(II)-mediated coupling reaction, followed by base-induced cyclization, cf., **A** + **B** → **C** (Scheme 1).[1−3] Obviously, for effective use of this transformation, an efficient synthesis of alkenylhalides such as **B** is required.[4] In this letter, we report a practical synthesis of the vinyl iodide **B** (R = CH_2CH_2OTBS), using a regiospecific and stereoselective S_N2' reaction.

Scheme 1



For the synthesis of **B**, at least two issues need to be addressed; one is a method to incorporate the alkenylhalide functionality itself and the other is a method to selectively incorporate the two stereocenters at C23 and C25. We recognized the possibility that the transformation of **I** → **II** might give a solution to both issues (Scheme 2). The preferred conformation of an allylic system is known to be eclipsed.[5] Among the three eclipsed conformers, **Ia** and **Ib**

Scheme 2



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(1) (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343. (c) Stamos, D. P.; Chen, S. S.; Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552.

(2) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

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are expected to be preferred over **Ic** for the steric reason (Figure 1). Assuming that this conformational preference is reflected in the transition state and also that the hydroxyl group directs the delivery of a "Me" anion, one would expect that the proposed reaction preferentially proceeds through the transition state resembling **Ia**, to furnish the desired vinyl iodide in a stereo- and regioselective manner.[6,7] Relevant to the proposed delivery of a "Me" anion by a hydroxy group, Gallina[8] demonstrated that *N*-phenylcarbamate group is an effective directing group in a cuprate-mediated S_N2' reaction, whereas Nakamura[9] showed that the stereochemical outcomes of cuprate-mediated S_N2' reactions of δ-alkoxy allylic chlorides are explained by simple steric effects. To the best of our knowledge, there is no study reported in which a hydroxyl group serves as a directing group in an organocuprate-mediated addition in an acyclic system.[10,11] Also, there is no study reported on the stereochemical course of an organocuprate-mediated S_N2' reaction for an acyclic homoallylic alcohol or its derivatives.[10] It should also be noted that an impressive level of regio- and enantioselectivity has been realized in chiral-auxiliary based, asymmetric S_N2' reactions in recent years,[12] and these reactions could be applied selectively to transform **I** (X = a leaving group bearing a chiral-auxiliary) into **II**, but we opted to study the hydroxyl-directed S_N2' displacement because of the simplicity of the synthetic operations as well as the cost considerations.

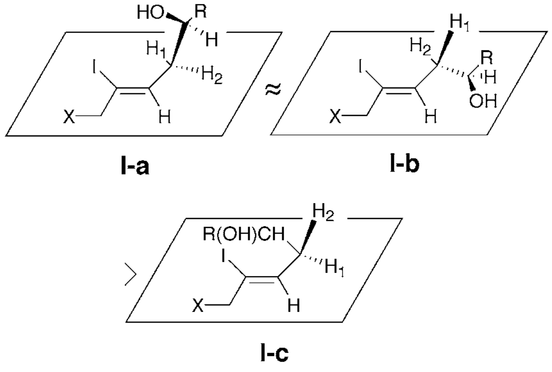
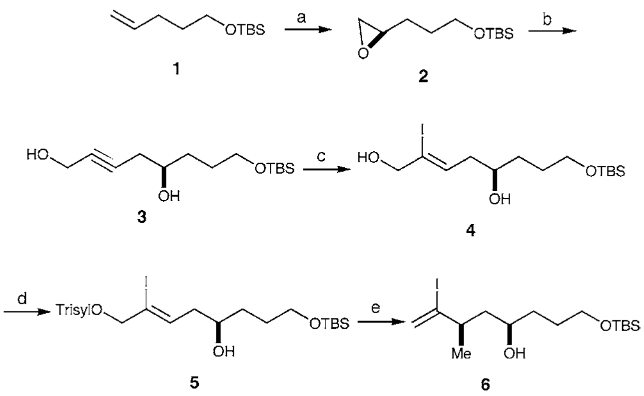


Figure 1.

With this background, we began the experimental work (Scheme 3). A kinetic resolution of racemic epoxide prepared from 4-penten-1-ol *tert*-butyldimethylsilyl (TBS) ether (**1**) with the Jacobsen catalyst[13] furnished the optically active epoxide (**2**). Under the Yamaguchi conditions,[14] **2** was coupled with propargyl alcohol triethylsilyl (TES) ether, followed by acidic workup, to yield the diol **3**.[15] Hydrostannation of **3**, followed by iodine quench, furnished a 55:6:2:1 mixture of all four possible products, with the desired product being the major.[16] Use of slightly less than 1 equiv of tributyltin hydride[17,18] not only gave the best product ratio but also greatly facilitated separation/isolation of the products from tin-derived byproducts. In addition, a KF-based workup allowed the tin-derived byproducts to be removed as a solid precipitation.

Scheme 3[a]



[a] Reagents and conditions: (a) (1) MCPBA, CH_2Cl_2 (90%); (2) (*R,R*) Jacobsen's catalyst (0.2 mol %), H_2O (0.55 equiv), *t*-BuOMe (47%). (b) $TESOCH_2C{\equiv}CH$, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C (87%). (c) (1) *n*-Bu_3SnH (0.95 equiv), AIBN (10 mol %), 80 °C; (2) I_2, CCl_4, followed by KF workup (94%). (d) Trisyl-Cl, $(Bn)(Et)_3NCl$ (5 mol %), 15% aq NaOH, PhMe (85%). (e) (1) MeLi, CuI, DME, −78 °C then **5** (92%); (2) EDCI, 3,5-dinitrobenzoic acid, DMAP (20 mol %), CH_2Cl_2 ($\geq$99%); (3) crystallization twice from aq $EtOH/H_2O$ (53%);[23] (4) K_2CO_3, THF, MeOH, H_2O ($\geq$99%).

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(3) For recent reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Saccomano, N. A. *Comprehensive Organic Synhesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 1, p 173.

(4) Vinyl iodides, bromides, and triflates are known to be smoothly activated under the standard conditions of the Ni/Cr-mediated coupling reaction.[2,3]

(5) (a) Kilb, R. W.; Lin, C. C.; Wilson, E. B., Jr. *J. Chem. Phys.* **1957**, *26*, 1695. (b) Herschbach, D. R.; Krisher, L. C. *J. Chem. Phys.* **1958**, *28*, 728.

(6) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(7) For reviews relevant to this subject, see: (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186.

(8) (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. (b) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3093.

(9) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121.

(10) In cyclic systems, allylic and homoallylic alcohols are known to direct the stereochemical course in conjugate additions of Grignard and cuprate reagents. For example, see: Fleming, F.; Guo, J.; Wang, Q.; Weaver, D. J. *Org. Chem.* **1999**, *64*, 8568 and references therein.

(11) In the studies on asymmetric conjugate addition of organometallic reagents to α,β-unsaturated cyclic-diol monoesters, Sakai suggested a chelation complex involving a free hydroxy group and an ester carbonyl group: Sakai, K.; Suemune, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2109 and references therein.

(12) For examples of chiral-auxiliary based, asymmetric S_N2' reactions, see: (a) Gais, H.-J.; Müller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453. (b) Caló, V.; Fiandanese, V.; Nacci, A.; Scilimati, A. *Tetrahedron* **1994**, *50*, 7283. (c) Tamura, R.; Watabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895. (d) Marino, J. P.; Viso, A. *J. Org. Chem.* **1991**, *56*, 1349. (e) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. (f) Alexakis, A.; Mangeney, P.; Chribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J. *Pure Appl. Chem.* **1988**, *60*, 49.

(13) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(14) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1982**, *23*, 3093.

(15) This coupling was possible without protection of propargyl alcohol but with slightly lower (ca. 70%) chemical yields.

Treatment of the monotosylate prepared from **4** with lithium dimethylcuprate in THF furnished a 2.7:1:1 mixture of the desired product **6**, the undesired C25 stereoisomer, and the undesired regioisomer. Encouraged with this result, we screened "Me" anions, solvents, and leaving groups. Among cuprates tested, lithium dimethylcuprate gave the best stereoselectivity. The regio- and stereoselectivity was found to be dramatically affected by solvents. Most notably, formation of the regioisomer was completely eliminated in 1,2-dimethoxyethane (DME), with an increase in the stereoselectivity as well.[19] The best selectivity (the product ratio = 6.5:1:0) was obtained with a trisyl leaving group.[20]

Use of the trisyl group gave two additional benefits. First, a selective activation of the primary alcohol over the secondary alcohol was effectively achieved under phase-transfer conditions.[21] Second, under this condition, two *E*-regioisomers formed at the hydrostannation/iodination step were transformed into the corresponding cyclic ethers, which further simplified the purification/isolation.

Related to the hydroxyl group as a directing group for lithium dimethylcuprate, it is worthwhile noting two observations. First, with protection of the C23 hydroxyl group, the stereoselectivity observed in the S_N2' displacement was completely abolished.[22] Second, we were unable to cleanly transform **5** to the corresponding C23 *N*-phenylcarbamate[23] and thus unable to compare the directing capacity of the hydroxyl group with that of the *N*-phenylcarbamate for the S_N2' displacement.

Separation of **6** from its stereoisomer was accomplished through 3,5-dinitrobenzoate (DNB) preparation, recrystallization twice from aqueous ethanol, and DNB hydrolysis. This purification method allowed us to avoid chromatographic purification. Thus, the stereochemically homogeneous[24] vinyl iodide **6** was obtained in 37% overall yield from **3** in a 20-g scale.

Acknowledgment. We are grateful to the National Institutes of Health (CA 22215) and Eisai Research Institute for generous financial support.

Supporting Information Available: Complete experimental details for the synthesis outlined in Scheme 3 and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The structure of **4** was assigned on comparison with the sample prepared by the Corey method: Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. Because of the sluggishness of reaction and the relatively low chemical yield, we opted to use the hydrostannation route for the preparative purpose. The structures of the three minor products were not rigorously established. However, the chemical shifts of the vinyl protons suggested that the first, second, and third byproducts (the order of the amount formed) correspond to *E*-regioisomer, *Z*-isomer, and the *Z*-regioiosmer of **4**, respectively. This tentative assignment was consistent with the observation that *Z*-isomer and *Z*-regioisomer formed a cyclic ether on the trisylation.

(17) To the best of our knowledge, the first hydrostannylation of a propargyl group was reported by Neumann, Niermann, and Sommer in 1961 (Neumann, W. P.; Niermann, H.; Sommer, R. *Angew. Chem.* **1961**, *73*, 768). For the work relevant to this study, see: (a) Nativi, C.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 820. (b) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.

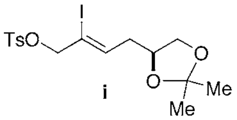
(18) For a review on metal-catalyzed hydrostannations, see: Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257.

(19) In the monotosylate series, the ratio of the desired product, the C25 stereoisomer, and regioisomer was found to be 1.5:1:5 (Et_2O), 2.7:1:1 (THF), 3.2:1:0.3 (THF/TMEDA), and 4.1:1:0 (DME), respectively, at −78 °C.

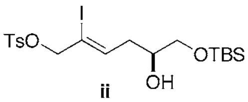
(20) Under the condition of Me_2CuLi/DME/−78 °C, the substrates bearing a tosyl or camphorsulfonyl group in **5** gave a 4.1:1.0:0 (tosyl) or 6.0:1.0:0 (camphorsulfonyl) mixture of the desired product **6**, the undesired C25 stereoisomer, and the undesired regioisomer.

(21) Szeja, W. *Synthesis* **1979**, 822.

(22) This conclusion is based on the experiments conducted on **i** and **ii**.



i



ii

(23) We were able to prepare the C23 *N*-ethylcarbamate of **5**, but an attempted S_N2' displacement did not give conclusive results.

(24) The stereochemical purity was at least >125:1 for the first crop obtained in the second recrystallization.