Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 953-956, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02337-2

Total Synthesis of Curacin A

Michael Z. Hoemann, Konstantinos A. Agrios, and Jeffrey Aubé*

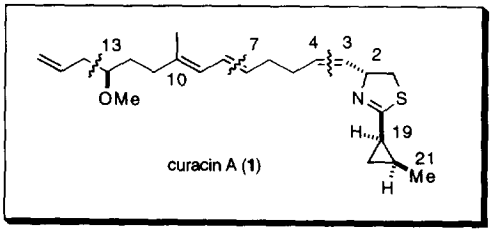
Department of Medicinal Chemistry
The University of Kansas
Lawrence, Kansas 66045-2506

Abstract: Curacin A (**1**) was synthesized in a convergent manner. The key steps were (1) a Julia coupling to establish the stereochemistry of the C(7-10) diene, (2) a Wittig reaction to establish the stereochemistry of the C(3-4) alkene, and (3) a dehydrative cyclization to form the thiazoline ring system.

Curacin A (**1**) is a potent cytotoxic agent recently isolated by Gerwick et al. from the cyanobacterium *Lyngbya majuscula*.[1] It was determined to be an inhibitor of tubulin polymerization, inhibiting mitosis by interacting with the colchicine binding site.[2] Most other known colchicine-type tubulin inhibitors share related topographical features which provide a structure-activity relationship of that binding site.[3,4] Curacin A shows little evident structural similarity with these known agents. Its biological activity and novelty of structure make curacin A an interesting probe for the colchicine binding site and a potentially attractive pharmacological target.

Several papers describing synthetic approaches to curacin A have been published.[5-7] The absolute stereochemistry of the natural product was determined through combined degradation and synthetic studies.[5,7] These studies ultimately led White to achieve the first total synthesis of curacin A,[6] in which a Suzuki coupling was used to establish the *E,E*-diene at C(7-10). In this paper, we describe own total synthesis of curacin A.

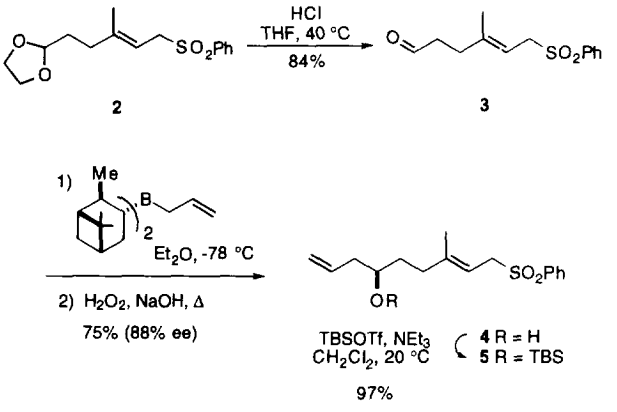
Our plan was to devise a general approach that would allow preliminary structure-activity relationship (SAR) studies. The strategic disconnections are depicted below. We envisioned procuring the necessary double bond geometries from geraniol (C(9-10)), a Julia coupling[8] (C(7-8)) and an unstabilized Wittig reaction (C(3-4)). The isolated stereocenters of C(2) and C(13) would be derived from L-serine and an asymmetric allylation reaction, respectively.[9] Finally, the relative and absolute stereochemistry of the cyclopropane portion would be prepared from an asymmetric Simmons-Smith procedure previously reported by Charette.[10]



curacin A (**1**)

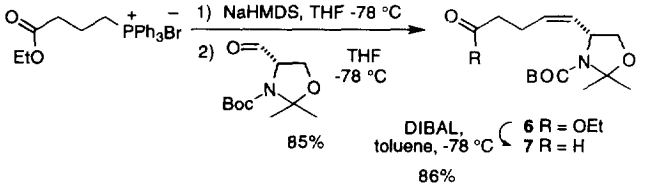
The synthesis of the C(8-16) segment began from known acetal **2** (Scheme 1).[11] Deketalization followed by allylation with Brown's allyl diisopinocampheylborane reagent under salt-free conditions[12] gave homoallylic alcohol **4** in 88% ee, as determined by integration of the ^{19}F-NMR peaks in the derived Mosher's ester. As alkylation of this alcohol proved problematic due to the acidity of the allylic sulphone, it was protected as the *tert*-butyldimethylsilyl ether.

Scheme 1



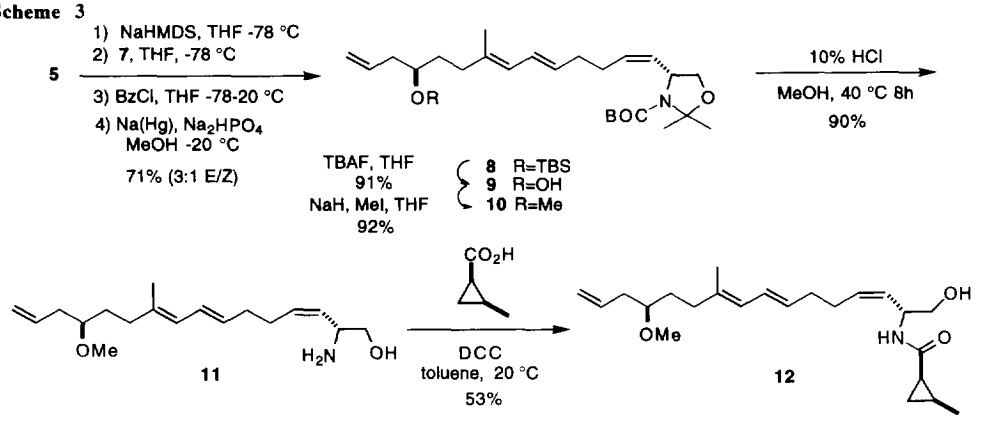
The C(1-7) portion of curacin A was prepared in good yield by an unstabilized Wittig reaction between Garner's aldehyde[13] and ethyl 4-(triphenylphosphonium)butyrate (Scheme 2).[14] Only the *Z* isomer was detected by ^{1}H-NMR. Reduction of the ester with DIBAL at low temperature afforded aldehyde **7** in good yield.

Scheme 2



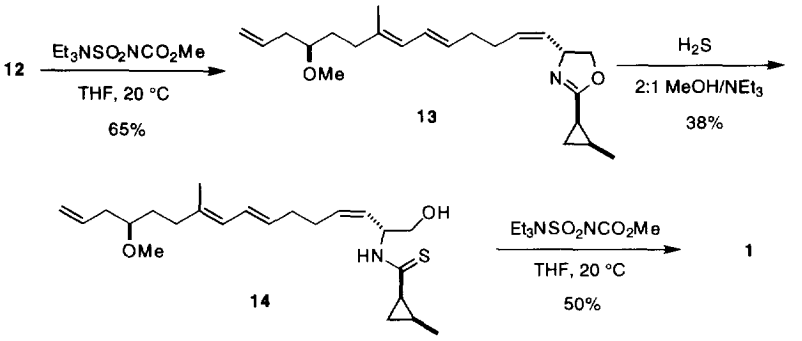
The Julia coupling between allylic sulphone **5** and aldehyde **7** provided diene **8** in moderate yield and stereoselectivity (57%, 3:1 *E*/*Z*) (Scheme 3). The use of samarium diiodide for the reductive elimination afforded little improvement in the stereoselectivity and resulted in significantly lower yields.[15a-c] The stereoisomers could not be separated by flash chromatography so they were carried on in the hope that they would be separable at some later stage. The C(13) alcohol was deprotected and methylated in 75% overall yield. The product **10** represents a formal synthesis of curacin A as discerned by comparison with spectra from material produced in White's synthesis.[6] However, we wished to examine alternative methods for thiazoline formation and to complete the total synthesis.[16] Accordingly, the oxazolidine and carbamate groups were deprotected simultaneously and the crude vicinal aminoalcohol **11** was coupled with enantiomerically pure (1*S*, 2*R*)-2-methylcyclopropanecarboxylic acid.[10,17] At this point there was still a 3:1 mixture of *E*/*Z*-stereoisomers of amide **12**.

Scheme 3



Initially, we intended to form the thiazoline ring of curacin A by cyclization of the thioamide corresponding to compound **12**.[16] Unfortunately, attempts to convert the amide directly to the thioamide **14** using Lawesson's reagent and derivatives thereof failed. Protection of the free alcohol prior to treatment also met with failure. An alternative two-step procedure reported by Wipf and coworkers was employed successfully (Scheme 4).[18] Cyclization of the amide to the oxazoline followed by treatment with hydrogen sulfide yielded the desired thioamide in 38% yield.[19] Finally, dehydrative cyclization using Burgess reagent followed by flash chromatography (silica gel, hexane/EtOAc 3:1) to remove the minor diastereomer gave curacin A (**1**) in 50% yield. The physical properties (^{1}H- and ^{13}C-NMR, specific rotation) of synthetic curacin A matched those of an authentic sample kindly provided by Professor Gerwick.[20]

Scheme 4



In conclusion, curacin A was synthesized in a convergent manner. Efforts are currently underway to optimize this synthesis and to prepare analogues for biological evaluation.

Acknowledgments. We wish to acknowledge Professors James White, William Gerwick, and Peter Wipf for kindly sharing spectra and information prior to publication. In addition, we thank Professor Gerwick for an authentic sample of curacin A. This work was supported by the National Institutes of Health and through an Alfred P. Sloan fellowship awarded to J.A.

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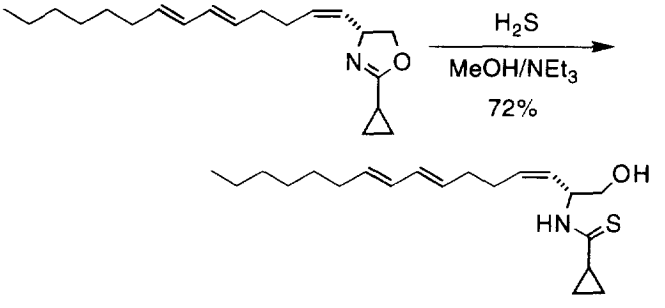
17. (2*S*, 3*R*)-Methylcyclopropanecarboxylic acid was prepared in ca. 95% ee from *cis*-2-buten-1-ol using an asymmetric Simmons-Smith reaction[10] as the key step (as described in reference 6).
18. Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395-6398.
19. Compare the conversion of **13**→**14** (Scheme 4) to the following model reaction.



20. The specific rotation of synthetic curacin A prepared herein ($[\alpha]_D^{20}$ +56.3 (c = 0.40, $CHCl_3$)) matched that of an authentic sample provided by Professor Gerwick ($[\alpha]_D^{20}$ +57.9 (c = 0.47, $CHCl_3$)). The originally reported value, obtained from a small sample of the naturally isolated material, was $[\alpha]_D^{20}$ +86.0 (c = 0.64, $CHCl_3$)[1] but this value has been revised using a larger sample of newly-isolated curacin A to $[\alpha]_D^{20}$ +62.0 (c = 1.10, $CHCl_3$); J.D. White, personal communication.

(*Received in USA* 16 *November* 1995; *accepted* 5 *December* 1995)