ORGANIC LETTERS

2007
Vol. 9, No. 21
4303−4306

Synthesis of the ABCD Trioxadispiroketal Subunit of Azaspiracid-1: An Iodoetherification–Dehydroiodination Strategy for Complex Spiroketals

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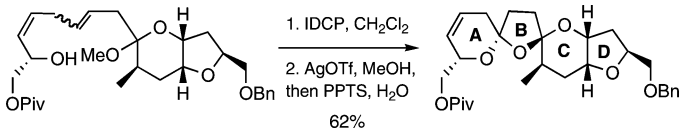
Received August 1, 2007

ABSTRACT



An unusual spiroketalization strategy in which a hydroxyalkene serves as a precursor to a cyclic enol ether was applied to the synthesis of the ABCD trioxadispiroketal subunit of azaspiracid-1. The trioxadispiroketal product, which represents a double anomeric effect, was obtained as a single trioxadispiroketal diastereomer. A key ploy in the synthesis of the CD segment was the use of a cyclopropane as a synthon for the C-14 methyl group.

The unique bioactivity and structural complexity of the marine shellfish toxin azaspiracid-1 **1**[1,2] (Figure 1) has led to considerable interest in its synthesis. Total syntheses of **1** by the Nicolaou group led to correction of the originally reported structure.[3] The synthesis of **ent-1** was subsequently reported by the Evans group.[4] In the correct structure, the alkene in ring A is located at C_7-C_8 and the configuration of the trioxadispiroketal corresponds to a double anomeric effect, which appears to be thermodynamically favored.[3f,5g] The laboratories of Carter and Forsyth have also completed

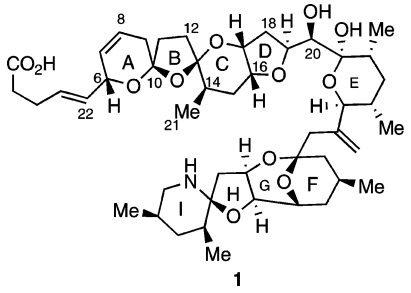


Figure 1. Revised structure of azaspiracid-1.

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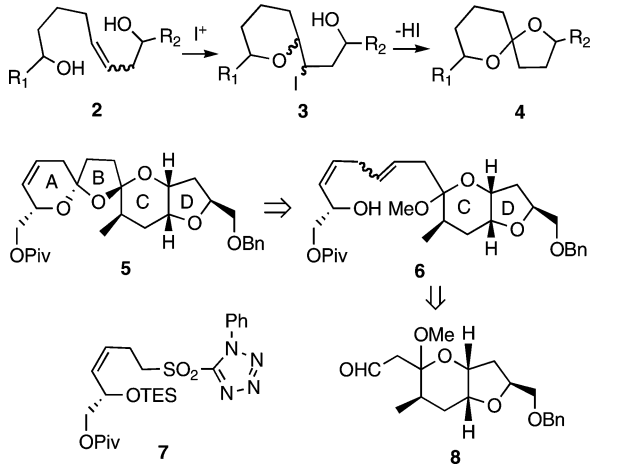
10.1021/ol701866v CCC: $37.00
Published on Web 09/20/2007

syntheses of the ABCD subunit,[5g,6f] and several other synthetic studies have been reported.[5−7]

At the onset of our studies, we were interested in a plan that would be compatible with the different functional groups contained in the ABCD subunit, not the least of which was the potentially sensitive homoallylic acetal that comprises the trioxadispiroketal residue. In this vein, we envisaged a strategy in which a hydroxy-iodo-THP such as **3** could serve as a precursor to spiroketal **4** through the intermediacy of an exocyclic enol ether. Since highly functionalized variants of iodo cyclic ether **3** could be obtained from the iodoetherification of dihydroxyalkenes such as **2**,[8] which may be assembled in a convergent fashion, such an approach would be especially appropriate for complex spiroketal frameworks.[9,10] In essence the alkene moiety in **2** is regioselectively elaborated to an acetal, a transformation that is synthetically similar to the metal-mediated elaboration of an alkyne.[11] A possible application of this plan to the ABCD azaspiracid-1 subunit **5** calls for a hydroxy−hemiacetal−alkene precursor **6** and provided an opportunity for examination of this spiroketalization strategy in a complex setting.[12] The $C_{10}-C_{11}$ (azaspiracid numbering) alkene in **6** provides a practical point for retrosynthetic dissection into olefination partners **7** and

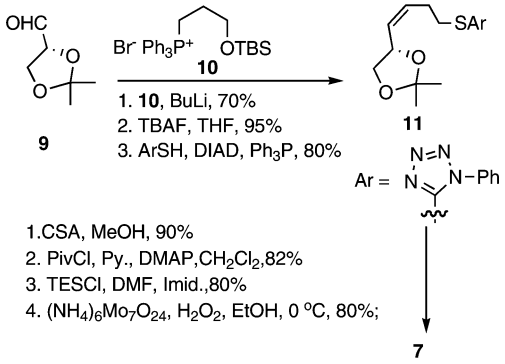
Scheme 1. Retrosynthetic Analysis



8 (Scheme 1). The likelihood that alkene geometry is inconsequential to the synthetic outcome means that a stereoselective alkene synthesis would not be necessary.

Sulfone **7** was obtained from the known aldehyde **9** (Scheme 2)[13] via a reaction sequence involving standard

Scheme 2. Synthesis of Sulfone **7**



Wittig olefination, Mitsunobu, and thioether oxidation protocols.[14] We envisaged a synthesis of the CD fragment **8**, in which the C14 methyl group would be installed through the opening of a cyclopropanated glycal.[15] Thus, the D-ring was identified in the known C-allylated ribofuranoside **12**,[16] which was transformed to the 3-deoxy derivative **14** through straightforward alcohol protection and deoxygenation steps (Scheme 3).[17,18]

Hydroxyalkene **14** was next transformed to bicyclic glycal **16** following the protocol developed by Postema (Scheme

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(12) For a strategically similar approach to the ABCD subunit, based on alkyne functionalization, see ref 6f.

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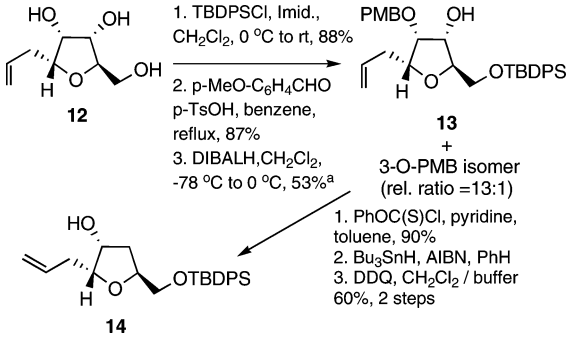
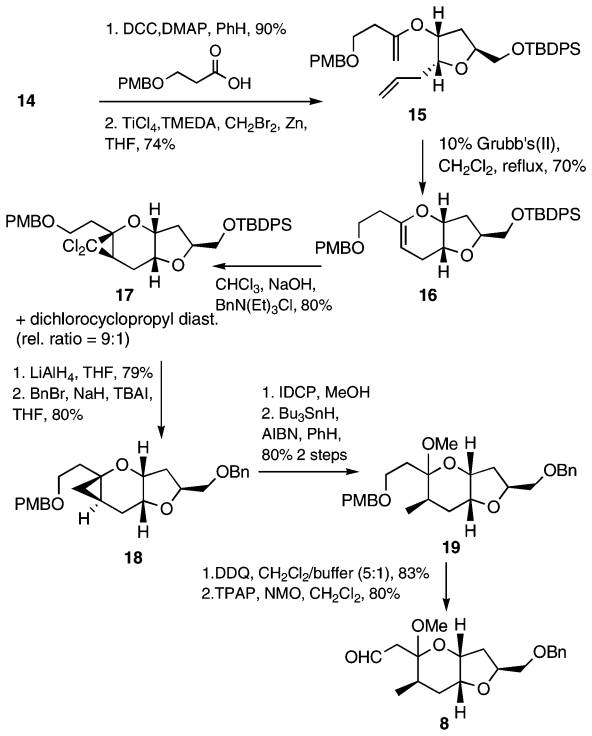
Scheme 3. Synthesis of the D-Ring Synthon[a]



[a] The product resulting from the cleavage of the silyl ether in **13** was obtained in 33% yield. This material was re-silylated to **13** in close to quantitative yield.

4).[19] An esterification−ester olefination sequence on **14** and 3-*p*-methoxybenzyloxypropanoic acid provided **15**, which was subjected to RCM using Grubbs second-generation catalyst. The resulting bicyclic glycal **16** was transformed to the key cyclopropane **18**. The required cyclopropane

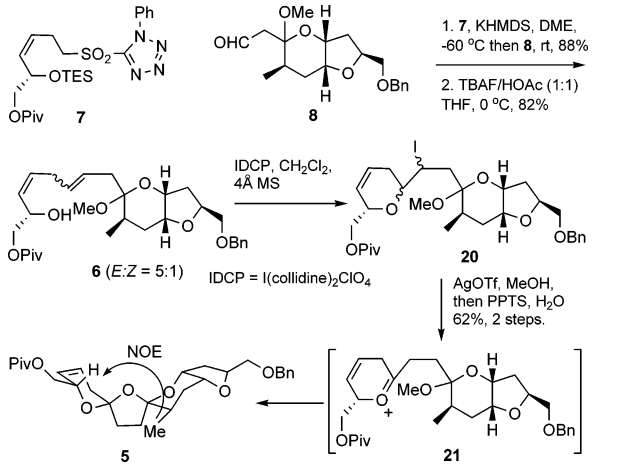
Scheme 4. Synthesis of CD Adehyde **8**



stereoselectivity was achieved by dichlorocyclopropanation of **16**, followed by LAH reduction.[15] The reducing conditions effected clevage of the silylether, and this necessitated reprotection of the resulting primary alcohol as the benzyl ether. The stereochemistry of **18** was deduced from the structure of the final product (vide infra). An attempt to access **18** directly from **16** using Simmons−Smith conditions favored the undesired cyclopropane diastereomer, presumably due to chelation control involving the homoallylic oxygen substituent. Exposure of **18** to IDCP in methanol followed by Bu_3SnH reduction of the resulting C14-iodomethyl methyl acetal product provided a single C14 methyl isomer **19**, for which the configuration of the acetal was not determined. Removal of the PMB ether and oxidation of the primary alcohol provided **8**, which contains the CD segment of precursor **6**.

Julia−Kocienski olefination on **7** and **8** followed by desilylation of the product provided **6** as a 5:1 mixture in which the major component was presumed to be the E alkene (Scheme 5). Treatment of **6** with iodonium dicollidine

Scheme 5. Trioxadispiroketal Synthesis



perchlorate (IDCP), in anhydrous CH_2Cl_2, afforded **20** as an unstable mixture of products. NMR analysis of the partially purified material indicated two major iodo−THP products in an approximately 1:1 ratio. Dissolution of the mixture in methanol and treatment with silver trifluoromethanesulfonate followed by addition of water and PPTS to the reaction mixture afforded **5** as a single trioxadispiroketal product in 62% isolated yield from hydroxy diene **6**. We presume that the spiroketalization step proceeds via the six-membered ring oxocarbenium ion **21**, which could arise from an initially formed exocyclic enol ether or via iodide activation and cation formation, followed by hydride transfer. The structure of **5** was assigned by 2D COSY, NOESY, HSQC, NMR, and HRMS. In particular, the stereochemistry of the C14-methyl group was confirmed by an NOE between CH_3-14 and H-6, which is diagnostic of the stereochemical motif represented in **5**.[3d] The NMR data for **5** were also in close agreement with the previously reported, 20-*O*-TBDPS, 22-*O*-PMB, derivative.[6f]

In conclusion, this synthesis of the ABCD trioxadispiroketal subunit of azaspiracid-1 **5** illustrates an unusual intramolecular iodoetherification−spiroketalization strategy

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and also entails a novel approach to the CD segment. The complexity represented in **5** and the convergent nature of this synthesis suggest that the spiroketalization methodology may be suitable for other classes of highly functionalized spiroketals. In principle, spiroketals with different ring sizes could originate from appropriate dihydroxyalkene precursors. More detailed mechanistic and synthetic studies are underway and will be reported in due course.

Acknowledgment. This investigation was supported by grants R01 GM57865 and SCORE S06 GM60654 from the National Institute of General Medical Sciences of the National Institutes of Health (NIH). "Research Centers in Minority Institutions" award RR-03037 from the National Center for Research Resources of the NIH, which supports the infrastructure and instrumentation of the Chemistry Department at Hunter College, is also acknowledged.

Supporting Information Available: Procedures and characterization of all new compounds and NMR charts for selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701866V