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COMMUNICATIONS

Published on Web 11/08/2006

Highly Convergent Total Synthesis of (+)-Acutiphycin

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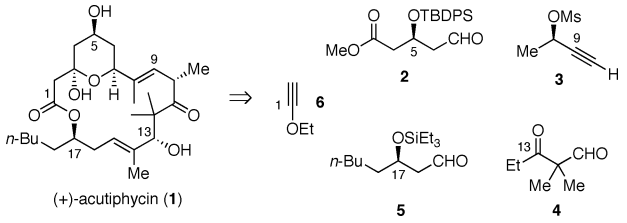
Received October 2, 2006; E-mail: tfj@mit.edu

The complex macrolide (+)-acutiphycin (**1**) was isolated in 1984 by Moore and co-workers and possesses potent in vivo antineoplastic activity against murine Lewis lung carcinoma, as well as significant cytotoxicity against KB and NIH/3T3 cell lines.[1] The natural source of acutiphycin (the blue-green alga *Oscillatoria acutissima*), however, no longer produces this metabolite. Thus, detailed investigations of the mechanism of action and therapeutic potential have been very limited, and further studies must be fueled by chemical synthesis. Smith reported the first total synthesis of **1** in 1995, and, despite the elegant and extensive efforts of Kiyooka,[2,3] it remains as the only total synthesis to date. Whereas the strategies employed in both the Smith synthesis and Kiyooka approach are linear in nature, we report herein a convergent total synthesis of (+)-acutiphycin. Demonstrated for the first time in a natural product synthesis is macrolactonization via intramolecular addition of an alcohol to a ketene transiently generated by a thermal retro-ene reaction of an alkoxyacetylene.

We envisioned constructing **1** via the assembly of four simple fragments (**2**,[4] **3**,[5] **4**,[6] and **5**[7]) and using a fifth piece, ethoxyethyne (**6**), as a lynchpin to close the macrocycle (Scheme 1). The preparation of each of the four fragments required five or fewer steps.[8] Palladium-catalyzed coupling of **3** and **4** following the protocol of Marshall[9] gave β-hydroxy ketone **7**[10] in excellent yield, enantioselectivity, and diastereoselectivity (Scheme 2). Noteworthy are the tolerance of the ketone and the observation of both high ee and anti selectivity with the quaternary center adjacent to the reacting aldehyde.[11] Protection and methylation afforded **8**, which was joined with **2** via the hydrozirconation−transmetallation−stereoselective carbonyl addition method of Wipf.[12] This sequence provided **9** as a single observable regioisomer and a 5.2:1 mixture of easily separable diastereomers.[13]

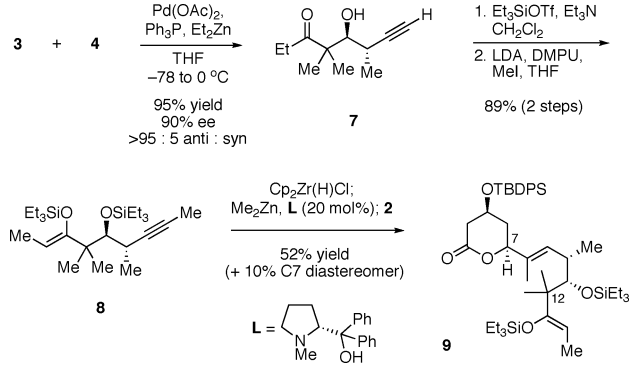
Scheme 1



The coupling of **9** (or its functional equivalent) to **5** proved to be quite challenging. Mukaiyama aldol, Horner−Wadsworth−Emmons, cross-metathesis, and other strategies were explored in turn. However each of these was unsuccessful, most likely because of the steric hindrance conferred by the *gem*-dimethyl substitution at C12.

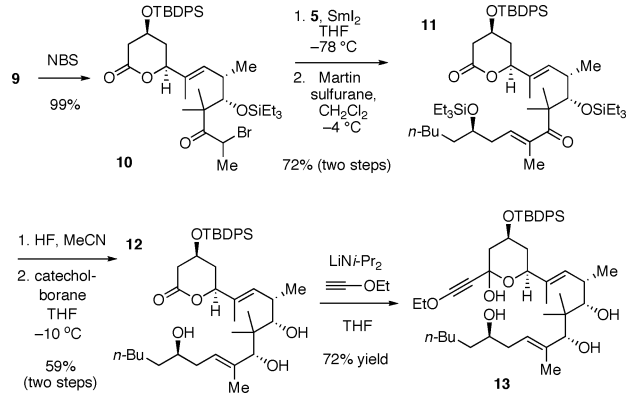
An unusual application of the Reformatsky reaction, however, provided an efficient solution to this problem (Scheme 3). Electrophilic bromination of **9** provided the requisite α-bromoketone (**10**) in quantitative yield. While activated zinc failed to generate the desired enolate,[14] SmI_2 did so, affording a β-hydroxy ketone

Scheme 2



derived from **10** and **5** in excellent yield (90%, 1.0 mmol scale) as a mixture of diastereomers. Dehydration with the Martin sulfurane provided **11** in an overall yield of 72% for the two-step procedure.[15]

Scheme 3



While SmI_2 has been commonly employed in intramolecular Reformatsky reactions, its use in intermolecular cases has been extremely limited because of the numerous side reactions that can occur.[16,17] We propose that the α-quaternary center of **10** prevents oxidative dimerization of the samarium enolate and other competing SmI_2-mediated pathways. When coupled with subsequent dehydration, this two-step sequence is complementary to Horner−Wadsworth−Emmons strategies, and it may find use in other sterically hindered systems. Further studies to investigate the generality of this approach are currently underway.

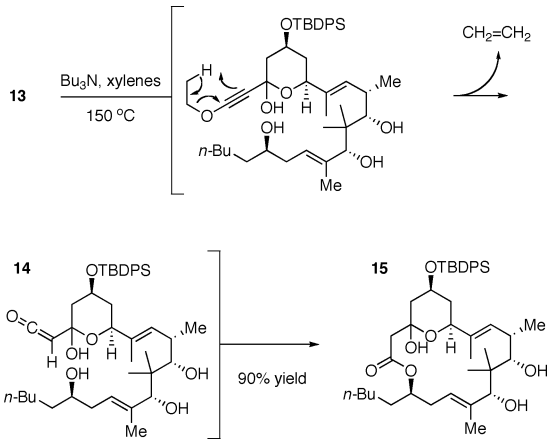
Selective removal of the Et_3Si groups in the presence of the TBDPS group and subsequent directed reduction provided solely the syn 1,3-diol (**12**).[18] Although syn-selective directed reductions of β-hydroxy ketones are well-known, there appear to be no prior examples with an all-carbon quaternary center between the directing alcohol and the carbonyl undergoing reduction, as is the case here.[19,20] As a surrogate of C1 and C2 in the natural product, a lithium anion derived from ethoxyethyne (**6**) was added to the

10.1021/ja0670660 CCC: $33.50

carboxyl at C3, in the presence of the three hydroxyl groups of **12**, giving tetraol **13** in 72% yield.

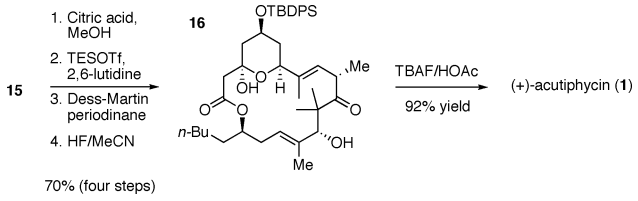
As shown in Scheme 4, slow addition of **13** to refluxing xylenes and Bu_3N effected a thermal retro-ene reaction[21] to form ethylene and ketene **14** that then underwent a highly group-selective coupling with the least hindered (yet most remote) of the 4 hydroxyl groups to give the desired macrocycle (**15**) in excellent yield (90%). This macrolactonization method was originally reported by Funk as a mechanistic probe[22] but has not been employed previously in the context of total synthesis.[23] As alkynyl ethers lack acidic α-hydrogens, they avoid the problem of competing enolate formation that plagues many alternative techniques.[24,25] Because of these features, as well as the fact that macrolactonization is one of the most commonly utilized strategies in complex molecule synthesis, this retro-ene-macrocyclization certainly warrants further investigation.

Scheme 4



Five further steps completed the synthesis (Scheme 5). Methyl ketal formation, selective silylation of the allylic alcohol, Dess−Martin oxidation,[26] and exposure to HF afforded **16**.[2] Crystallization from diethyl ether/pentanes allowed for an X-ray crystal structure determination of this compound, the only such crystal structure of a compound that contains the macrocycle (as well as all of the stereogenic centers) of (+)-acutiphycin (**1**). This experiment, in conjunction with conversion of **16** to **1**, confirms both the relative and absolute stereochemistry of the natural product. Finally, the TBDPS group was removed by treatment with acetic acid-buffered TBAF,[2] thus completing the total synthesis of (+)-acutiphycin (**1**).

Scheme 5



In summary, a highly convergent synthesis of (+)-acutiphycin (**1**) was accomplished in a longest linear sequence of 18 steps from commercial materials. The overall yield was 4.0% from methyl-acetoacetate (84% average yield per step) and 3.1% from isobutyraldehyde (82% average). Unique features of this work include the first application of an alkynyl ether as a macrolactone precursor in total synthesis and the first use of an intermolecular, SmI_2-mediated Reformatsky reaction as a fragment coupling operation. The modular nature of the route should enable rapid and systematic investigation of the structure−activity relationships of this potent natural product.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (Grant GM-063755). We are grateful to Dr. Li Li for obtaining mass spectrometric data for all compounds (MIT Department of Chemistry Instrumentation Facility, which is supported in part by the NSF (Grants CHE-9809061 and DBI-9729592) and the NIH (Grant 1S10RR13886−01)) and to Dr. Peter Müller (MIT Department of Chemistry X-ray Diffraction Facility) for obtaining crystal structures of **7** and **16**.

Supporting Information Available: Experimental procedures and spectral data for all new compounds; X-ray data (CIF) for **7** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0670660