Total Synthesis of (+)-Ambruticin S

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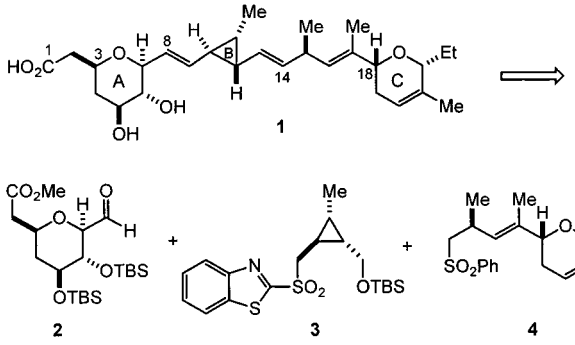
Received July 31, 2001

Ambruticin S (**1**), a structurally novel antifungal antibiotic, was isolated from fermentation extracts of *Polyangium cellulosum var. fulvum* in 1977 by researchers at Warner Lambert.[1] The absolute configuration of **1** was established several years later through the independent synthesis of ozonolysis fragments.[2] The potent in vivo antifungal activity and low toxicity of ambruticin S and many of its derivatives coupled with its unique structural features, most notably a divinyl cyclopropane, make it a compelling target for synthesis.[3] However, despite numerous synthetic efforts, only Kende has reported the enantioselective synthesis of **1**.[4]

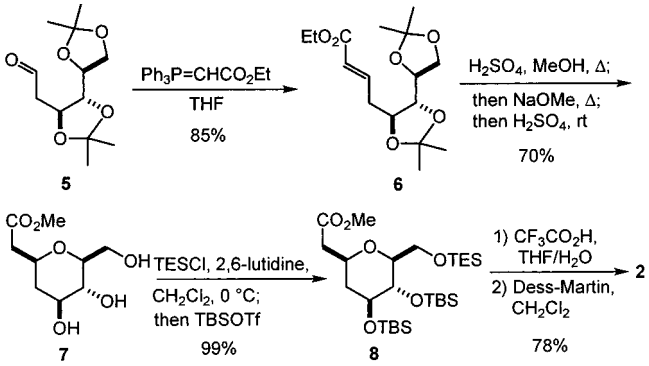
Our attraction to ambruticin S owed its origins to our long-standing involvement in developing enantioselective methods for the synthesis of natural products containing hydropyran and cyclopropane rings. These interests inspired the retrosynthetic analysis of **1** that is depicted in Scheme 1. Disconnection at the two disubstituted olefinic linkages led to three fragments that would serve as our initial subgoals. These structural subunits were the A-ring aldehyde **2**, the bifunctionalized B-ring cyclopropane **3**, and the C-ring sulfone **4**. Each of these fragments embodies a similar degree of stereochemical and functional complexity, thereby allowing the synthesis to be highly convergent. We now report the successful implementation of this strategy to the total synthesis of (+)-ambruticin S.

The synthesis of A-ring aldehyde **2** commenced with the Wittig olefination of aldehyde **5**[5] to provide ester **6** (Scheme 2). The acetonides in **6** were cleaved with H_2SO_4 in MeOH. Excess NaOMe was added, and the reaction mixture was heated under reflux (24 h) to equilibrate the various Michael adducts and furnish the thermodynamically more stable hydropyran **7**. Small quantities of the corresponding acid were also produced during this process,

Scheme 1



Scheme 2



but this was esterified in situ by acidification of the mixture with H_2SO_4 to give **7** in 70% overall yield from **6**. The epimerization at C(3) and saponification of a compound related to C(3)-*epi*-**7** has been previously reported.[6] Selective protection of the primary alcohol of triol **7** as a TES ether followed by protection of the two secondary alcohols as TBS ethers was accomplished in a one-pot process to provide **8**. Selective deprotection of the TES group and oxidation of the resulting primary alcohol with Dess−Martin periodinane[7] afforded the requisite aldehyde **2**.

The enantioselective intramolecular cyclopropanation of allylic diazoacetates that we and Doyle have jointly developed served as the key step in the synthesis of sulfone **3** (Scheme 3).[8] Thus, reaction of diazoacetate **9** with Rh_2[5(*S*)-MEPY]$_4$ provided the known cyclopropyl lactone **10** in 80% yield (92% ee).[9] The lactone ring of **10** was opened by using morpholine and $AlMe_3$, and the resulting alcohol was protected as its TBS ether to provide amide **11**.[10] Epimerization α to the cyclopropyl amide group in **11** to give **12** was driven by release of steric congestion about the *all-cis*, trisubstituted cyclopropane ring. Hydride reduction of the amide moiety in **12** with LDA and borane-ammonia according to the Myers protocol provided alcohol **13**,[11] which was converted into the benzothiazole sulfone **3** by a Mitsunobu reaction followed by oxidation of the intermediate sulfide.

Benzothiazole sulfone **3** was specifically selected for coupling with the aldehyde **2** because 1,2-elimination of the intermediate hydroxy sulfone adduct would proceed spontaneously, thus obviating production of a cyclopropyl carbinyl radical that might undergo ring opening under standard Julia conditions.[12] Indeed, this methodology has been previously employed to join cyclopropyl sulfones to aldehydes.[13] In the event, addition of NaHMDS to a solution of **2** and **3** provided a mixture (2.6:1) of isomeric *E*- and *Z*-alkenes. Although this mixture was difficult to separate, the corresponding primary alcohols were readily separable. Hence,

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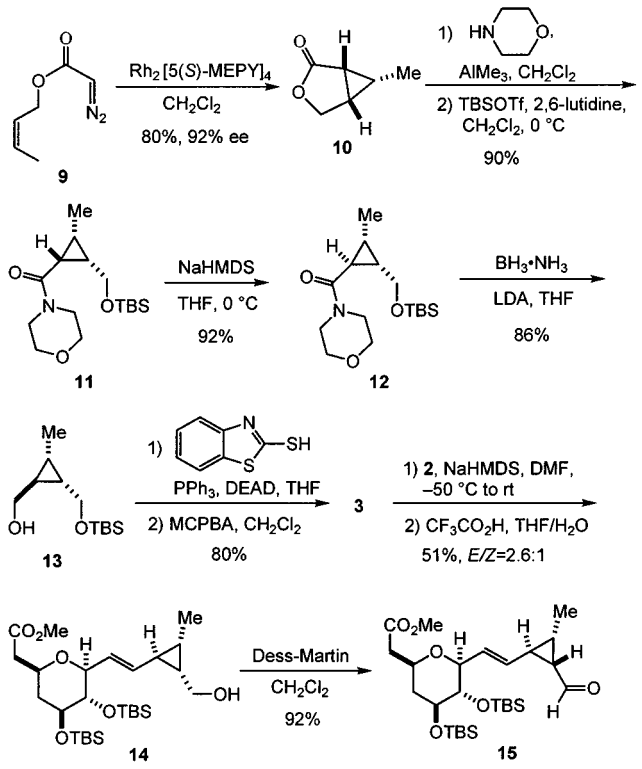
10.1021/ja011867f CCC: $20.00
Published on Web 11/16/2001

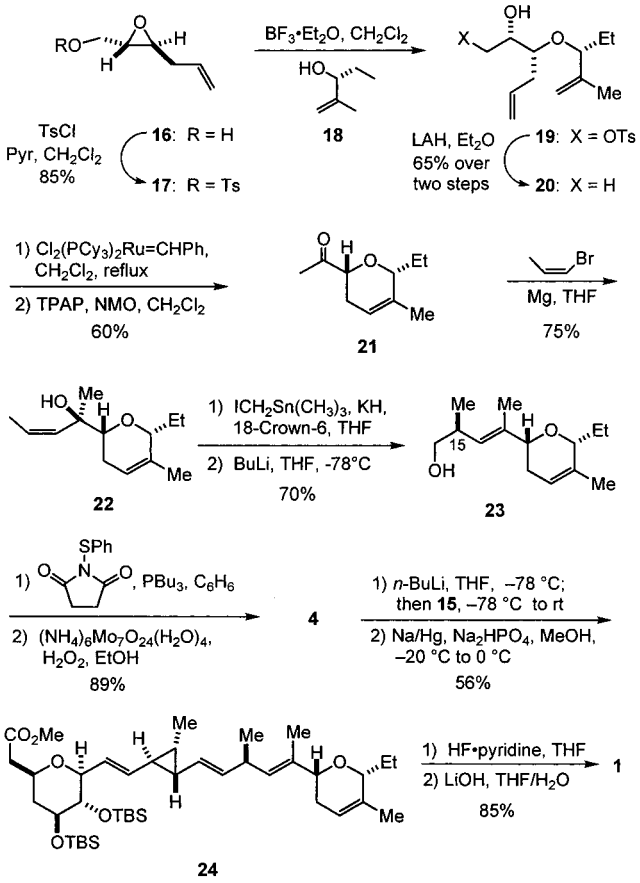
Scheme 3



selective removal of the primary TBS protecting group with CF_3CO_2H gave a separable mixture of **14** (51% from **3**) and its *Z*-isomer. Oxidation of **14** with Dess−Martin periodinane delivered the aldehyde **15**.

The key steps in the synthesis of the C-ring subunit **4** were a ring-closing metathesis (RCM) and a [2,3]-Wittig rearrangement (Scheme 4). Synthesis of the RCM precursor **20** began with converting the known epoxide **16**[14] into its corresponding tosylate **17**. Directed addition of the known alcohol **18**[15] to **17** proceeded regioselectively according to the Hoffmann protocol with use of a catalytic amount of BF_3•Et_2O to provide **19**.[16] Hydride reduction of **19** with LAH gave diene **20**, which underwent facile RCM in the presence of Grubbs' catalyst,[17] and subsequent oxidation of the secondary alcohol moiety with catalytic TPAP/NMO afforded the ketone **21**. Chelation-controlled addition of propenylmagnesium bromide to **21** gave alcohol **22** with >10:1 diastereoselectivity.[18] The tertiary alcohol was alkylated with trimethyltinmethyl iodide,[19] and when the resulting allylic ether was treated with *n*-BuLi, a rapid and highly diastereoselective (>20:1) [2,3]-Wittig rearrangement ensued to give **23**.[20] This alcohol, which possesses both the requisite *S*-stereochemistry at C(15) and *E*-olefin geometry at C(16), was converted to the corresponding C-ring phenyl sulfone **4** by sequential reaction with thiophenyl succinimide in the presence of PBu_3 followed by oxidation with ammonium molybdate/H_2O_2.[21]

Scheme 4



The key transformation in the end-game was the Julia coupling of the aldehyde **15** with the C-ring sulfone **4**. Deprotonation of **4** with *n*-BuLi and addition of **15** provided a mixture of diastereomeric hydroxy sulfones that was treated with Na/Hg to deliver an inseparable mixture of **24** and its *Z*-isomer (*E*/*Z* ≈ 10:1). Removal of the TBS ethers with HF•pyridine followed by separation of the diastereoisomers by HPLC and saponification of the methyl ester group with LiOH provided (+)-ambruticin S (**1**).[22]

This highly convergent synthesis of **1** required a total of 28 steps with only 13 steps (9.2% overall yield) in the longest linear sequence from the known cyclopropyl lactone **10**. The synthesis features a catalytic enantioselective cyclopropanation for the construction of the central B ring component, a RCM to prepare the C-ring, and both traditional and modified Julia couplings in the fragment assembly steps that preferentially form the requisite *E*-alkenes.

Acknowledgment. We thank the National Institutes of Health, the Robert A. Welch Foundation, Pfizer, Inc., Merck Research Laboratories, and the Alexander von Humboldt Stiftung for their generous support of this research. We also thank Pfizer, Inc. for a sample of natural ambruticin and Professor Kende (University of Rochester) for providing us with ^{1}H NMR spectra of ambruticin and an advanced intermediate in his synthesis.

Supporting Information Available: Copies of ^{1}H NMR spectra of all compounds and ^{1}H and ^{13}C NMR spectral data and HRMS for compounds **7**, **2**, **3**, **15**, **21**, **4**, and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The ^{1}H NMR spectrum of the methyl ester of ambruticin S was consistent with that reported,[4b] and synthetic ambruticin S was identical with an authentic sample of natural ambruticin S by TLC, ^{1}H and ^{13}C NMR (including HMQC), mass spectrum, and optical rotation.