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Benzothiazines in organic synthesis. An approach to floresolide B

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Abstract

The intramolecular conjugate addition of a sulfoximine carbanion to an α,β -unsaturated ester results in the formation of a benzothiazine bearing a benzylic stereocenter with extremely high fidelity. We have used this methodology to complete a formal total synthesis of the antitumor agent (+)-floresolide B.

Keywords

Floresolide B; Benzothiazine; Sulfoximine; Michael Addition; Diastereoselectivity

In the course of our work on antitubercular agents like pseudopteroxazole,¹ we became interested in another compound that appeared to be amenable to asymmetric synthesis using the methodology we had developed in the context of pseudopteroxazole and related natural products. This was the cytotoxic agent (+)-floresolide B (**1**).

Floresolide B (**1**) was isolated from a sea squirt (*Aplidium* sp.) along with two analogues, one of which could be assigned absolute stereochemistry by means of X-ray analysis.² This allowed the assignment of stereochemistry to **1**. The unusual metacyclophane structure of **1** combined with some evidence of cytotoxicity against KB cells has attracted some interest from the synthetic community. Dudley and co-workers reported a synthesis of the hydroquinone lactone substructure of **1** using a ring closing metathesis. Nicolaou and Xu reported a total synthesis of racemic **1** that involved a ring-closing metathesis³ as a key step in the formation of the macrocyclic lactone portion of the natural product.⁴

Our goal in pursuing a total synthesis of **1** was based on our interest in discovering if we could effect the process shown in Scheme 1: a highly stereoselective S_N2' reaction of **2** that would set the appropriate benzylic stereochemistry and create an isopropenyl group in one step, affording **4**. This would then be followed by the conversion of **4** to **5**. The latter has been converted to racemic floresolide B in ten steps.⁴

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Supplementary Material

Supplementary data (experimental procedures and characterization data) is available free of charge via the Internet at <http://www.sciencedirect.com/science/journal/00404039> associated with this Letter can be found, in the online version, at doi:xxxxxxxxx.

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In the event, it has not yet proved possible to effect the desired S_N2' reaction, though various congeners of **2** have been prepared and treated with base. We thus decided to proceed to our objective via means that we had firmly established as successful. The idea for the S_N2' reaction arose out of our discovery that related Michael additions proceeded with exquisite transfer of stereochemical information. For example, the reactions of (*E*)-**6** and (*Z*)-**6** with base produced high yields of single, diastereomerically pure cyclization products **7a** and **7b** (Scheme 2). This process is thus stereospecific, and we continue to investigate the basis of the stereoselectivity and use the reaction in synthesis.^{1,5}

We thus set out to perform this reaction in the context of a synthesis of **5**. To that end, commercially available diester **8** was protected, exhaustively reduced and regioselectively brominated with NBS to afford **9** in 86% overall yield (Scheme 3). Mono-protection with TIPSCl and a Swern oxidation gave aldehyde **11**. This was followed by a Wadsworth-Horner-Emmons homologation and the key Buchwald-Hartwig coupling with (*S*)-**13**⁶ and stereoselective cyclization to give **14**. The stereochemistry at the stereocenter alpha to the ester was ignored, but prior work in our group has shown that reasonable (ca 10:1) diastereoselection at such centers is possible.^{1b} Reduction of the ester in **14** to the corresponding alcohol and elimination of water afforded **4**.⁷ Alkylation of the corresponding organolithium species and reductive desulfurization gave **16**. All attempts to convert **16** to **5** failed, a result we ultimately attributed to the presence of the MOM protecting group.

To circumvent the problem, we pursued the synthesis using a methyl protecting group on the phenolic oxygen. Thus, commercially available **17** was brominated, protected and oxidized to give aldehyde **18** (Scheme 4). Chemistry already described led to the aniline **22** efficiently. This compound, unlike its congener **16**, could be oxidized to quinone **23** using ceric ammonium nitrate (CAN) in good yield.⁸ Reduction of the quinone with dithionite and protection of the resulting hydroquinone afforded **5** in excellent yield. Its identity was confirmed by a comparison of ¹H and ¹³C spectra with those of authentic racemic material.

In summary, we prepared an enantiomerically pure intermediate in a known racemic synthesis of floresolide B. Our route required 15 steps and proceeded in an overall yield of 11%. The corresponding racemic material was prepared in 11 steps in 14.6% overall yield. Being able to circumvent certain transformations, such as the conversion of an ester to an alkene, would increase the efficiency of our approach. Given the reliability of stereochemical information transfer that we have observed in the intramolecular Michael addition reaction, it seems quite reasonable to continue to pursue this chemistry in an attempt to broaden scope and increase efficiency in selected applications. Further results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1, (+)-floresolide B

Figure 1.
Structure of (+)-floresolide B.

Scheme 1.
Outline of initial synthetic plan.

Scheme 2.
Stereospecific, intramolecular Michael addition.

Scheme 4.
Successful synthesis of **5**.