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Synthesis of Bistramide A

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In 1988, Verbist reported isolation of a novel marine metabolite of *Lissoclinum bistratum* designated as bistramide A.[1,2] Isolation of four additional congeners of the family followed in 1994.[3] Initially demonstrated to elicit potent cytotoxicity (GI_{50} 22−45 nM), bistramide A (**1**) was reported to have a profound effect on cell cycle regulation, leading to growth arrest, differentiation, and apoptosis in several cell lines.[4] Subsequent studies revealed that bistramide A induced highly selective activation of a single protein kinase C (PKC) isotype δ.[5] Given the suggested proapoptoic function of PKC δ,[6] the ability to selectively modulate the activity of this isotype in vivo is of pivotal significance to PKC biology.[7]

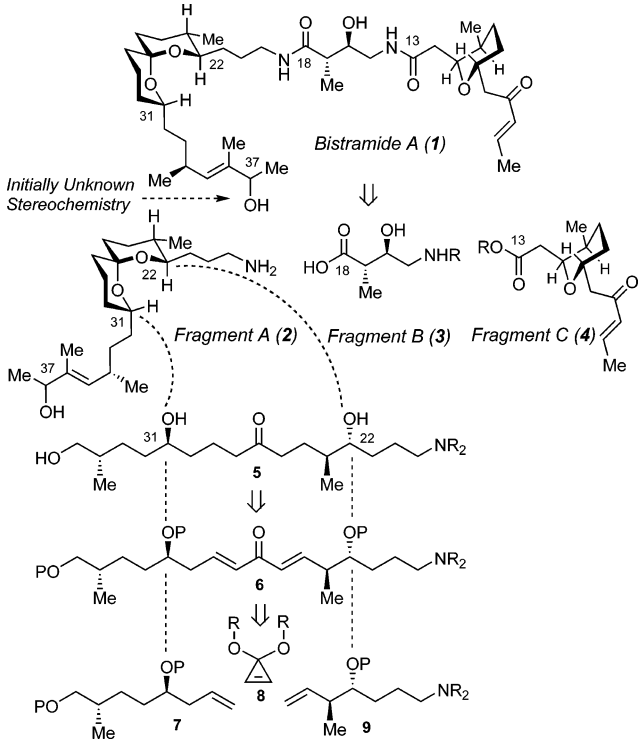
Stimulated by the intriguing biological profile and unique molecular architecture of the bistramides, we established a program directed at the synthesis, structure elucidation, and evaluation of the chemical biology of this unique family of marine metabolites. In this Communication, we present the first synthesis of bistramide A, featuring a novel strategy for spiroketal construction. Our investigation provided unambiguous structural determination of this natural product,[8] including assignment of the previously unknown C_{37} stereochemistry. Furthermore, the synthesis confirmed Wipf's recent stereochemical assignment of bistramide C, which relied on the total synthesis of the C_{34}-stereoisomer of this natural product and the use of chiroptical analysis.[9]

From the outset, our objective was to design a flexible and convergent strategy to bistramide A which would enable efficient assembly of both diastereomers at C_{37} for direct comparison of the two synthetic samples with the natural product. The synthesis plan called for disconnections of bistramide A at the C_{13} and the C_{18} amide linkages, dissecting the target into three subunits A (**2**), B (**3**), and C (**4**) (Scheme 1). For the synthesis of spiroketal fragment A, we designed a bidirectional approach featuring a sequential ring-opening/cross-metathesis of highly strained cyclopropenone acetal **8** with terminal alkenes **7** and **9**.[10] Importantly, this tactic would enable a highly convergent entry into an advanced polyol motif **5**, starting with readily available homoallylic alcohols.

Implementation of this approach is depicted in Scheme 2. Following extensive investigation of the ring-opening/cross-metathesis sequence, the optimized synthetic route began with the ring-opening metathesis of cyclopropene acetal **11** with alkene **10**. Acid-mediated removal of the initially produced acetal, which proved to be inert toward subsequent metathesis, furnished dienone **12** in 63% yield. Treatment of **12** with the second metathesis partner **13** afforded the desired cross-metathesis product **14** in 68% yield.[11] Hydrogenation of dienone **14** with concomitant hydrogenolysis of three benzyl ethers, followed by Dess−Martin oxidation,[12] produced spiroketal **15** as a single diastereomer. Completion of the synthesis of (37*S*)-fragment A (**2**) entailed Cr-mediated olefination,[13] Itsuno−Corey reduction,[14] and phthalimide deprotection. Alternatively, the (37*R*)-diastereomer was obtained using the antipode of the oxazaborolidine reagent (not shown).[15]

Synthesis of the central amino acid fragment **(3**) relied on Brown crotylboration[16] of aldehyde **16** (Scheme 3). Subsequent installation

Scheme 1



of the acetonide protecting group, oxidative cleavage of the terminal alkene, removal of the Boc and acetonide protection, and installation of the Fmoc group gave N-protected amino acid **3** (94% ee, >97% de).

Assembly of the pyran fragment C (**4**) began with the Brown crotylboration[16] of aldehyde **17**, followed by acylation with acryloyl chloride to afford diene **18** (Scheme 4). Ring-closing metathesis,[11] followed by hydrogenation, furnished lactone **19** (72%, two steps). DIBAL reduction and acetylation, followed by $ZnCl_2$-promoted C-glycosidation with silyl dienol ether **20**, gave the desired enone **21** with good efficiency and distereoselectivity.[17] Stereochemical assignment of **21** was confirmed by NOESY. Protodesilylation and oxidation of the resulting alcohol to the acid, followed by DCC-mediated coupling with *N*-hydroxysuccinimide, afforded fragment C (**4**).

Final fragment coupling began with PyBOP-mediated condensation of primary amine **2** with Fmoc-protected amino acid **3** (Scheme 5). Fmoc deprotection, followed by treatment of amine with activated ester **4** in acetonitrile, afforded the final target **1** with the longest linear sequence of 15 steps. This route was utilized to generate both diastereomers at C_{37}.[15] Direct comparison of the two synthetic samples with the natural product, including preparation of the mixed samples, revealed that the (37*S*)-congener **(1**, Scheme 5**)** was identical in every respect (500 MHz ^{1}H NMR, 125 MHz

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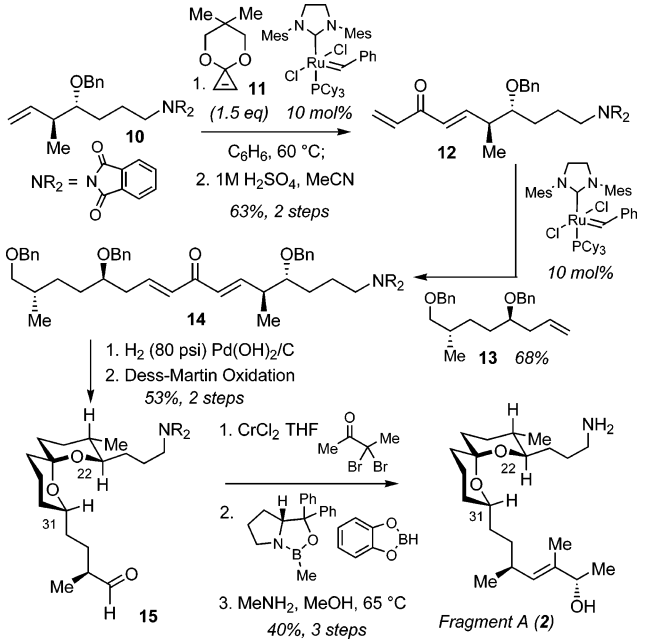
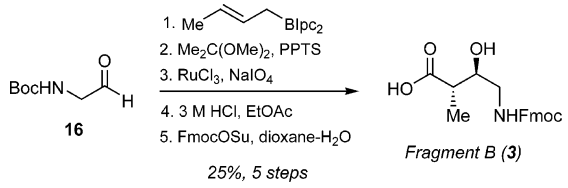
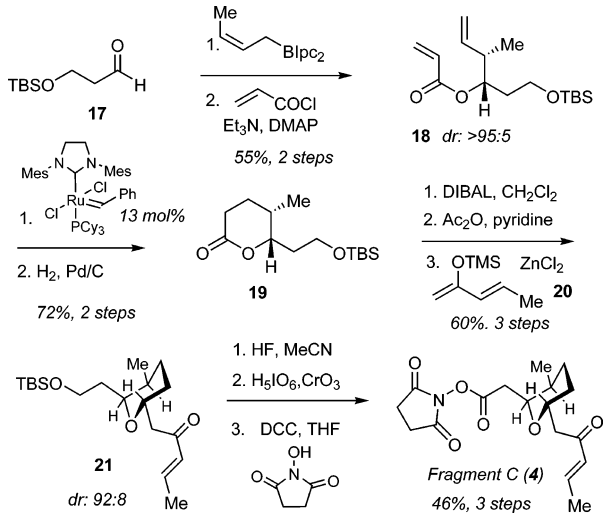
Scheme 2



Scheme 3



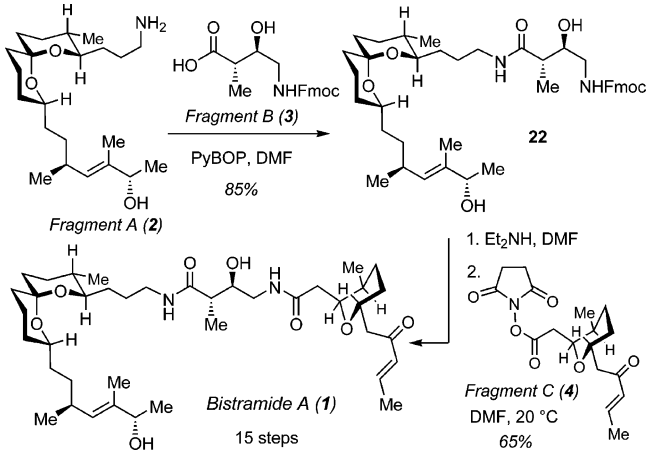
Scheme 4



^{13}C NMR, HPLC, optical rotation) with the natural sample of bistramide A.

In closing, we have developed a highly convergent, fully diastereocontrolled and efficient synthesis of bistramide A, which provided unambiguous structural assignment of this complex natural product and set the stage for the detailed investigation of its chemical biology. Our approach featured a novel and potentially broadly applicable olefin metathesis-based strategy for the spiroketal construction.

Scheme 5



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Supporting Information Available: Full characterization of new compounds and selected experimental procedures. This information is available free of charge via the Internet at http://pubs.acs.org.

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