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Synthesis of the spiroketal fragment of bistramide A via an exocyclic enol ether

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ABSTRACT

An efficient synthesis of the spirocyclic fragment **1** of bistramides is reported. An olefination reaction of lactone **4** with sulfone **5** gave the enol ether **3**, which upon cyclization in acidic media provided the spiroketal ring system. This compound was then converted into the C19–C36 fragment of the bistramides via successive Julia–Kocienski and Horner–Emmons olefinations.

The bistramides are marine metabolites isolated from *Lissoclinum bistratum* by Verbist in 1988 in the case of bistramide A (bistratene A, Fig. 1),[1] and in 1994 for the four additional members of the family (bistramide B–D and K).[2] These molecules lead to growth arrest, differentiation, and apoptosis and have thus emerged as potential anti-inflammatory and anti-tumor agents.

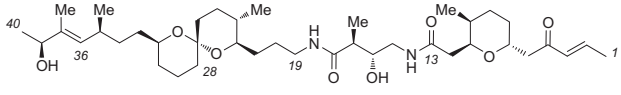
The first total synthesis of bistramide A was reported by Kozmin and co-workers in 2004.[3] Crimmins et al.,[4] Panek and co-workers[5] and Yadav et al.[6] later also performed total syntheses of the natural compound. Each of these prepared the spiroketal by spirocyclization of a dihydroxyketone or equivalent, which they approached via a double crossed metathesis, addition of an acetylene anion to a lactone, and by Wittig reaction or double TosMIC alkylation, respectively. Bistramide C has been synthesized by Wipf[7] who used a hypervalent iodine-mediated C–H insertion to form the spiroketal. We report herein the synthesis of the spiroketal fragment of the bistramides using a new route to enol ethers,[8] which could eventually provide access to novel analogs, such as those substituted at the C28 position.[9]

We recently reported the synthesis of functionalized *exo*-glycals from sugar-derived lactones using Julia–Kocienski olefination reagents, and their conversion into spiroketals.[10] This approach is extended here to the synthesis of enol ethers from non-carbohydrate lactones under newly optimized conditions. Thus, the C19–C40 fragment of bistramides can be obtained via the advanced intermediate **1** described by Crimmins et al.[4] (Fig. 2). The spiroketal **2** in turn can be prepared through the enol ether **3** by coupling the lactone **4** with the benzothiazolyl sulfone **5**. Fragment **4** and **5** can be prepared from a common mannitol-derived precursor **6**.

The synthesis of both lactone **4** and sulfone **5** are shown in Scheme 1. The ester **6**[11] was deprotected to the diol, which was differentially protected with a silyl and tetrahydropyranyl ether to provide the compound **7** in 77% overall yield. The methyl group was introduced based on the Hanessian's procedure by the addition of lithium dimethylcuprate to the unsaturated ester **8** in the presence of trimethylsilyl chloride.[12] Homologation of the ester by Dibal-H reduction and Wittig reaction furnished the enol ether **9**. Finally, acidic hydrolysis and oxidation of the lactol intermediate provided the lactone **4**.

For the synthesis of the Julia–Kocienski reagent **5**, ester **6** was converted into the tosylate derivative **10**, which provided the sulfone upon substitution with 2-mercaptobenzothiazole and sulfur oxidation using ammonium molybdate and hydrogen peroxide.[13]

The key step of the synthesis is the construction of the spiroketal subunit by the coupling of lactone **4** and the Julia–Kocienski



Bistramide A

Figure 1. Structure of bistramide A.

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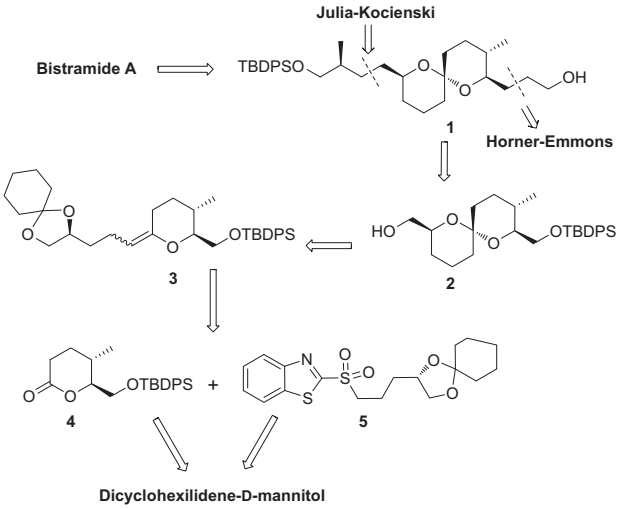
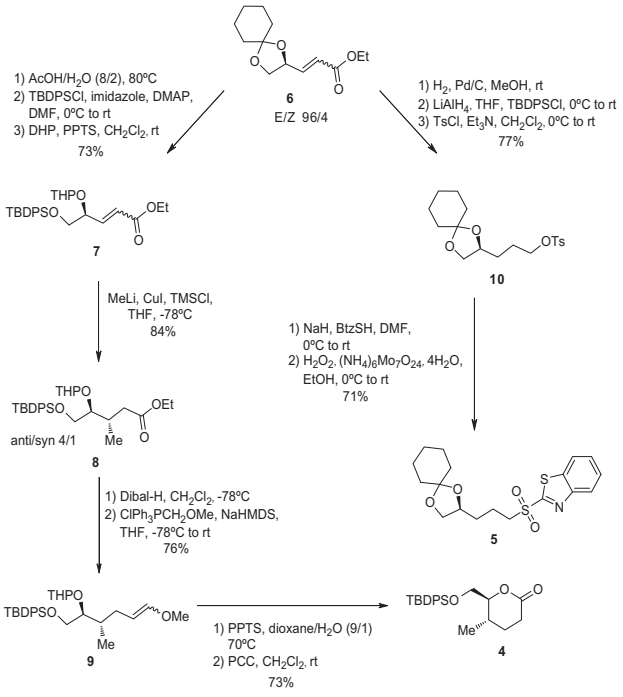
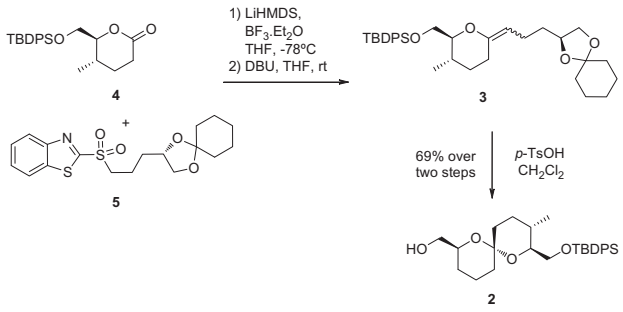


Figure 2. Retrosynthetic analysis of the C19–C36 fragment.

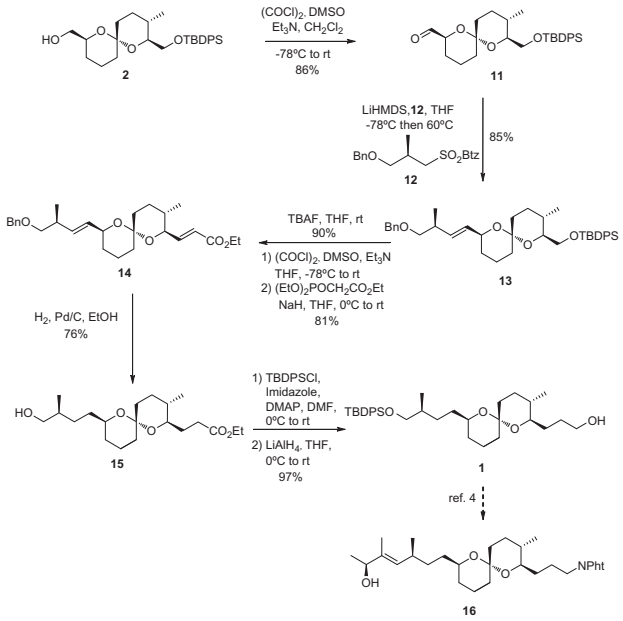


Scheme 1. Synthesis of the lactone **4** and benzothiazolyl sulfone **5**.

reagent **5**, followed by elimination in the presence of DBU, to afford the intermediate enol ether **3**. Under previously reported conditions,[10,14] the reaction gave virtually none of the desired products (5–10% yield). As the enol ether was found to be more sensitive to chromatography than its carbohydrate counterparts, it was cyclized directly under thermodynamic conditions to provide the differentially protected spiroketal **2** (Scheme 2). However, the yields remained disappointing. After investigating a number of conditions, we found that the addition of a Lewis acid, such as BF_3–etherate, along with the lithiated Julia–Kocienski reagent to the lactone improved the reaction considerably.[15] The spiroketal **2** was thus obtained in 69% yield over the two steps on gram scale as a single stereoisomer.[16] The expected thermodynamically favored, bis-anomeric stereochemistry at the spiroketal center was ultimately confirmed by correlation to the Crimmins' structure.



Scheme 2. Spiroketal synthesis.



Scheme 3. Functionalization of the spiroketal **2**.

The completion of the C19–C36 fragment synthesis was performed as illustrated in Scheme 3. Functionalization of the spiroketal **2** was started by Swern oxidation providing the aldehyde **11** which was subjected to a Julia–Kocienski reaction[17] with sulfone **12**. This reaction gave surprisingly poor results under the various reported experimental conditions: neither the order of addition (Barbier or premetalation), the solvent (THF or DMF), nor the choice of base (LiHMDS or KHMDS) significantly improved the yields, which ranged from 13% to 34%. However, running the reaction at −10 °C, then warming to 40 °C increased the yield to 69%. Finally, the best results were obtained by performing the coupling step at −78 °C and *then heating directly* to 60 °C, instead of warming progressively.[18] The resulting spiroketal **13** was thus obtained in 85% yield.

The silyl group of compound **13** was deprotected to the corresponding spiroketal alcohol, which was then oxidized to undergo a Horner–Emmons olefination with triethylphosphonoacetate providing the α,β-unsaturated ester **14** in good yield. Finally, the latter product was treated by palladium on charcoal under hydrogen atmosphere to furnish the compound **15**. The alcohol was subsequently protected as a silyl ether using TBDPSCl and submitted to reduction of the ester function to obtain compound **1** which was previously described by Crimmins et al.[4] The structure was confirmed by correlation with the NMR data.

In conclusion, we demonstrated a new access to the C19–C36 fragment of the bistramides using an original enol ether synthesis.

Such an approach may eventually allow for the preparation of novel analogs, for example those substituted at the C28 position. The basic spiroketal subunit **2** can be obtained in 22% overall yield on gram scale from dicyclohexylidene-D-mannitol. This key intermediate was converted on to Crimmins' C19–C36 fragment **1** with sequential olefination reactions. The total synthesis of bistramide A will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (analytic data and spectra (^{1}H and ^{13}C) for compound **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.006.

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15. A more detailed report of the Lewis acid-catalyzed enol ether synthesis will appear in due course.
16. Procedure for spiroketal **2** is as follows: To a solution of compound **4** (3.2 mmol, 1 equiv) in tetrahydrofuran (5.3 mL) was added boron trifluoride etherate (3.16 mmol, 1 equiv) and benzothiazolylsulfone **5** (1.37 g, 3.8 mmol, 1.2 equiv). The mixture was cooled to −78 °C and lithium hexamethyldisilazide (1 M in tetrahydrofuran, 6.3 mmol, 2 equiv) was added dropwise. The reaction was stirred at -78 °C for 30 min, quenched at −78 °C with acetic acid (9.48 mmol, 3 equiv), stirred at room temperature for 15 min, and extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation in vacuo, the residue was dissolved in tetrahydrofuran (30 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.32 mmol, 2 equiv) was added over 5 min. The reaction was stirred at room temperature for 30 min, quenched by an aqueous NH_4Cl solution and diluted with ethyl acetate. The mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. Filtration and evaporation in vacuo, provided a mixture of geometrical isomers. The crude mixture was dissolved in methylene chloride (45 mL), *para*-toluenesulfonic acid (300 mg, 1.6 mmol) was added and the reaction mixture was stirred at room temperature for 25 min, hydrolyzed with an aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography over silica gel (85:15 petroleum ether/ethyl acetate) to afford the spiroketal **2** as a colorless oil (2.2 mmol, 69% yield). $[\alpha]_D^{25}$ +26.2 (*c* 1. 0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 0.84 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H), 1.22–2.05 (m, 12H), 3.33 (ddd, *J* = 3.1, 4.4 and 9.4 Hz, 1H), 3.48 (dd, *J* = 6.9 and 11.2 Hz, 1H), 3.58 (dd, *J* = 3.4 and 11.3 Hz, 1H), 3.73–3.84 (m, 3H), 7.35–7.42 (m, 6H), 7.73–7.78 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 135.8, 135.7, 134.1, 134.0, 129.6, 127.7, 127.6, 96.0, 76.1, 69.5, 66.3, 65.2, 35.7, 35.4, 30.7, 28.0, 26.8, 26.6, 19.4, 18.5, 17.7; IR, ν (cm^{-1}): 2931, 2858, 1456, 1428, 1382, 1225, 1105, 984, 738; MS (ESI) *m/z* = 491 $[M+Na]^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{40}O_4SiNa$ $[M+Na]^+$ 491.2594, found 491.2593.
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18. The working hypothesis behind this procedure is that the fragmentation is expected to have a positive entropy of activation and thus a strictly enthalpic barrier; higher temperatures will therefore favor the fragmentation over possible side reactions. For a discussion, please see for example: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*; Plenum: New York, 1977. Chapter 4, p 139.