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Progress Toward the Synthesis of Sarain A: An Unanticipated Rearrangement.

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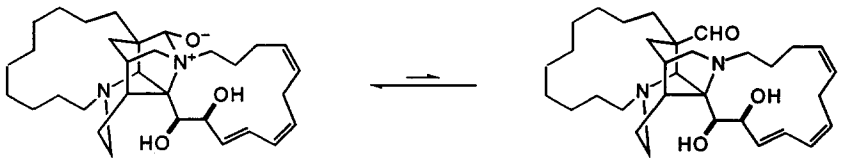
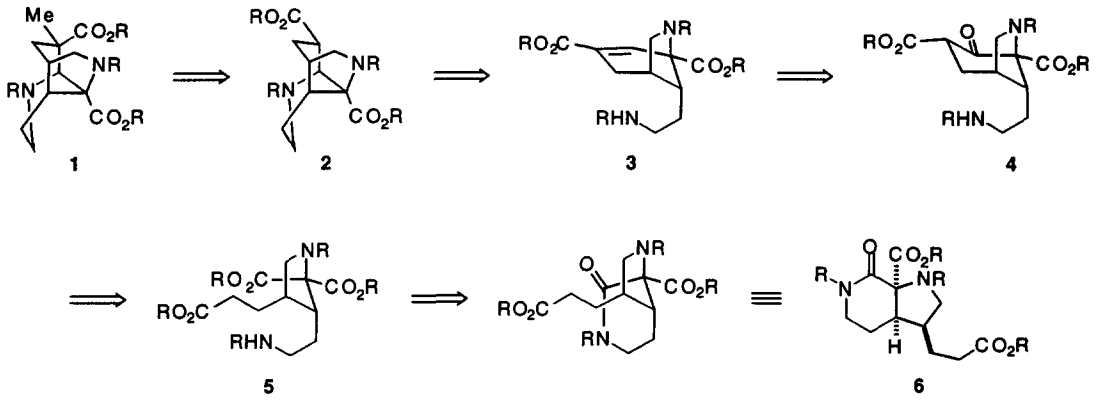
Abstract: An unanticipated rearrangement of a bicyclo[3.2.1]octane to a bicyclo[2.2.2]octane occurred in attempt to prepare the core of sarain A.

In connection with our continuing interest in the synthesis of piperidine derived alkaloids[1] we have been developing methodology for the synthesis of sarain A. This unusual alkaloid, recently isolated from the sponge *Reniera Sarai*,[2] displays a number of unusual features which include the zwiterionic hemiaminal, the highly functionalized unsaturated 14-membered ring, and the diazatetracyclic core. Our initial approach envisioned a 1,3-dipolar cycloaddition followed by an intramolecular Mannich reaction to prepare the core.[3] A remarkably similar approach was recently reported from the Weinreb group.[4] Herein we report an unanticipated structural rearrangement which we encountered while investigating a revised approach to the sarain A core.

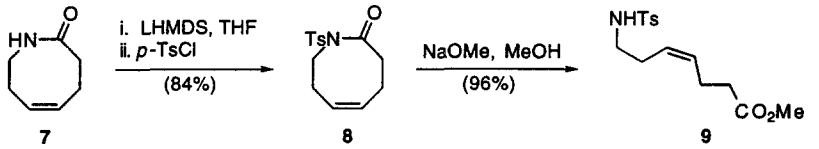


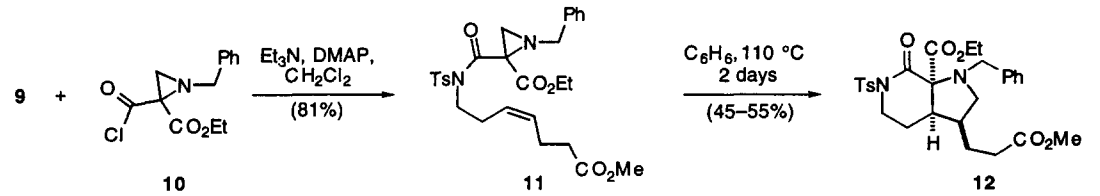
Sarain A

The initial goal of our current approach to the sarain core is the synthesis of model system **1** in which we intend to introduce the quaternary methyl substituent by alkylating ester **2**. The tricyclic system was seen to come from the intramolecular conjugate addition of a nitrogen nucleophile into α,β-unsaturated ester **3**, which should be readily available from β-keto ester **4**. The key step in the formation of the bridge bicyclic system was to be the base-mediated Dieckman reaction of triester **5**. The preparation of this intermediate was simplified by assuming that the amine could have been connected to one of the geminal esters. We therefore needed to prepare bicyclic lactam **6**, wherein an electron-withdrawing substituent would be attached to the lactam nitrogen to facilitate the expulsion of nitrogen during the Dieckman reaction. The diazabicyclo[4.3.0]nonane ring system was to be prepared following the protocol previously described for the preparation of similar system.[3] Finally, we think that the compounds like **2** will be eventually transformed into sarain A.

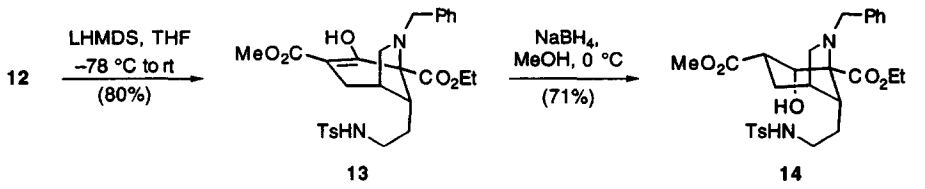


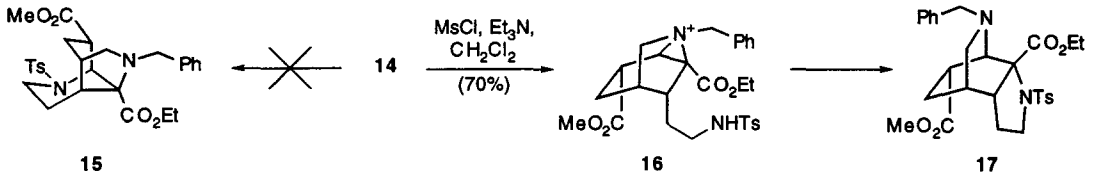
Tosylation of lactam **7**[5] provided sulfonimide **8**,[6] which was treated with methanolic sodium methoxide to efficiently provide sulfonamide **9**. Acylation of the sulfonamide with acid chloride **10**[7] provided the requisite cycloaddition precursor **11** in 81% yield. When this material was then subjected to the flash vacuum pyrolysis conditions which we had previously developed[3] only extensive decomposition of the sulfonimide was observed. The predominant product isolated from this experiment was sulfonamide **9**. Cleavage of the nitrogen–carbonyl carbon bond is apparently facilitated by the electron-withdrawing sulfonyl group. Fortunately we were able to obtain reasonable yields of the desired bicyclic material (**12**) when the cycloaddition was performed in a sealed tube at 110 °C with benzene as solvent. Cleaved sulfonamide **9** was still isolated as a minor product (35–40%) under these conditions.



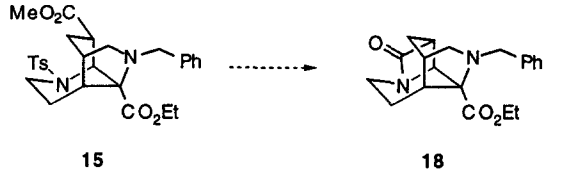


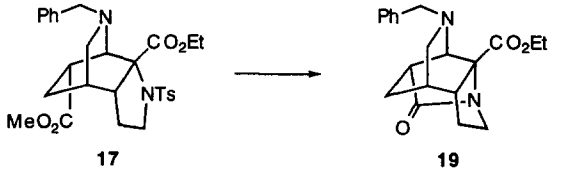
With sulfonimide **12** in hand we next examined its reaction in a Dieckman-like fashion to give the requisite bridged-bicyclic system. In the event, treatment of **12** with lithium hexamethyldisilylamide readily provided β-keto ester **13** which existed primarily as its enol tautomer as evidenced by ^{1}H NMR spectroscopy. In order to introduce the α,β-unsaturated ester needed for the preparation of the tricyclic system, **13** was reduced to β-hydroxyester **14**. Portionwise addition of $NaBH_4$ to a methanolic solution of **13** at 0 °C was necessary in order to minimize overreduction of **13** to the corresponding 1,3-diol. When **14** was then mesylated to effect the elimination of the alcohol a tricyclic compound was isolated (m.p. 174.5–176 °C) that initially appeared to have spectral characteristics consistent with the desired core system (**15**). However, a number of subsequent transformations suggested that the structural assignment was incorrect.





Had we isolated **15** from **14** the next step was to alkylate the methyl ester to introduce the α-quaternary center (i.e. **2** → **1**). However, we were concerned that deprotonation of **15** would cause β-elimination of the β-sulfonamido group. The sulfonyl group was therefore cleaved with sodium naphthalenide (THF, –78 °C) in 71% yield. Analysis of this material indicated that the methyl ester had reacted to form a strained lactam (^{13}C NMR carbonyl resonance at 187 ppm, IR 1735 cm^{-1}). The highly strained β-lactam (**18**) which would have been formed from **15** seemed unlikely. We therefore determined the structure of the tricycle by x-ray analysis. The crystal structure obtained indicated that the transformation of **14** had provided the isomer **17** which has the same carbon-connectivity as **15** (Figure 1). This unexpected material presumably arises by a rearrangement through aziridinium ion **16**. The lactam isolated after dissolving metal reduction of **17** was therefore the corresponding 5-membered lactam **19**. Recent work has demonstrated that the undesired rearrangement may be suppressed by using an acyl rather than a benzyl protecting group on the nitrogen. Further work toward the synthesis of sarain A will be reported in due course.





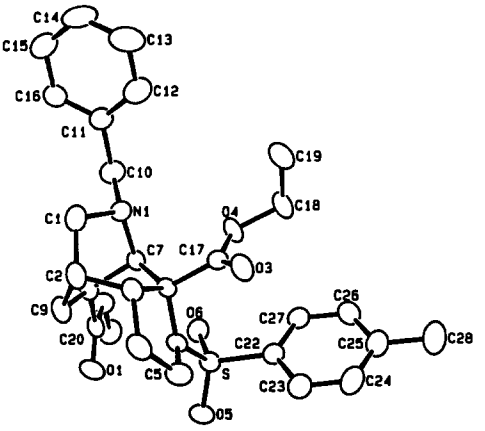


Figure 1. ORTEP Structure of Compound **17**

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6 All new materials were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, in addition to combustion analysis.

7 The acid chloride **10** was prepared and then used, *in situ*, from the corresponding aziridine diester: treatment of the diester with one equivalent of potassium trimethylsilanolate provided the potassium carboxolate[8] which was then treated with one-equivalent of thionyl chloride.

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