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# Studies towards an Enantioselective Total Synthesis of Sarain A: A Concise Asymmetric Construction of the Diazatricyclic Core

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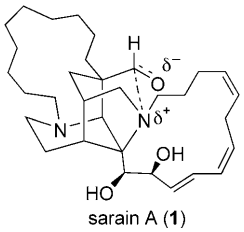
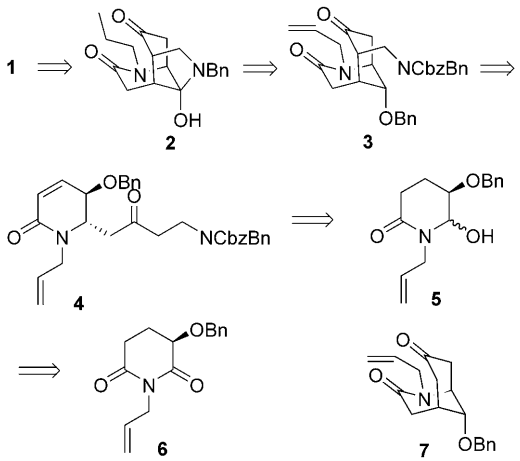


sarain A (**1**)

Sarain A (**1**) is a structurally complex alkaloid isolated from the sponge *Reniera sarai*.[1] This alkaloid contains seven chiral centers and a unique diazatricyclic core structure connected to two macrocyclic side rings. The complex 14-membered macrocycle contains a pinacolic substructure bearing vicinal chiral centers, a triene moiety, and an unusual polycyclic structure. In addition to its challenging structural features, sarain A (**1**) also exhibits antitumor, antibacterial, and insecticidal activity,[2] which make it an attractive synthetic target.[3]

The first synthetic study towards the total synthesis of sarain A was reported by Weinreb in 1991.[4] Since then, several research groups[5,6a] have been working on the construction of the diazatricyclic core of sarain A. Recently, Porter and co-workers reported the synthesis of bicyclic aminals and their evaluation as precursors to the sarain A core.[7] All of these studies, however, focused on racemic syntheses of the core of sarain A. Not until 2006 was the first asymmetric total synthesis of sarain A accomplished by Overman's group, which involves a 46-step synthesis.[6] As a continuation of our longstanding interest in the asymmetric synthesis of bioactive alkaloids and N-containing, pharmaceutically relevant molecules,[8] we have been engaged in attempting the total synthesis of sarain A.

Our retrosynthetic analysis of the sarain A core is outlined in Scheme 1 and comprises compound **2** as the diazatricyclic core and building block **6**[9] as the starting material.




Scheme 1. Our retrosynthetic analysis of the sarain A core **2**. Cbz = benzyloxycarbonyl; Bn = benzyl.

Compound **2** could be constructed from bicyclic intermediate **3** by deprotection and oxidation. Compound **3** was envisioned to be synthesized from *N,O*-acetal **5** through a tandem Horner–Wadsworth–Emmons–aza-Michael reaction followed by an intramolecular Michael addition reaction.

To assess the feasibility of our synthetic strategy, bicyclic system **7** was selected as a model system. The synthesis of model compound **7** started with a regioselective partial reduction of the protected (*R*)-3-hydroxyglutarimide **6**.[8g,l] Treatment of 3-benzyloxyglutarimide **6** with $NaBH_4$ (6.0 equiv) in a mixture of saturated aqueous $NaHCO_3$ and THF at −30 to −25 °C for 1 h produced a regioisomeric mixture of hemiaminals **5** and **8**, which were separated by column chromatography in 82 and 10% yields, respectively (Scheme 2). Compound **5** contained two diastereomers in a

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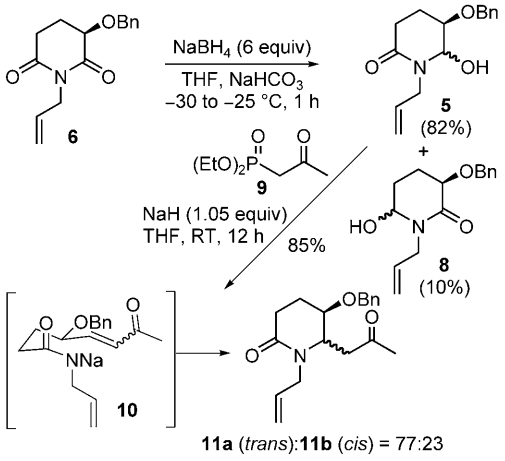
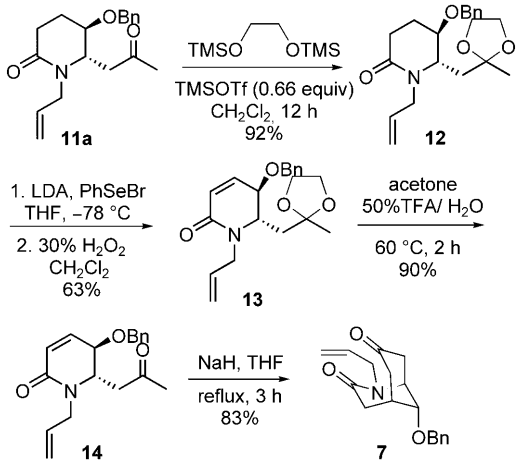



Scheme 2. The tandem Horner–Wadsworth–Emmons–aza-Michael reaction in a model system.




Scheme 3. The intramolecular Michael addition reaction in a model system. TMS = trimethylsilyl; TMSOTf = trimethylsilyl triflate; LDA = lithium diisopropylamide; TFA = trifluoroacetic acid.

ratio of 11:1. The major diastereomer had a larger vicinal coupling constant between H-5 and H-6 ($J_{5,6}=3.3$ Hz) than that of the minor diastereomer ($J_{5,6}=2.2$ Hz). According to literature precedents,[9a,b] the stereochemistry of the major diastereomer was, therefore, assigned as *cis*. We were able to use the two diastereomers in the subsequent step without further separation.

To introduce the 2-oxopropyl group at the C-6 position of intermediate **5**, a tandem Horner–Wadsworth–Emmons–aza-Michael reaction[10] was envisaged. Treatment of the diastereomeric mixture of hemiaminals **5** with the ylide derived from diethyl 2-oxopropylphosphonate **9**, presumably, gave the intermediate enone **10** and then an intramolecular Michael addition followed to produce diastereomeric methyl ketones **11a** (*trans*) and **11b** (*cis*) in a ratio of 77:23 and a combined yield of 85%. The stereochemistry of the two diastereomers was deduced from their vicinal coupling constants, between H-5 and H-6 ($J_{5,6}=4.7$ Hz for the *cis*-diastereomer and 2.3 Hz for the *trans*-diastereomer).

In order to obtain the requisite α,β-unsaturated lactam, the ketone group had to be protected. In the presence of TMSOTf (0.66 equiv), acetalization of the major diastereomer **11a** with 1,2-bis(trimethylsilyloxy)ethane gave the desired lactam–acetal **12** in 92% yield (Scheme 3). Lactam **12** was then converted into α,β-unsaturated lactam **13** by a known method;[11] namely, treatment of compound **12** with LDA and PhSeBr, followed by oxidation of the resulting α-phenylselenide with $H_2O_2$, and, finally, in situ elimination of the selenoxide to give compound **13** in 63% overall yield. Cleavage of the acetal in **13** was performed with 50% aqueous TFA, in acetone at 60°C, giving the corresponding keto–amide **14** in 90% yield.

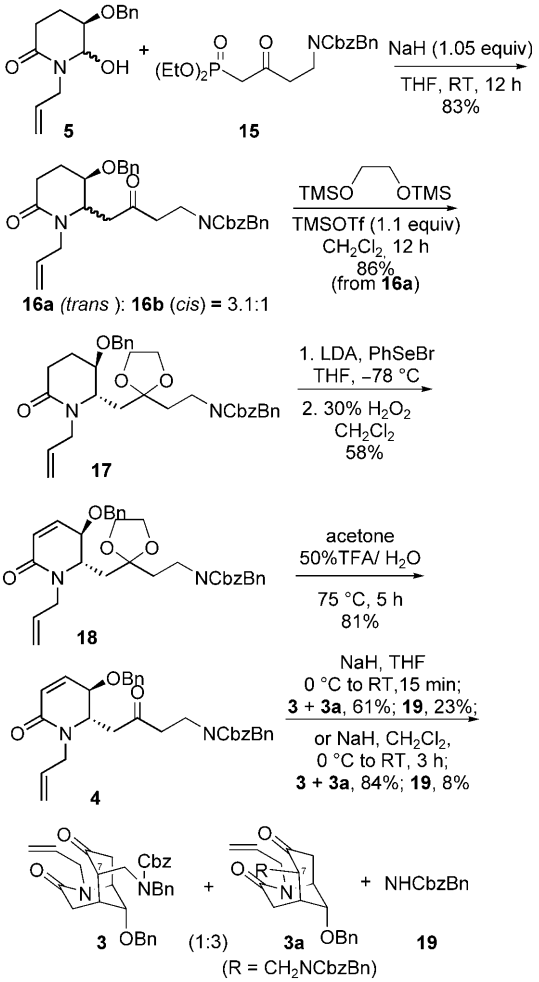
With keto–amide **14** in hand, we then undertook the key intramolecular Michael addition. Initial attempts involving the treatment of compound **14** with LDA led to complete destruction of the starting material. Gratifyingly, if a suspension of compound **14** and NaH (3.0 equiv) in THF was heated at 70°C for 3 h, the desired cyclization product **7** was obtained in 83% yield.

Having accomplished the synthesis of model compound **7**, we turned our attention to the synthesis of the diazatricyclic core **2**. Treatment of hemiaminals **5** with the ylide generated from diethyl 2-oxopropylphosphonate **15** and NaH produced diastereomeric methyl ketones **16a** (*trans*) and **16b** (*cis*) in a ratio of 3.1:1 and a combined yield of 83% (Scheme 4). The carbonyl in **16a** is more difficult to acetalize than that in **11a**, perhaps because of the increased steric hindrance. In spite of this, in the presence of TMSOTf (1.1 equiv), lactam–acetal **17** was obtained in 86% yield. Lactam **17** was then converted into the corresponding α,β-unsaturated lactam (**18**) by the same procedure described for lactam **12**, affording **18** in 58% overall yield. Treatment of lactam–acetal **18** with 50% aqueous TFA, in acetone at 75°C, gave the desired keto–amide **4** in 81% yield.

Next, we investigated the base-promoted intramolecular Michael addition of compound **4**. The challenge in this reaction was caused by β-elimination from the enolate intermediate. To suppress this side reaction, the intramolecular Michael addition of **4** needed to be run under milder conditions than those used for **14**. It was found that treatment of **4** with NaH, in THF, at room temperature, for 15 min produced cyclization product **3** and its diastereomer **3a** smoothly, in a combined yield of 61%. The elimination side product **19**, produced by a retro-aza-Michael reaction, was isolated in 23% yield. The two diastereomers **3** and **3a** were separable by column chromatography and the ratio of **3**/**3a** was determined to be 1:3. However, if the reaction was carried out in $CH_2Cl_2$, the combined yield of **3** and **3a** was significantly improved to 84% and that of **19** decreased to 8%; although, the diastereoselectivity was somehow decreased to 1:2.1.

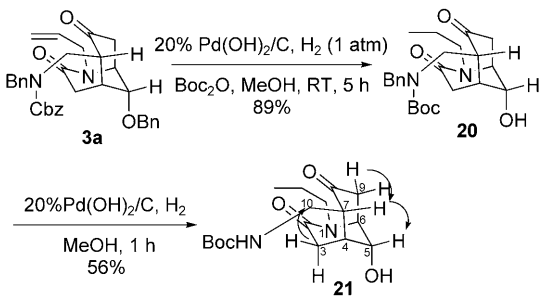
To determine the stereochemistry of cyclization products **3** and **3a**, **3a** was subjected to catalytic hydrogenolysis in the presence of di-*tert*-butyl dicarbonate ($Boc_2O$), giving alcohol



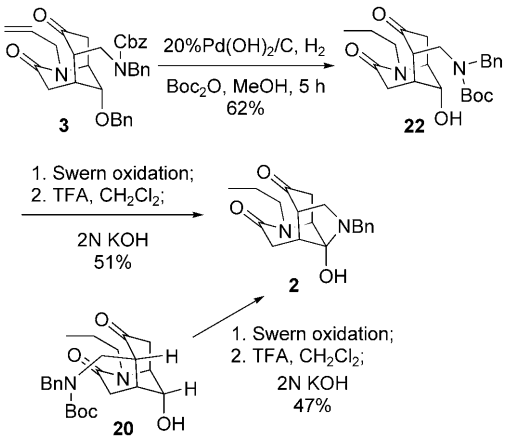

Scheme 4. The construction of the aza-bicyclic core of sarain A.

**20** in 89% yield (Scheme 5). Compound **20** was further hydrogenolyzed with excess $Pd(OH)_2/C$, to produce debenzylated product **21**, which gives a well-resolved $^1H$ NMR spectrum. From the observed correlations between H-7 and H-9, H-7 and H-5, and H-10 and H-3 in the 2D NOESY spectrum of **21**, we assigned the configuration at C-7 of diastereomer **3a** to be *R*. Thus, the configuration at C-7 of diastereomer **3** was deduced to be *S*.




Scheme 5. The preparation of compound **21** for an indirect establishment of the stereochemistry of compound **3a** by NOESY spectroscopy.

Finally, we investigated the construction of the tricyclic core from **3**. To this end, diastereomer **3** was first subjected to catalytic hydrogenolysis in the presence of $Boc_2O$, affording alcohol **22** in 62% yield (Scheme 6). Next, alcohol **22** was subjected to a Swern oxidation and the resulting ketone was then treated with TFA to cleave the Boc group. After workup with KOH (2 N), the diazatricyclic core (**2**) was formed in 51% yield.




Scheme 6. The diastereoconvergent synthesis of the diazatricyclic core of sarain A.

As **3a** was the predominant diastereomer we synthesized, the transformation of **3a** into core **2** was crucial for the efficiency of our synthetic approach. It was envisaged that the same procedures developed for the synthesis of **2** from **3** would also be applicable to its diastereomer **3a**, because the final basic workup would allow concomitant epimerization at C-7, leading to the formation of the thermodynamically more stable cyclization product **2**. Indeed, the Swern oxidation of **20** and treatment of the resulting product with TFA, followed by a basic workup with KOH (2 N), eventually gave the diazatricyclic core **2** in 47% yield.

## Conclusion

Starting from the versatile chiral building block **6**, we have developed a concise asymmetric synthesis of the tricyclic core (**2**) of sarain A, the *N*-propyl group of which could be cleaved by oxidation[12] to give the corresponding mixed imide, or by an amide-reduction/N-dealkylation procedure.[13] It is worth mentioning that, although several innovative approaches have been developed for the construction of the core of sarain A, this is the second enantioselective approach to the tricyclic core since the first asymmetric total synthesis by Overman. Work is in progress towards an asymmetric total synthesis of sarain A.

## Experimental Section

Experimental procedures and characterization for all new compounds can be found in the Supporting Information.

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**Keywords:** alkaloids · asymmetric synthesis · cyclization · Michael addition · Sarain A · total synthesis

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