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# Synthetic Studies toward Sarain A. Formation of the Western Macrocyclic Ring

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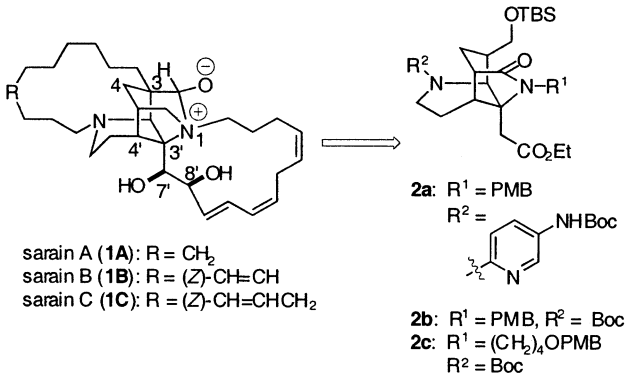
Starting with the tricyclic core **2b**, annulation to form the 13-membered western ring of sarain A has been achieved to afford the macrocycle **30a** by initial construction of the sterically congested quaternary center at C-3, followed by elaboration of the C-3 side-chain and ring-closing olefin metathesis. Also included is a parallel conversion of tricycle **2c** to macrocycle **30b** containing a functionalized side-chain at N-1 suitable for attachment of the eastern macrocyclic ring.

Sarains A−C (**1A**−**C**) belong to a new family of structurally intricate alkaloids found in marine sponges. They were isolated by Cimino and co-workers from the sponge *Reniera sarai*[1a,b] and reported to possess moderate antitumor, antibacterial, and insecticidal activity.[1c] The biosynthesis of sarains has been postulated to involve reductive condensation of a bispyridinium macrocycle,[2] and their fascinating architecture has attracted considerable synthetic interest.[3] The stereoselective synthesis of the tricyclic core of sarain A has been achieved by three groups and also in our laboratory.[4−7] Although sarain A has not succumbed to a total synthesis to date, the Weinreb group reported the construction of the "western" macrocyclic ring by employing a Grubbs' ring-closing olefin metathesis strategy.[4c] The "eastern" macrocyclic ring assembly of sarains was addressed by the Heathcock group in a synthesis of an appropriately designed model system.[5b] Toward a total synthesis of **1A**, we herein report a successful annulation of a western macrocyclic ring onto **2b** and **2c** (Scheme 1) by adaptation of Weinreb's previous work.

**SCHEME 1**




## Results and Discussion

By a slight modification of our previously reported synthesis of **2a**,[7] we first secured multigram quantities of the *N*-Boc-protected tricyclic core **2b** in order to facilitate removal of the N-substituent at a later stage under mild conditions.[8] Annulation to form the western macrocyclic ring onto **2b** required initial construction of the quaternary center at C-3. Our initial plan was to utilize Weinreb's alkylation of a nitrile anion at C-3 (Scheme 2).[4c] The nitrile **5** was prepared as an epimeric mixture via alcohol **4** by standard methods. Despite considerable experimentation, alkylation of **5** afforded none of the desired C-alkylation product **6**; instead, the amide **7** was isolated in 50% (unoptimized) yield, presumably arising from N-alkylation. This disappointing result was in sharp contrast to Weinreb's previous observation that a nitrile bearing an exocyclic carbamate functionality (rather than an endocyclic lactam in **5**) was amenable to C-3 alkylation; subtle, as yet unidentified,

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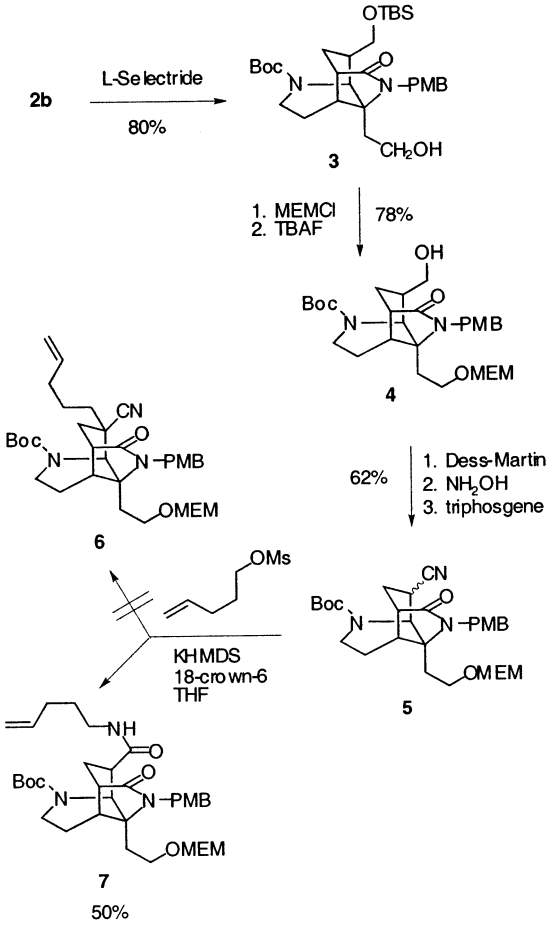
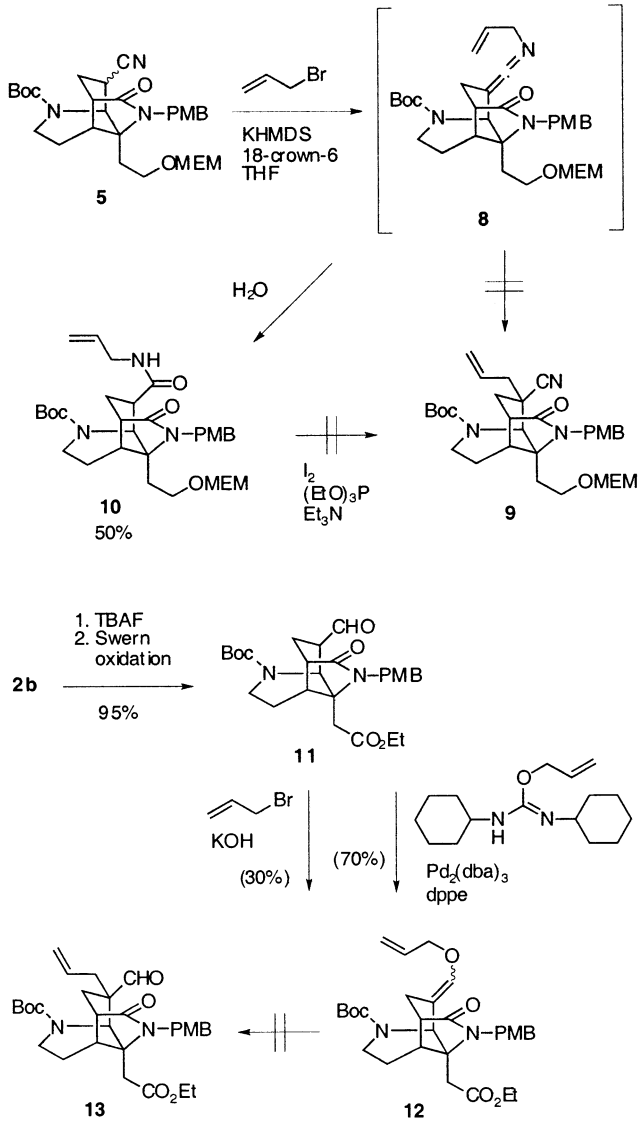
**SCHEME 2**




**SCHEME 3**




electronic factors seem to play an important role in the successful nitrile alkylation.

The exclusive N-alkylation of the nitrile **5** prompted us to investigate N-allylation in tandem with a 3-aza-Claisen rearrangement of the presumed intermediate **8** (Scheme 3). Walters had shown that the Claisen rearrangement of 3-aza-1,2,5-hexatrienes could take place under exceptionally mild conditions.[9] Unfortunately, in lieu of the 3-aza-Claisen rearrangement product **9**, only amide **10** was obtained in 50% yield. When the amide **10** was subjected to Walters' rearrangement protocols [$I_2$/$(EtO)_3P$/$Et_3N$] or other dehydrating reagents, it was recovered unchanged. Similarly, the Claisen rearrangement of allyl ether **12**, which was readily prepared by palladium-mediated allylation of aldehyde **11**,[10] was also futile under either thermal or Lewis-acid-catalyzed conditions. It became apparent that these approaches to the construction of the quaternary center at C-3 were thwarted by severe steric congestion.[11]

Ultimately, treatment of aldehyde **11** (or its more stable epimer obtained upon silica gel column chromatography) with an excess of aqueous formaldehyde in the presence of sodium carbonate gave diol **15a** in 90% yield, along with minute amounts of the initial aldol product **14** (Scheme 4). Formation of **15a** presumably involved a Tishchenko reaction and subsequent in situ hydrolysis of the resulting formate (structure not shown). The aldol condensation−Tishchenko reaction sequence could not be extended to other nonenolizable aldehydes such as 3-trimethylsilylpropargyl aldehyde and acrolein for easy installation of a longer side chain. Elaboration of the side chain of **15a** proved to be challenging and required intramolecularity to overcome unfavorable steric effects. Toward this end, the two hydroxyl groups in **15a** were first differentiated by the THP protecting group to provide an equal mixture of **16**, **17**, and **18**. These were easily separated by column chromatography, and **18** was readily re-converted to **15a** by a catalytic amount of *p*-TsOH in MeOH for recycling. Treatment of **16** with diethylphosphonoacetyl chloride (**19**) in the presence of pyridine, followed by removal of the THP protecting group with *p*-TsOH, afforded alcohol **20a**. Dess−Martin oxidation of **20a** and subsequent intramolecular Wittig olefination of **21a** then provided *δ*-lactone **22a** in excel-

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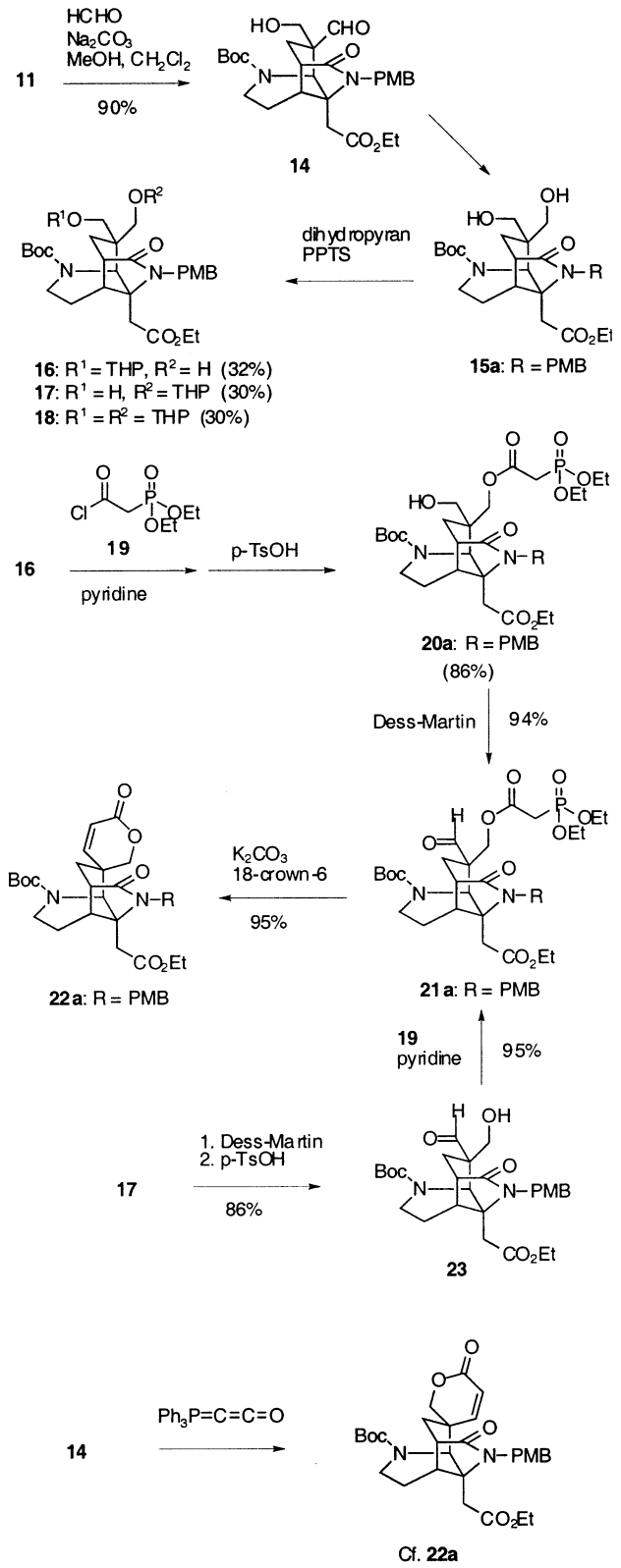
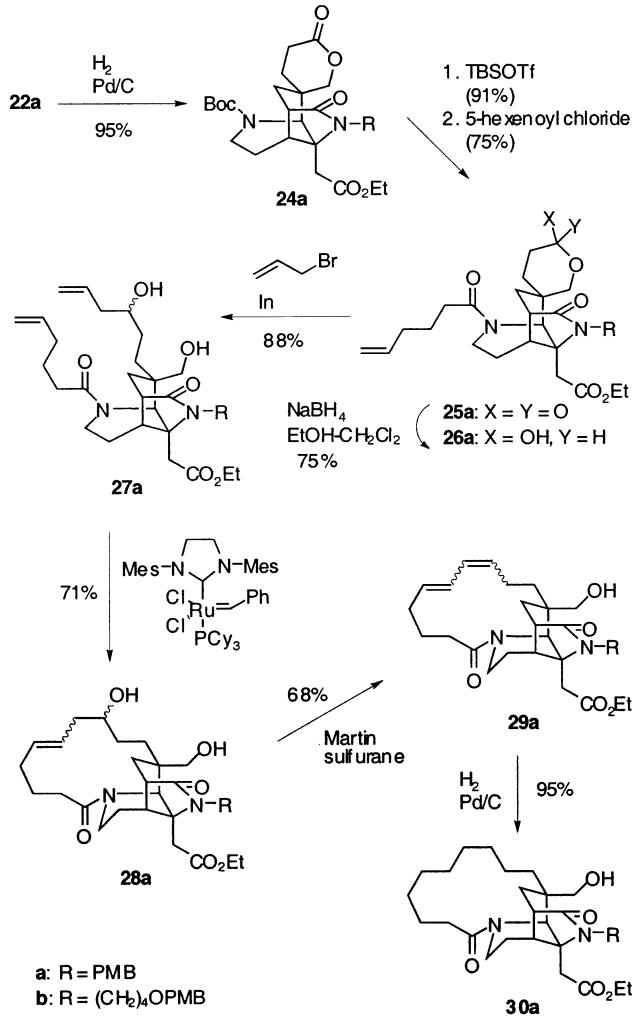
**SCHEME 4**




lent overall yields. Similarly, **17** was converted to **22a** via **23** in comparable yields. Treatment of **14** with Bestmann's ylide[12] furnished the respective lactone (35% yield) that was regioisomeric to **22a**; although the yield was not high, this control experiment allowed us to establish the regiochemistry of **16** and **17**.

**SCHEME 5**




To set the stage for building a 13-membered ring by ring-closing olefin metathesis, the saturated lactone **24a** was next prepared in 97% yield by hydrogenation of **22a** (Scheme 5). Following removal (91%) of the Boc protecting group by either TBSOTf or TFA, amide **25a** was obtained by acylation with 5-hexenoyl chloride in 75% yield. The other terminal olefin moiety was then introduced by selective reduction (75%) of the lactone with $NaBH_4$, followed by indium-mediated allylation[13] (88%) of the resulting lactol **26a** to provide **27a** as a diastereomeric mixture. The key cyclization of the diene **27a** took place smoothly (a 0.4 mM solution in refluxing $CH_2Cl_2$) using Grubbs' second-generation catalyst[14] to afford the 13-membered lactam **28a** in 71% yield. Dehydration of **28a** with the Martin sulfurane[15] provided conjugated

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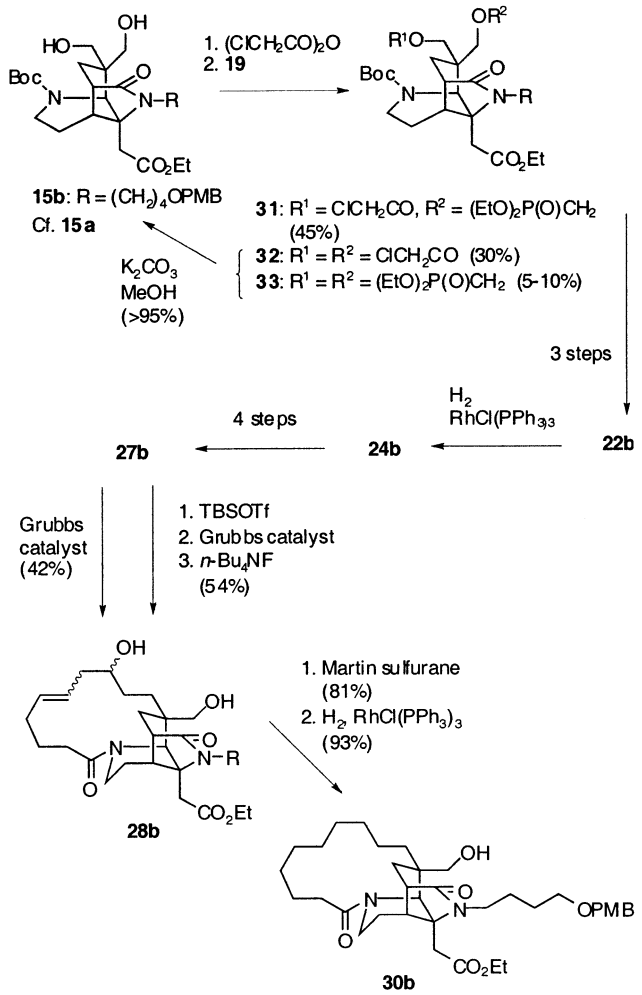
**SCHEME 6**




diene **29a** in 60% yield at 88% conversion. For convenience, **27a**, **28a**, and **29a** were used as obtained in isomeric mixtures. These isomers complicated characterization but were inconsequential: hydrogenation (10% Pd/C) of **29a** gave the macrolactam **30a** (95%).

We next introduced an alkoxybutane N-substitutent in place of the PMB group prior to the construction of the pyrrolidinone ring so as to facilitate subsequent annulation of the eastern macrocyclic ring (Scheme 6). By this simple alteration in the amine starting material, large amounts of **15b** were prepared in comparable yields.[8] The requisite differentiation of the two alcohols in **15b** was more conveniently achieved by means of chloroacetylation compared to the above-mentioned use of the THP protecting group. The chloroacetate group was chosen over the acetate because of its facile removal by thiourea and $Et_3N$.[16] Protection of **15b** with chloroacetic anhydride was selective for $-OR^1$ (in preference to $-OR^2$), but an excess of chloroacetic anhydride was used for rapid processing. Thus, sequential treatment of **15b** with chloroacetic anhydride and diethylphosphonoacetyl chloride (**19**) gave an easily separable mixture of **31** (45%), **32** (30%), and **33** (5−10%). The last two compounds were recycled to afford **15b** by basic hydrolysis ($K_2CO_3$, MeOH) in nearly quantitative yield. Diene **27b** was then obtained by adaptation of the above-mentioned procedure for **27a**; use of the Wilkinson catalyst was necessary for conversion of **22b** to **24b** to avoid concomitant hydrogenolysis of the PMB group. In contrast to uncomplicated ring closure of **27a**, it was surprising that treatment of diene **27b** with the Grubbs catalyst gave **28b** in lower (42%) yield, along with formation of a dimer. Silylation of **27b** prior to ring-closing olefin metathesis gave a reliably higher yield of the desired macrocycle, and subsequent desilylation furnished **28b** in 54% overall yield. Upon treatment of **27b** with TBSOTf, the secondary alcohol was selectively protected as the *tert*-butyldimethylsilyl ether, validating steric congestion around the primary alcohol. Finally, **28b** was converted smoothly to the desired macrolactam **30b**, which we plan to utilize for installation of the eastern macrocyclic ring.

In summary, we have achieved the assembly of the western macrocyclic ring by initial construction of the sterically congested quaternary center at C3, followed by elaboration of the side-chain and ring-closing olefin metathesis. Refinement of the present approach to streamline the overall steps, as well as formation of the remaining eastern macrocycle in **30b**, is currently in progress to complete a total synthesis of sarain A.

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**Supporting Information Available:** Experimental procedures and copies of $^1H$ and $^{13}C$ NMR spectra of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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