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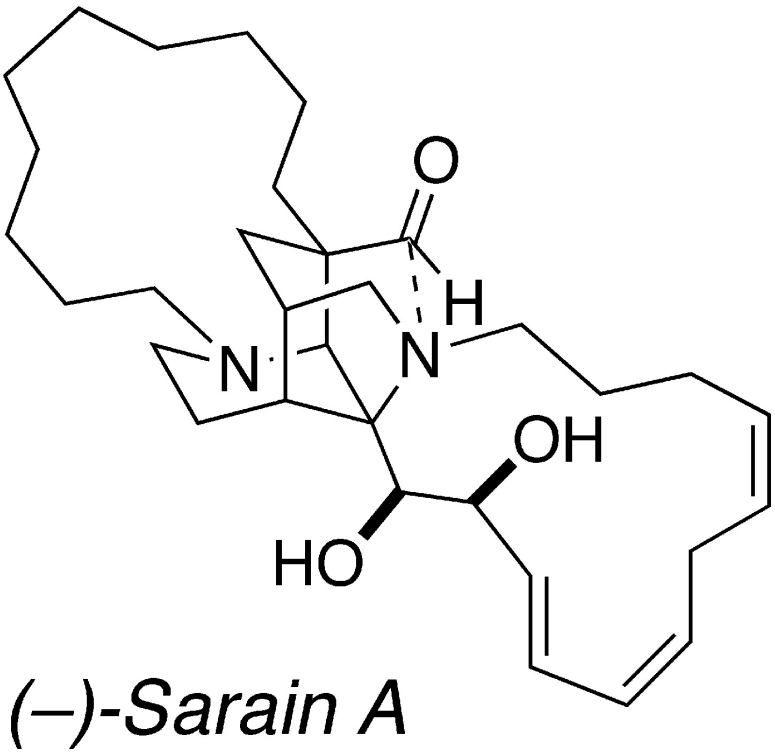

(–)-Sarain A

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Total Synthesis of (−)-Sarain A

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Abstract: This article describes the details of our synthetic studies toward the complex marine alkaloid sarain A. Various strategies were conceived, setbacks encountered, and solutions developed, ultimately leading to a successful enantioselective total synthesis. Our route to (−)-sarain A features a number of key steps, including an asymmetric Michael addition to install the C4′−C3′−C7′ stereotriad, an enoxysilane-*N*-sulfonyliminium ion cyclization to set the C3 quaternary carbon stereocenter, and assemble the diazatricycloundecane core, a ring-closing metathesis to construct the 13-membered ring, an intramolecular Stille coupling to fashion the unsaturated 14-membered macrocycle, and a late-stage installation of the tertiary amine−aldehyde proximity interaction.

Introduction

Complex molecules isolated from marine environments continue to spark the interest of synthetic chemists. In 1986, Cimino and co-workers discovered the sarain alkaloids (**1**−**3**, Figure 1) from the marine sponge *Reniera sarai*, which was collected in the Bay of Naples.[2,3] Although attempts to resolve the structures of sarains A−C were unsuccessful for several years, a diacetate derivative of sarain A (i.e., **4**) eventually provided crystals suitable for X-ray diffraction.[2c,4] The results of these studies revealed the impressive architecture of sarain A, which contains a number of daunting synthetic challenges, namely: (a) a densely functionalized diazatricycloundecane core, which contains five contiguous stereogenic centers, one of which is quaternary (C3); (b) a saturated 13-membered macrocycle;

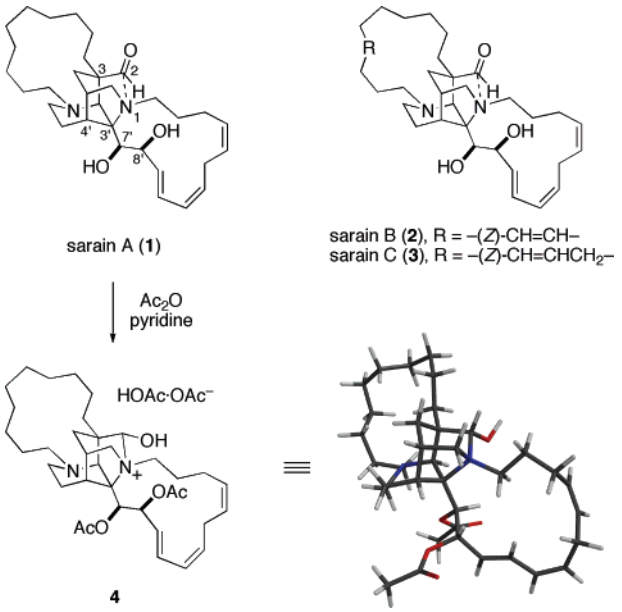

Figure 1. Sarain alkaloids (**1**−**3**) and the X-ray structure of diacetate derivative **4**.

(c) a 14-membered ring containing both skipped-triene and vicinal diol functional groups; and (d) a tertiary amine−aldehyde proximity interaction, which was not only found to be sensitive to pH and solvent environment, but also complicated the purification and characterization of the natural product.[5] It should be noted that related proximity interactions have previously been studied,[6,7] though sarains A−C (**1**−**3**) mark the first reported instance of such an interaction between a trialkylamine and an aldehyde occurring in a natural product.[8] In addition, the

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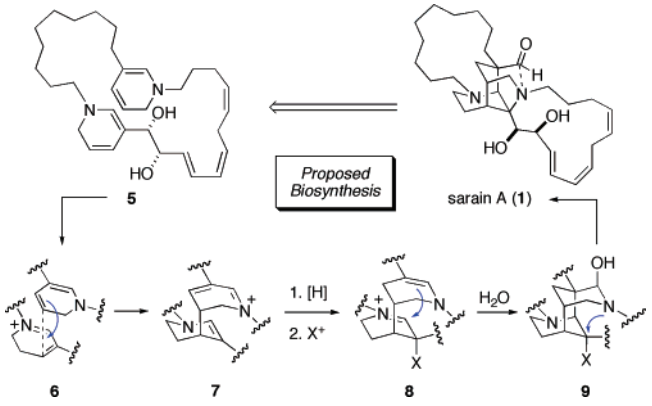
(2) (a) Cimino, G.; De Stefano, S.; Scognamiglio, G.; Sodano, G.; Trivellone, E. *Bull. Soc. Chim. Belg.* **1986**, *95*, 783−800. (b) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863−3872. (c) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519−1525. (d) Guo, Y.; Madaio, A.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341−8348.

(3) Although referred to as "sarains A−C" in an initial publication,[2b] these alkaloids were called "saraines A−C" in later publications from the Cimino group. These alkaloids have most commonly been termed "sarain" in the literature.

(4) Cambridge Structural Database (CSD) reference code for diacetate **4**: SAZRAM.

(5) Chromatographic purifications of sarains A−C were described as seldom being reproducible, possibly because of the zwitterionic character of these natural products; see reference 2b.

Scheme 1



absolute configurations of sarains A−C (**1**−**3**) have been proposed on the basis of Mosher's ester analysis and are depicted accordingly in Figure 1.[2d] Sarains A−C are reported to display modest antibacterial, insecticidal, and antitumor activities.[9]

Biosynthetically, sarains A−C belong to a larger group of natural products believed to be derived from bis(dihydropyridine) macrocycles.[10] It was initially proposed that, in nature, sarain A (**1**) could be accessed from pyridinyl cyclophanes, such as **5**, through a series of unspecified transannular reactions (Scheme 1).[2c,d] Subsequently, Marazano and co-workers suggested a possible mechanism for these transformations.[11] Protonation of bis(dihydropyridine) **5** would afford iminium species **6**, which could undergo an intramolecular cyclization to provide enamine **7**. Reduction of the α,β-unsaturated iminium of **7** and reaction of the enamine with an electrophile X^+ would deliver iminium ion intermediate **8**. Another intramolecular cyclization would take place, followed by trapping with water to form hemiaminal **9**. Finally, displacement of leaving group X by the proximal nitrogen would construct the pyrrolidine ring of sarain A (**1**). Although alternative biosynthetic proposals have surfaced in recent years,[12] credibility for the initial hypothesis stems from the notion that related alkaloids, such as manzamine A and keramaphidin B, are thought to be biosynthetically derived from similar precursors.[10] These natural products, as well as other congeners that possess a minimum of two nitrogen atoms and contain macrocyclic rings of at least eight atoms, are shown in Figure 2.[13]

Soon after the unprecedented structures of sarains A−C (**1**−**3**) were disclosed, laboratories worldwide initiated synthetic

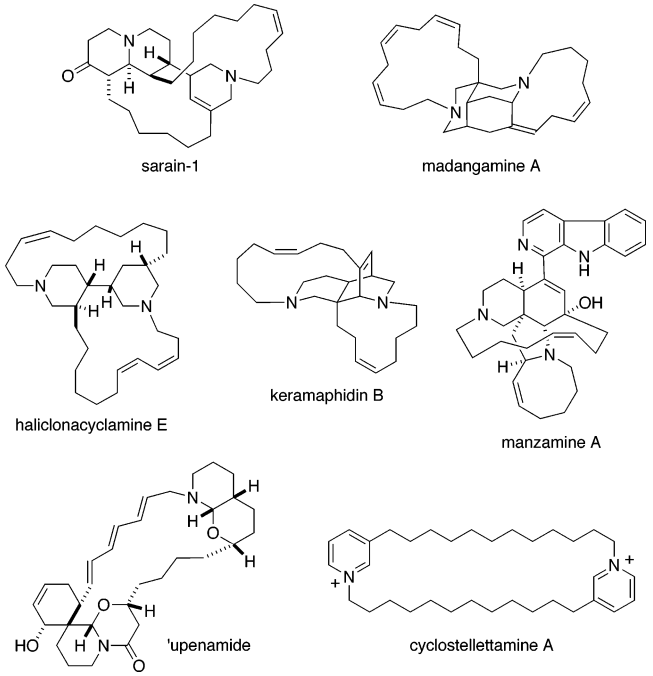


Figure 2. Alkaloids biosynthetically related to sarains A−C (**1**−**3**).

efforts toward these remarkable alkaloids. Aside from the work previously carried out in our laboratory,[14] significant progress has been made by the Weinreb,[15] Heathcock,[16] Cha,[17] and Marazano[12] groups. The details surrounding these endeavors have recently been reviewed.[14d] To summarize, successful preparations of the diazatricycloundecane core and the saturated macrocycle have been reported;[12b, 15c,d,16d,17b,c] however, aside from recent work in our laboratory,[14e] studies involving the synthesis of the highly functionalized 14-membered ring have been limited,[16c] and those concerning the tertiary amine−aldehyde proximity interaction have been nonexistent. Herein, we provide a comprehensive account of our efforts toward (−)-sarain A, which recently resulted in the first total synthesis of this intriguing natural product.[14e]

(6) For pioneering studies involving ketone−amine proximity interactions, see: (a) Leonard, N. J.; Oki, M.; Chiavarelli, S. *J. Am. Chem. Soc*. **1955**, *77*, 6234−6237. (b) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067.
(7) For studies involving tertiary amine−aldehyde proximity interactions, see: (a) McCrindle, R.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 61−62. (b) Kirby, A. J.; Komarov, I. V.; Bilenko, V. A.; Davies, J. E.; Rawson, J. M. *Chem. Commun.* **2002**, 2106−2107.
(8) Since the isolation of sarains A−C, another alkaloid that displays a tertiary amine−aldehyde proximity interaction was isolated; see: Guo, Y.; Trivellone, E.; Scognamiglio, G.; Cimino, G. *Tetrahedron* **1998**, *54*, 541−550.
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(12) (a) Hourcade, S.; Ferdenzi, A.; Retailleau, P.; Mons, S.; Marazano, C. *Eur. J. Org. Chem*. **2005**, 1302−1310. (b) Ge, C. S.; Hourcade, S.; Ferdenzi, A.; Chiaroni, A.; Mons, S.; Delpech, B.; Marazano, C. *Eur. J. Org. Chem*. **2006**, 4106−4114.
(13) For sarain-1, see: reference 2a. For keramaphidin B, see: (a) Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. *Tetrahedron Lett.* **1994**, *35*, 4383−4386. For madangamine A, see: (b) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008. For haliclonacyclamine E, see: (c) Clark, R. J.; Field, K. L.; Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C. *Tetrahedron* **1998**, *54*, 8811−8826. For manzamine A, see: (d) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404−6405. For upenamide, see: (e) Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465−8469. For cyclostellettamine A, see: (f) Fusetani, N.; Asai, N.; Matsugnaga, S. *Tetrahedron Lett.* **1994**, *35*, 3967−3970.
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(15) (a) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210−3211. (b) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945−4951. (c) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 587−595. (d) Hong, S.; Yang, J.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2078−2089.
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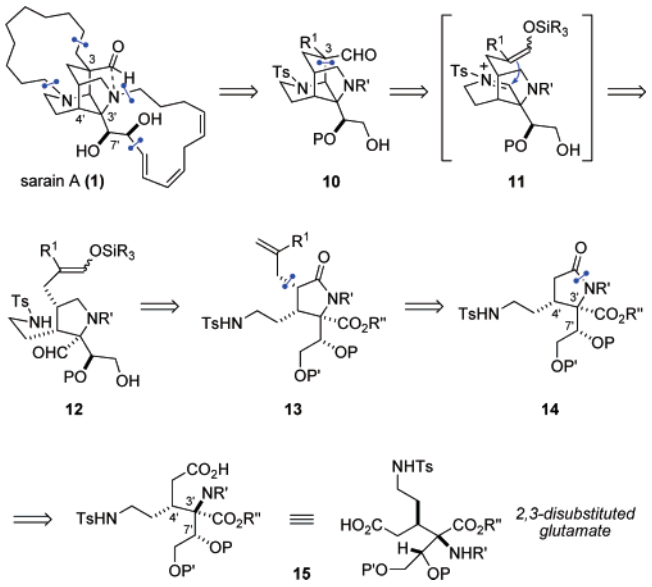
(17) (a) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett*. **1999**, *1*, 2017−2019. (b) Sung, M. J.; Lee, H. I.; Lee, H. B.; Cha, J. K. *J. Org. Chem*. **2003**, *68*, 2205−2208. (c) Lee, H. I.; Sung, M. J.; Lee, H. B.; Cha, J. K. *Heterocycles* **2004**, *62*, 407−422.

Scheme 2

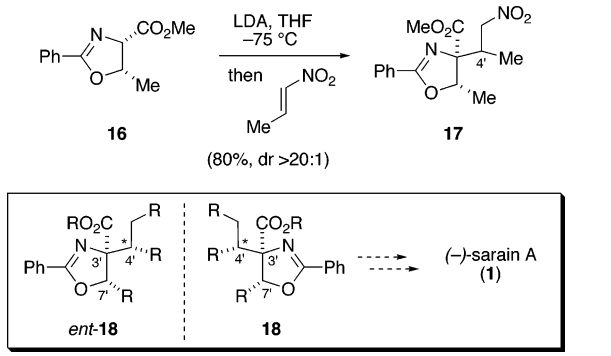


Initial Synthesis Planning. In our initial synthesis planning, we elected to focus efforts on construction of the diazatricycloundecane core and postulated that sarain A (**1**) could ultimately be derived from aldehyde **10** (Scheme 2). In turn, we hoped that aldehyde **10** would be accessed from enoxysilane **12** by intramolecular cyclization onto an *N*-sulfonyliminium ion species (e.g., **11**). Although Mannich-type transformations involving *N*-sulfonyliminium ion species were known,[18] no examples using enoxysilane nucleophiles had been reported in the literature. If successful, this new transformation would not only lead to assembly of the sarain A core, but would simultaneously set the congested C3 quaternary stereocenter. Enoxysilane **12** could be prepared from pyrrolidinone **13**, which in turn would be accessed from non-allylated precursor **14**. Further disconnection of lactam **14** revealed amino acid **15**, which was recognized as a being a 2,3-disubstituted glutamic acid derivative. Methods for constructing related, simpler structural frameworks had been reported in the literature,[19] and so began our total synthesis endeavor.

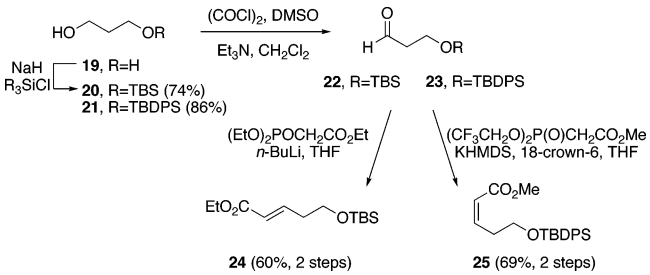
Results and Discussion

Constructing the C4′−C3′−C7′ Stereotriad. In the 1980s, Seebach and co-workers introduced a powerful asymmetric transformation that could potentially be used to prepare 2,3-disubstituted glutamate derivatives beginning from enantiopure oxazolines.[19a,b] As shown in Scheme 3, reaction of oxazoline **16** with lithium diisopropylamide (LDA), followed by quenching with (*E*)-1-nitro-1-propene afforded Michael adduct **17** in 80% yield, with excellent diastereoselectivity (dr > 20:1). Notably, two new stereogenic centers are generated in this process, although the stereochemical configuration β to the nitro group (i.e., C4′) was not determined. If this stereocenter could be controlled to provide the desired configuration at C4′, and if alternative Michael acceptors and oxazoline derivatives could be employed, a variety of useful products possessing the sarain

Scheme 3



Scheme 4



A C4′−C3′−C7′ stereotriad (*ent*-**18**) could be accessible. To initiate work in this area, oxazoline **16** was prepared by known methods beginning from L-threonine derivatives.[20] Although the use of this enantiomer of the starting material would provide access to *ent*-**18**, the strategy would later be amenable to the preparation of Michael adducts **18**, en route to the presumed naturally occurring (−) enantiomer of sarain A (**1**).[2d]

To explore the use of enoate electrophiles as partners with oxazoline **16** in Michael additions, *E* and *Z* enoates **24** and **25** were prepared as shown in Scheme 4. Monosilylation of 1,3-propanediol (**19**)[21] afforded TBS and TBDPS ethers **20** and **21**, respectively, which could be individually oxidized to aldehydes **22** and **23** using Swern conditions.[22] Horner−Wadsworth−Emmons homologation[23] of TBS ether **22** delivered (*E*)-enoate **24**, whereas the modified variant disclosed by Still and Gennari[24] using TBDPS ether **23** furnished (*Z*)-enoate **25**. These substrates were considered optimal for initial studies because they were readily accessible and contained robust silyl ethers, which potentially could be used as functional group handles for the eventual installation of an amine substituent.

Our studies of the use of enoates **24** and **25** as Michael acceptors are summarized in Scheme 5. Upon reaction of oxazoline **16** with LDA in DME, the corresponding lithium enolate was generated at low temperature. Subsequent introduction of either enoate **24** or **25** led to formation of Michael adducts **26** and **28**, respectively, both with excellent diastereoselectivity. Although the configuration at C4′ for these species was not known initially, the structural assignments were inferred upon derivatization as follows: the Michael addition product

(18) For an excellent review of *N*-sulfonyliminium ion chemistry, see: Weinreb, S. M. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1997; Vol. 190, pp 131−184.
(19) (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311−3314. (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592−1604. (c) Masahiko, Y.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377−380.
(20) Oxazoline **16** was prepared by reaction of methyl *N*-benzoyl-(L)-threoninate with thionyl chloride; see: Elliot, D. F. *J. Chem. Soc.* **1950**, 62−68.
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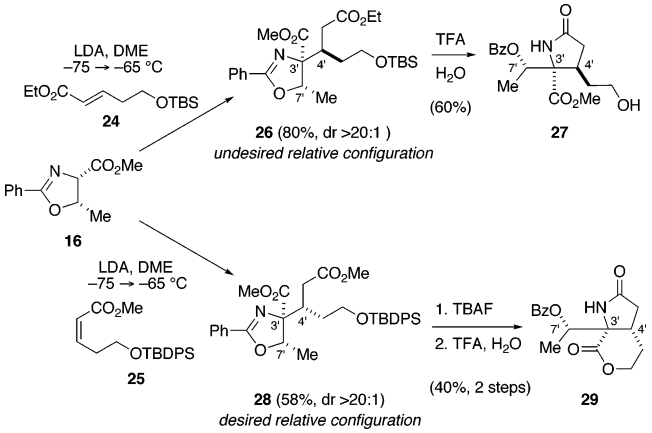
Scheme 5



obtained from (*E*)-enoate **24** was exposed to TFA to provide hydroxy ester **27**, whereas the Michael adduct derived from (*Z*)-enoate **25** was desilylated and reacted under the identical acidic conditions to afford δ-lactone **29**. Because the 2-pyrrolidinone intermediate having a cis relationship between the β-hydroxyethyl and ester functional groups should lactonize more readily than stereoisomer **27**, stereostructures **26** and **28** were assigned to the initial Michael adducts.[25] Thus, it became clear that the product possessing the desired relative stereochemical configuration at C4′−C3′−C7′ (i.e., **28**) could be obtained if a (*Z*)-enoate was employed in the Michael addition.

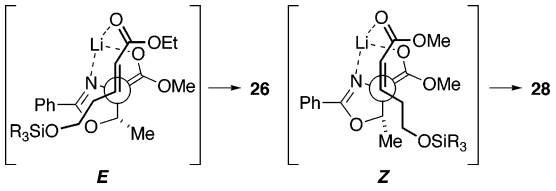
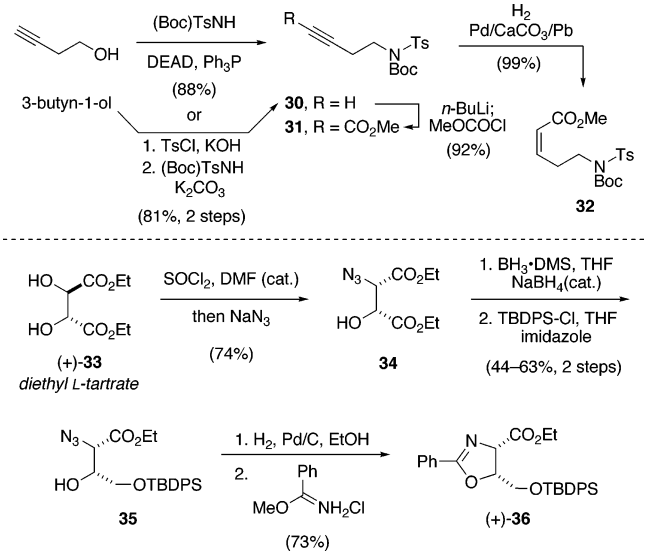


Figure 3. Plausible transition structures for Michael additions involving *E* and *Z* enoates **24** and **25**.

Plausible transition structures ***E*** and ***Z*** are suggested in Figure 3 to rationalize the stereochemical outcome of the Michael addition reactions involving enoates **24** and **25**.[26] The 5-methyl group of the oxazoline anion shields the α-face, forcing enoate approach to occur from the β-face of the Li enolate as depicted.[19] It is also believed that Li plays a critical organizational role in the transition state, as supported by the observation that diastereoselectivity is eroded in the presence of HMPA.[14b]

After identifying that *Z* enoates could be used as coupling partners with oxazoline anions to construct the stereotriad contained in sarain A, we designed enoate and oxazoline derivatives that would likely be useful for the total synthesis effort. Regarding the enoate fragment, a compound containing a terminal nitrogen substituent, rather than a silyl ether, would curtail the need for functional group interconversion steps at a later stage.[27] To arrive at the desired enoate, 3-butyn-1-ol was allowed to react with (Boc)TsNH under Mitsunobu conditions

Scheme 6



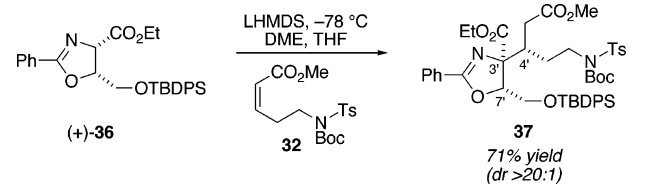
to afford Boc-protected sulfonamide **30** (Scheme 6).[28] Alternatively, sulfonamide **30** could be accessed using a tosylation/displacement procedure. This latter method was typically employed to access larger quantities of sulfonamide **30**, since the Mitsunobu approach required the difficult separation of Ph_3PO and excess DEAD from the desired product. Lithiation of **30** and quenching with methyl chloroformate afforded ester **31**, which in turn was reduced under Lindlar conditions to furnish (*Z*)-enoate **32**.[29] With respect to the oxazoline component, we chose to synthesize an alkoxymethyl derivative. Beginning from diethyl L-tartrate ((+)-**33**), azide **34** was prepared according to an established procedure.[30] Monoreduction of diester **34**,[31] followed by silylation of the primary alcohol, generated hydroxy azide **35**. After hydrogenation of azide **35**, the resulting amino alcohol was converted to oxazoline (+)-**36** in the presence of methyl benzimidate hydrochloride.[32] These routes to enoate **32** and oxazoline (+)-**36** proved quite robust and scalable; to date, several hundred grams of each of these fragments have been prepared.

With these new enoate and oxazoline coupling partners in hand, we explored the critical Michael addition with the hope that all substrate variations would be tolerated. Fortunately, deprotonation of oxazoline (+)-**36** with lithium hexamethyldisilazide (LHMDS) in a 2:1 mixture of DME and THF at −78 °C, in the presence of (*Z*)-enoate **32**, delivered Michael adduct **37** in 71% yield (Scheme 7). This product possesses the required relative configuration of the C4′−C3′−C7′ stereotriad of sarain A (**1**), as well as sufficient functional group handles to plausibly access the natural product. Although the enantiomer of Michael adduct **37** would also be accessible, beginning from diethyl D-tartrate, we elected to temporarily continue studies in the less-expensive enantiomeric series.

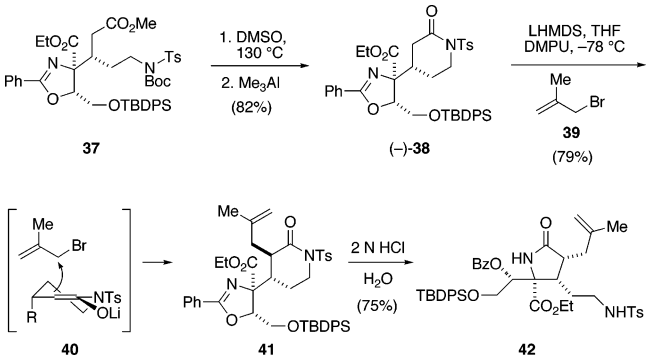
Initial Assembly of the Diazatricycloundecane Core by an Enoxysilane-*N*-Sulfonyliminium Ion Cyclization. Diester

(25) (a) Molecular mechanics calculations (MMFF) were performed using Spartan '02; Copyright 1991−2001; Wavefunction Inc.: Irvine, CA. (b) *cis*-fused lactone **29** was calculated to be more stable than its *trans*-fused counterpart by 6.4 kcal/mol.
(26) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413−1423.
(27) Prior to the use of sulfonamide **32**, we explored the use of triazinone- and phthalamido-containing enoates. Although these species were competent in the Michael addition chemistry, neither the triazinone or phthalamido groups were chemically inert in later transformations.
(28) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709−5712.
(29) Taschner, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1986**, *64*, 108−113.
(30) Satio, S.; Komada, L.; Moriwake, T. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, p 200.
(31) Sauret-Cladière, S.; Jeminet, G. *Tetrahedron: Asymmetry* **1997**, *8*, 417−423.
(32) For a comprehensive review of the chemistry of oxazolines, see: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360.

Scheme 7



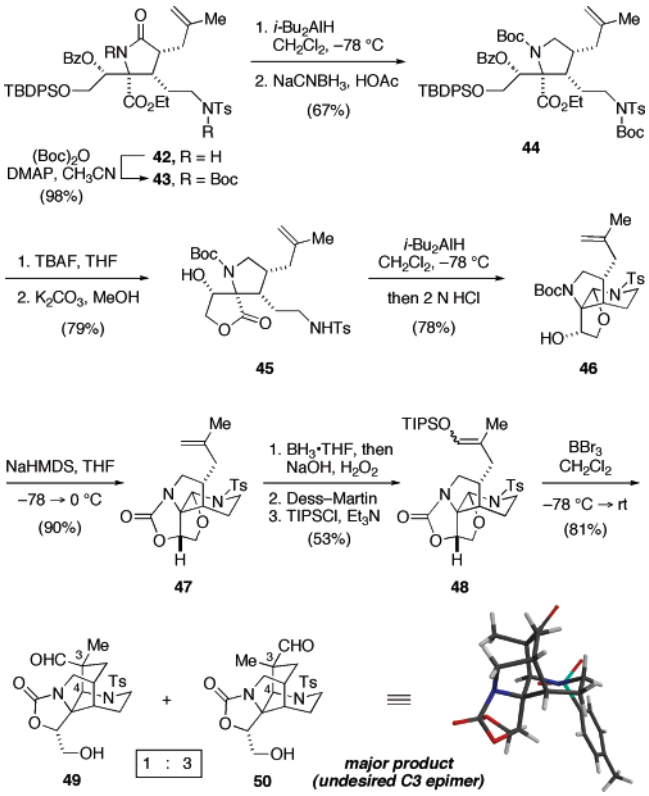
Scheme 8



37 was advanced in the total synthesis according to the approach depicted in Scheme 8. The Boc group of **37** was removed by thermolysis[28] to afford an intermediate tosylamide, which in turn was subjected to Me_3Al to induce amidation.[33] Next, we hoped to carry out an alkylation of lactam (−)-**38** with 3-bromo-2-methylpropene (**39**).[34] This reagent was strategically chosen for initial studies because: (a) it would provide all of the remaining carbon atoms of the sarain A diazatricycloundecane core, and (b) it would ultimately allow us to test the enoxysilane-*N*-sulfonyliminium ion cyclization, with concomitant formation of the C3 quaternary carbon center, in the absence of a complex side chain or macrocycle. Upon examining the alkylation reaction, we were gratified to find that deprotonation of lactam (−)-**38** with LHMDS, followed by quenching with excess bromide **39** provided lactam **41** as a single isomer in 79% yield. Although it would later be confirmed, the stereochemical assignment for **41** was made initially with the assumption that alkylation should occur from the enolate face opposite the oxazoline side chain (e.g., **40**).[35] In the final step shown in Scheme 8, alkylated compound **41** was allowed to react with HCl to promote oxazoline ring cleavage,[36] followed by translactamization. After workup, pyrrolidinone **42** was isolated in 75% yield.

A robust sequence was developed to elaborate pyrrolidinone **42** to a suitable enoxysilane-*N*-sulfonyliminium ion cyclization precursor. Boc-protection of **42**,[37] followed by a standard two-step reduction of pyrrolidinone **43**,[38] yielded pyrrolidine **44** (Scheme 9). The TBDPS protecting group of **44** was cleaved with TBAF to provide an intermediate primary alcohol, which

Scheme 9

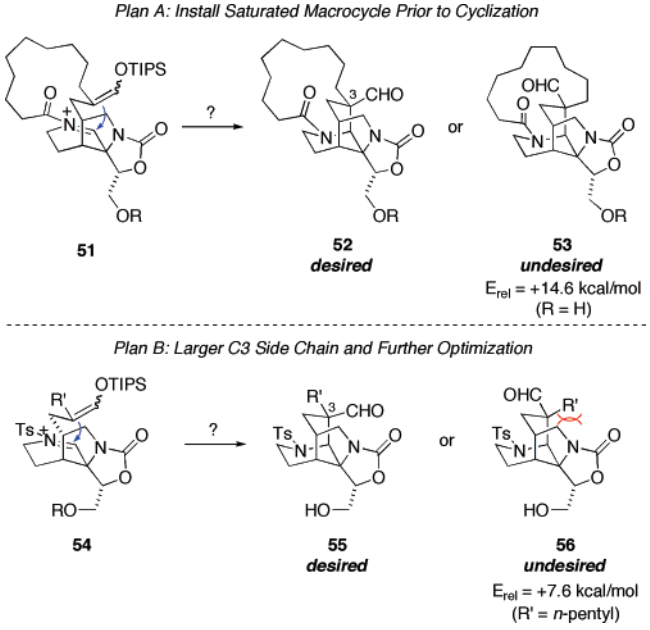


upon reaction with K_2CO_3 in MeOH underwent mono-Boc deprotection, benzoate cleavage, and lactonization to afford spirolactone **45**. Subsequent reaction of lactone **45** with *i*-Bu_2AlH led to partial reduction to the corresponding lactol, at which point the reaction mixture was quenched with HCl to provide tricyclic aminal **46** in 78% yield. At this stage, the stereochemical configuration of the methallyl group was confirmed by ^{1}H NMR NOESY studies. In the next transformation, reaction of secondary alcohol **46** with sodium hexamethyldisilazide (NaHMDS) promoted cyclization to smoothly furnish tetracyclic oxazolidinone **47**. Finally, a three-step sequence involving hydroboration with oxidative workup, Dess−Martin oxidation,[39] and treatment of the resulting aldehyde to TIPSOTf,[40] delivered cyclization precursor **48** as a 3:2 mixture of alkene stereoisomers.

With the appropriate substrate in hand, we attempted the crucial intramolecular iminium ion cyclization of enoxysilanes **48** (Scheme 9). Although construction of the C3−C4 bond of sarain A was at the time precedented by the early studies of Sisko and Weinreb,[15b] the use of an enoxysilane nucleophile and the simultaneous introduction of the critical C3 quaternary carbon stereocenter had not previously been demonstrated. A number of Lewis acids were examined to induce the desired cyclization. Whereas many Lewis acids were ineffective ($SnCl_4$, BF_3•OEt_2, Me_3Al),[41] addition of BBr_3 to enoxysilanes **48** in CH_2Cl_2 from −78 °C to room-temperature delivered a mixture of

(33) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4172.
(34) Attempts to directly alkylate ester **37** were unsuccessful, as were attempts to trap the intermediate lithium enolate from the Michael reaction of (+)-**36** and **32**.
(35) (a) Liu, L. T.; Hong, P.-C.; Huang, H.-L.; Chen, S.-F.; Wang, C.-L. J.; Wen, Y.-S. *Tetrahedron: Asymmetry* **2001**, *12*, 419−426. (b) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689−11698.
(36) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611−4624.
(37) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510−511.
(38) (a) Hubert, J. C.; Winjberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437−1441. (b) Lenz, G. R. *J. Chem. Soc., Perkin Trans.* **1990**, *1*, 33−38.
(39) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(40) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1−26.
(41) Attempts to cyclize the corresponding TES derivative of **48** led either to no reaction or substantial non-specific decomposition.

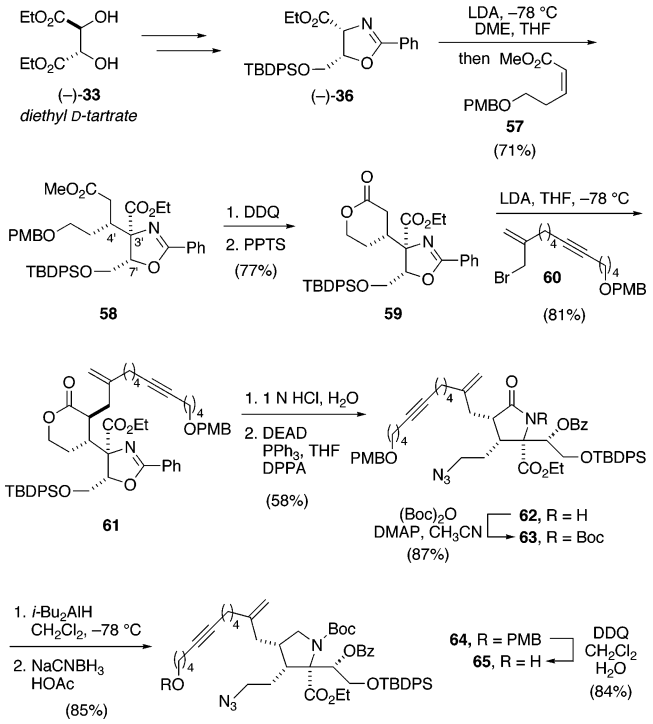
Scheme 10



two cyclization products in 81% overall yield. On the basis of NMR and X-ray diffraction studies,[14a,42] these products were assigned as aldehydes **49** and **50**, which formed in a 1:3 ratio favoring undesired epimer **50**. Although disappointed by the unfavorable diastereoselectivity observed in setting the C3 quaternary stereocenter, we felt that this problem might be surmounted by slight modification of our fundamental strategy. At this stage, we reasoned that optimization of the cyclization would best be deferred to future studies in nonmodel systems.

Strategies for Controlling the C3 Quaternary Carbon Stereocenter. Having successfully assembled a model system for the sarain A core (**49**, Scheme 9), we turned our attention to accessing related compounds that could ultimately provide access to the natural product. All future work was carried out in the postulated natural enantiomeric series, beginning from diethyl D-tartrate. A major concern from our earlier studies involved the unfavorable selectivity observed in the formation of the C3 quaternary carbon stereocenter. To circumvent this problem, two strategies were conceived and are illustrated in Scheme 10. In the first approach, the saturated macrocycle of sarain A would be installed prior to the iminium ion cyclization (*Plan A*). Although this strategy would not be amenable to the *N*-sulfonyliminium ion cyclizations developed earlier, an *N*-acyl iminium ion cyclization of enoxysilane **51** could potentially be used instead. On the basis of molecular modeling calculations, it was expected that formation of desired product **52** would be greatly favored over production of the undesired epimer **53** (R = H, E_{rel} = +14.6 kcal/mol).[25a] Alternatively, the use of a substrate containing a larger C3 side chain (e.g., **54**), together with further reaction optimization, could potentially lead to improved selectivity in forming the C3 quaternary carbon stereocenter (*Plan B*). In this latter scenario, the disfavorable *syn*-pentane interaction between the C3 side chain and the pyrrolidine ring methylene would be somewhat extenuated in the transition state leading to undesired epimer **56**. This hypothesis is in accord with molecular modeling calculations,

Scheme 11



which suggest that aldehyde **56** is higher in energy than its epimer **55**, by approximately +7.6 kcal/mol if R′ = *n*-pentyl.[25a]

An Initial Attempt to Control the C3 Quaternary Carbon Stereocenter: An Unproductive Detour. In our initial efforts, we implemented *Plan A* as a means to control installation of the C3 quaternary carbon stereocenter, as shown in Scheme 11. Following our earlier studies in the unnatural series (see Scheme 6), diethyl D-tartrate ((−)-**33**) was elaborated to oxazoline (−)-**36** using a five-step sequence. Subsequent lithiation of (−)-**36**, followed by addition of enoate **57**,[43] afforded Michael adduct **58** in 71% yield. Cleavage of the PMB protective group of **58** under oxidative conditions provided an intermediate alcohol, which in turn underwent acid-catalyzed cyclization to lactone **59**. Next, lactone **59** was alkylated with allylic bromide **60**[43] to deliver enyne **61**. Upon reaction of **61** with dilute aqueous HCl, oxazoline cleavage[36] and amidation occurred. The resulting intermediate was then converted to azide **62** under Mitsunobu conditions. Subsequent Boc-protection of the amide (**62** → **63**), followed by reduction of the amide carbonyl,[38] produced pyrrolidine **64**. This intermediate was allowed to react with DDQ to furnish alcohol **65** in 84% yield.

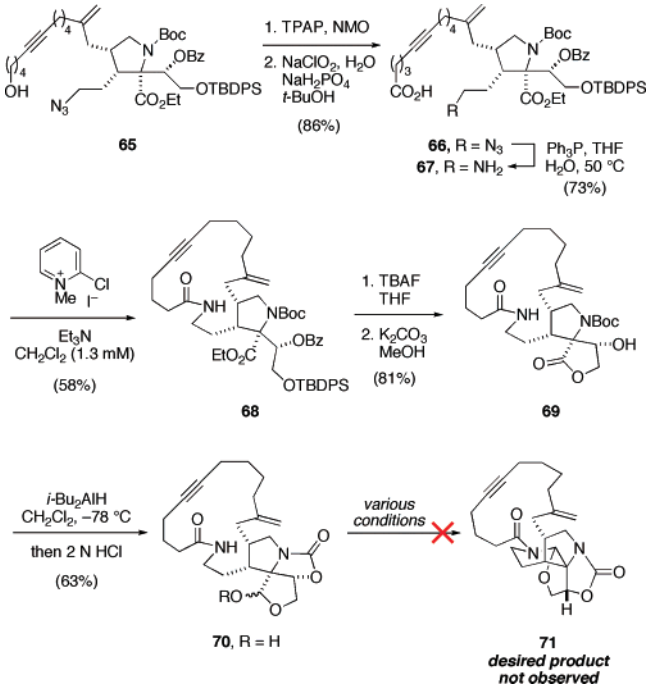
Our efforts to elaborate alcohol **65** toward a macrocycle-containing iminium ion cyclization substrate are depicted in Scheme 12. With the aim of fashioning the macrocycle by amide bond formation, alcohol **65** was oxidized to carboxylic acid **66** using a standard two-step procedure. Reduction of azide **66** with Ph_3P then afforded amino acid **67**, which resisted macrocyclization under a variety of standard conditions. However, by slowly adding a solution of amino acid **67** to Mukaiyama's salt[44] at high dilution, it was possible to obtain lactam **68** in 58% yield. Subsequent treatment of lactam **68** with TBAF in THF, followed by reaction with K_2CO_3 in MeOH, provided spirolactone **69**. Upon reaction with *i*-Bu_2AlH, intermediate **69** was

(42) Cambridge Structural Database (CSD) reference code for aldehyde **50**: GOCZON.

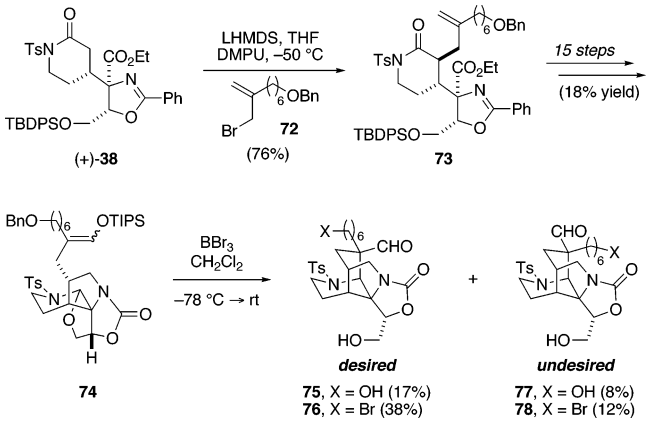
(43) See Supporting Information for details.

(44) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163−1166.

Scheme 12



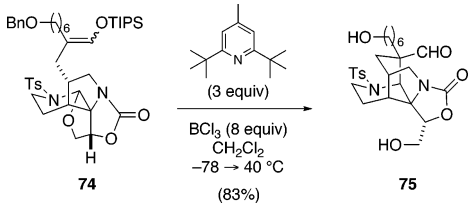
Scheme 13



reduced to the corresponding lactol, which was worked up under acidic conditions to afford oxazolidinone **70**. At this stage, to access an iminium ion cyclization precursor, the piperidine ring would need to be fashioned, conceivably by conversion of lactam **70** to pentacyclic aminal **71**. Unfortunately, it was not possible to promote this critical dehydration, despite extensive experimentation involving both protic and Lewis acids (e.g., PPTS, TsOH, BF_3•OEt_2, etc.). Moreover, exhaustive efforts to cyclize activated lactol derivatives of **70** (e.g., R = Ac, trichloroacetate) were also unsuccessful. Thus, we were forced to abandon this strategy.

A Second Attempt to Control the C3 Quaternary Carbon Stereocenter. As described earlier, an alternative strategy for potentially improving selectivity in the formation of the C3 stereocenter involved the use of a larger C3 side chain during the iminium ion cyclization, concurrent with further reaction optimization (Scheme 10, *Plan B*). To initiate studies in this area, lactam (+)-**38** (Scheme 13) was prepared following the route used to prepare its enantiomer in our earlier studies (see Scheme 8). Lactam (+)-**38** was lithiated, then quenched with allylic bromide **72**,[43] to afford alkylated product **73** in 76% yield. The use of bromide **72** as an alkylating reagent was thought to have two potential benefits: (a) it would lead to installation of a larger C3 side chain, which would hopefully improve the cyclization reaction, and (b) it could provide a means to install the saturated macrocycle of sarain A after the planned iminium ion cyclization, because it possesses a convenient functional group handle (i.e., the Bn-protected alcohol). Following the general approach developed earlier to access enoxysilanes **48** (see Scheme 9), lactam **73** was elaborated to enoxysilanes **74** in 15 steps, with an overall yield an 18%. With enoxysilanes **74** in hand, we explored the key enoxysilane-*N*-sulfonyliminium ion cyclization. Upon reaction of enoxysilanes **74** with excess BBr_3 in CH_2Cl_2 from −78 °C to room-temperature, a mixture of products was obtained that reflected a preference for forming the desired isomer (approximately 3:1).[45,46] Unfortunately, the Bn protecting group was not compatible with these BBr_3 conditions, and both alcohol-containing products (i.e., **75** and **77)** and the related bromide products (i.e., **76** and **78**) were observed. Nonetheless, this result supported the notion that a larger C3 side chain would lead to improved diastereoselectivity.

Scheme 14

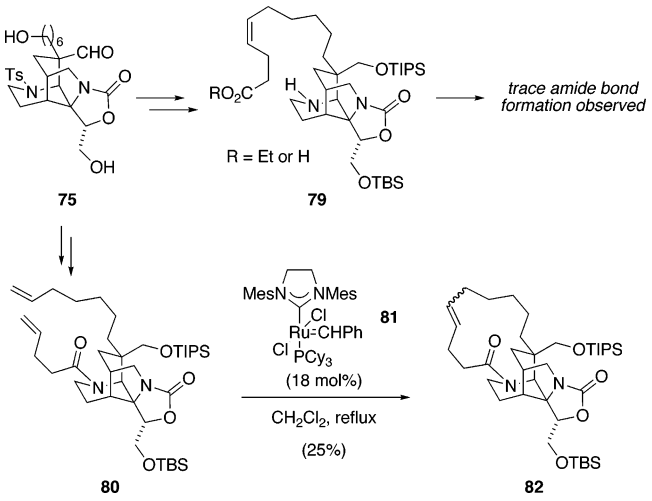


We next sought to further increase the yields and selectivity observed in the critical iminium ion cyclization of enoxysilanes **74**. A variety of experimental parameters were tested, with a particular emphasis on the Lewis acid promoter. Although many Lewis acids were examined (e.g., $TiCl_4$, $SnCl_4$, TMSOTf, BF_3•OEt_2, etc.), only BBr_3 and BCl_3 promoted the cyclization. Of these, BCl_3 proved advantageous as it exclusively furnished products containing a free hydroxyl group (i.e., **75** and **77**). Finally, as an additional modification, we elected to carry out cyclizations in the presence of 2,6-di-*tert*-butyl-4-methylpyridine,[47] which would serve to sequester protic acids and perhaps prevent premature cleavage of the TIPS group. Under optimal reaction conditions (BCl_3, 2,6-di-*tert*-butyl-4-methylpyridine, −78 → −40 °C), cyclization of substrate **74** occurred with improved diastereoselectivity (dr 6−8:1), with aldehyde **75** being isolated in 83% yield (Scheme 14).[46]

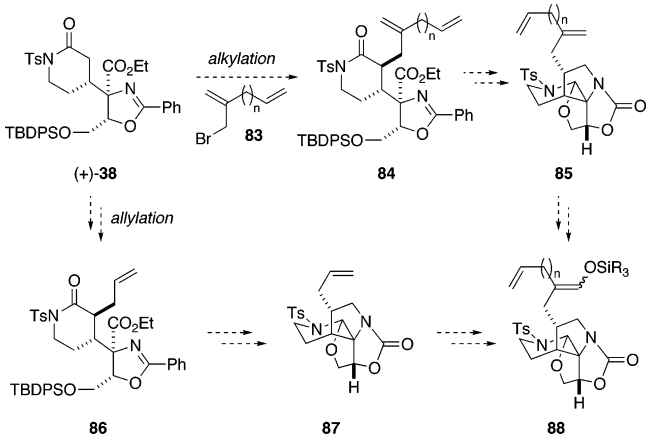
Forming the Saturated Macrocycle. Having significantly improved the enoxysilane-*N*-sulfonyliminium ion cyclization en route to sarain A, two viable strategies were explored for assembly of the saturated macrocycle beginning from diol **75** (Scheme 15). In the first scenario, alcohol **75** was elaborated to carboxylic acid and ester derivates (i.e., **79**) as a prelude to constructing the macrocycle by intramolecular lactam formation. Unfortunately, only trace amounts of the desired lactam product could be obtained from precursors **79** under a variety of conditions.

(45) Attempts to prepare the corresponding TMS or TBS enoxysilanes gave low yields of contaminated products, which performed poorly in the subsequent iminium ion cyclization.
(46) Stereochemical configuration was determined by $^1H-^1H$ NOESY experiments.
(47) Anderson, A. G.; Stang, P. J. *J. Org. Chem.* **1976**, *41*, 3034−3036.

Scheme 15



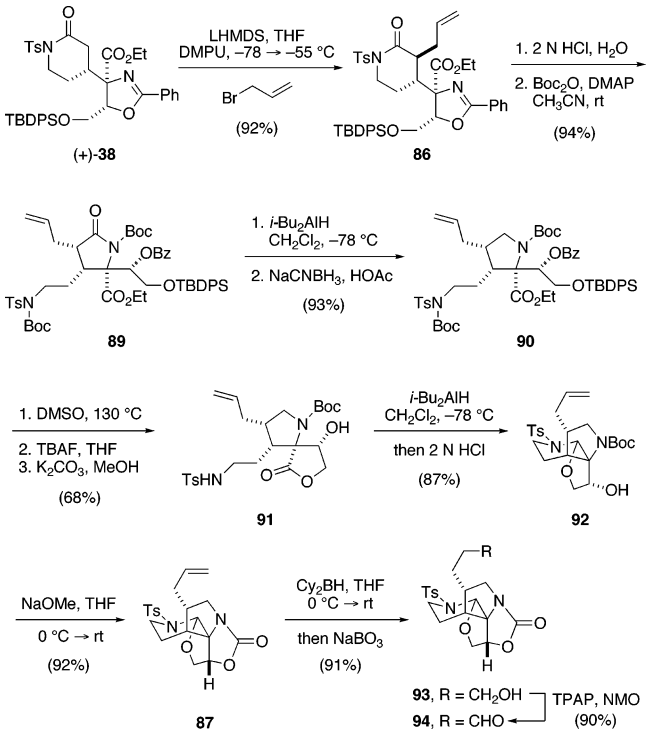
Scheme 16



The second approach relied on the use of ring-closing metathesis (RCM)[48] to construct the macrocycle, a strategy that drew precedent from Weinreb's studies in this area.[15c] To pursue this plan, diene **80** was generated from diol **75** and subjected to Grubbs's second generation catalyst **81**. Under these conditions, it was possible to obtain macrolactam **82** in 25% yield. Although the yield was modest, the RCM strategy appeared promising; thus, our attention turned to optimizing this approach.

Because we believed the tether lengths of the ring-closing metathesis substrate could play a critical role in the efficiency of macrocyclization, we wished to define a flexible route to RCM precursors. Two approaches were considered as depicted in Scheme 16. In the first, lactam (+)-**38** could be alkylated with any of a number of different reagents **83**. By varying the chain length (i.e., *n* value), several potentially useful products **84** could be obtained. Each of these could be elaborated further to dienes **85**. If the double bonds of **85** could be readily differentiated, it would likely be possible to arrive at the desired enoxysilane substrates **88**. In an alternative strategy, lactam (+)-**38** would be allylated to afford intermediate **86**, which in turn, could be elaborated to tetracycle **87**. If the terminal alkene could now be used as a functional group handle for installation of the C3 side chain and the enoxysilane, multiple cyclization precursors **88** would be accessible. As the latter of these routes allowed us to defer installation of the side chain to a later stage in the synthesis, it appeared advantageous and became the focus of our efforts.[49]

Scheme 17



Given our experience, initial forays into the allylation approach proceeded in a relatively straightforward manner (Scheme 17). Allylation of lactam (+)-**38** delivered substituted adduct **86** in 92% yield. Using a now standard sequence, **86** was converted to pyrrolidinone **89**, which in turn, was reduced to pyrrolidine **90**.[38] Next, mono-Boc deprotection, desilylation, and spirolactone formation with concomitant methanolysis afforded intermediate **91**. Tetracycle **87** was accessed in two additional steps, by reduction of the lactone (**91** → **92**), followed by reaction of β-amino alcohol **92** with NaOMe.[50] Although we would ultimately develop better methods for elaborating alkene **87**, we initially proceeded by carrying out a hydroboration/oxidation[51] sequence to furnish aldehyde **94**.

The alkylation of aldehyde **94**, and various derivatives thereof, proved to be challenging. After initial efforts to directly alkylate aldehyde **94** were deemed unsuccessful, we focused on the alkylation of metalloenamine derivatives.[52] Imine **95** was prepared by condensation of aldehyde **94** with *t*-butylamine in the presence of K_2CO_3 (Scheme 18). However, attempts to alkylate the derived metalloenamine species to furnish aldehyde **96**, under a variety of standard conditions, led to either recovery of starting material or decomposition. As an alternative, *N*,*N*-dimethylhydrazone **97** was prepared by reaction of aldehyde

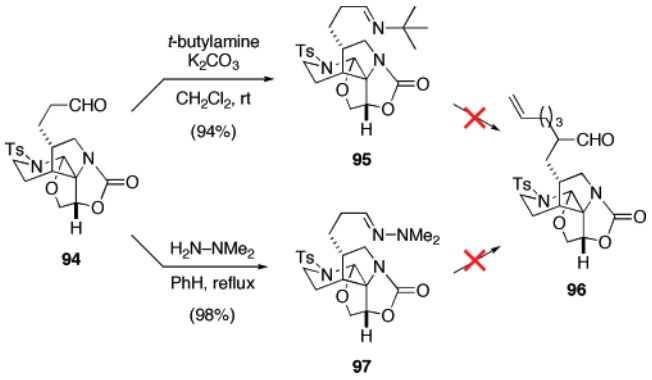
(48) For reviews on RCM reactions in alkaloid synthesis: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Felpin, F. -X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C. Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959−968. (d) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89.

(49) The earlier alkylation strategy was briefly pursued where $n = 4$; however, selective hydroboration of diene **85** proved difficult.

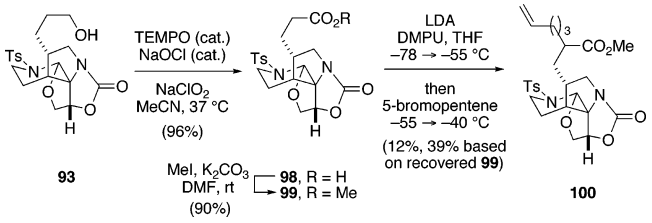
(50) In some instances, product **87** was isolated with a minor contaminant, which arose from cleavage of the Boc group of **92**. By reacting this crude mixture of products with triphosgene, it was possible to funnel the material to tetracycle **87**.

(51) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

Scheme 18



Scheme 19

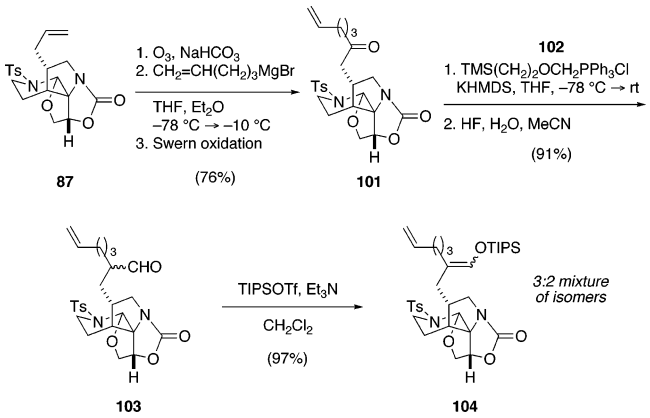


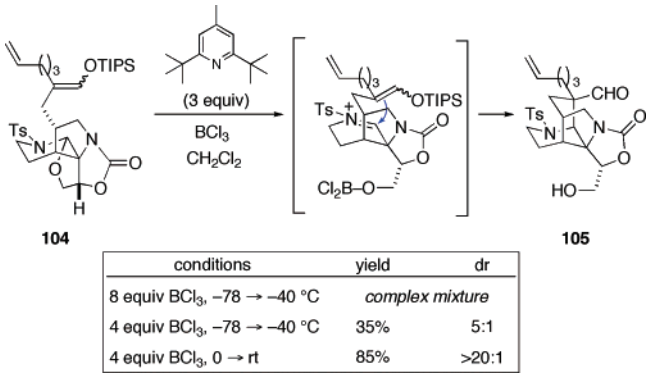
94 with 1,1-dimethylhydrazine under Dean−Stark conditions. However, all efforts to alkylate hydrazone **97** led to extensive decomposition, rather than to desired product **96**.

We also examined the alkylation of an ester enolate (Scheme 19). The requisite substrate, **99**, was prepared in two steps from alcohol **93** by oxidation with TEMPO/NaClO/$NaClO_2$ (**93** → **98**) in buffered MeCN,[53] followed by reaction of the carboxylic acid product with MeI and K_2CO_3. Fortunately, the desired alkylated product, **100**, could be obtained after low-temperature deprotonation of ester **99** and quenching with 5-bromopentene, albeit in low yields when stoichiometric quantities of base and electrophile were employed. As the mass balance from this reaction was largely attributed to recovered starting material **99**, more forcing conditions were probed that relied on the use of excess base and excess electrophile or increased temperatures. Regrettably, these conditions led to the formation of multiple byproducts, mostly involving alkylation of the tosyl group.[54]

Given the difficulties encountered in the attempted alkylation of various carboxylic acid derivatives, we chose to pursue an alternative method for installation of the alkene-containing side chain (Scheme 20). Returning to tetracyclic terminal alkene **87** (see Scheme 17), an ozonolysis/Grignard addition/oxidation sequence successfully delivered ketone **101** in 76% yield over three steps. With an appropriate side chain now in place,[55] we explored elaboration of the ketone to an enoxysilane substituent. Although direct conversion of ketone **101** to TIPS enoxysilane **104** by reaction with diethyl (triisopropylsilyloxymethyl)-phosphonate and LDA was not possible,[56] a related homologation using phosphonium salt **102** and KHMDS to give a 2-(trimethylsilyl)ethyl (TMSE) enol ether was fruitful.[57] Subsequent reaction of the intermediate enol ether with HF in $MeCN/H_2O$ provided aldehyde **103**. Aldehyde **103** was smoothly converted to TIPS enoxysilanes **104** as a 3:2 mixture of stereoisomers.[40]

Scheme 20





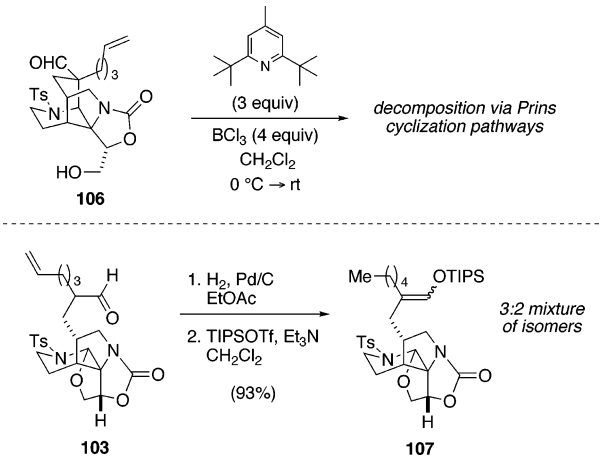
conditions	yield	dr
8 equiv BCl_3, –78 → –40 °C	*complex mixture*	
4 equiv BCl_3, –78 → –40 °C	35%	5:1
4 equiv BCl_3, 0 → rt	85%	>20:1

Figure 4. Optimization of enoxysilane-*N*-sulfonyliminium ion cyclization of substrate **104**.

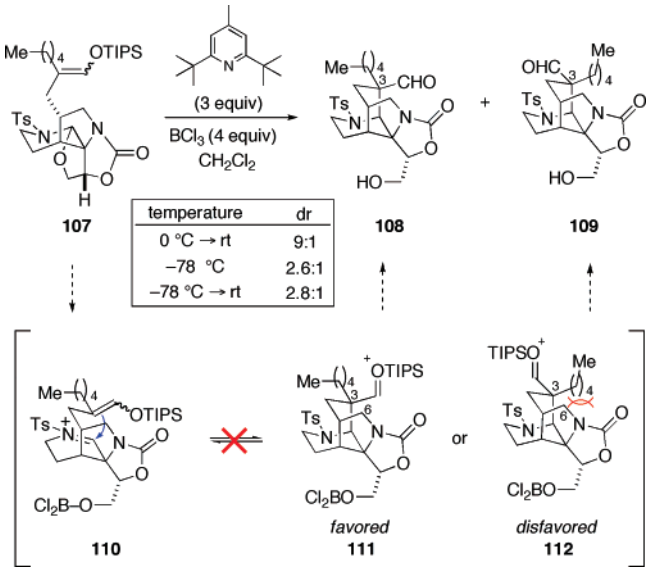
With a reliable route to enoxysilanes **104** established, we directed attention to the critical iminium ion cyclization (Figure 4). Use of the previously optimized buffered BCl_3 conditions, unfortunately, resulted in complex reaction products and low yields of desired aldehyde **105**. When the number of equivalents of BCl_3 was reduced from eight to four, fewer side products were obtained, and the observed diastereoselectivity was approximately 5:1 in favor of the desired product. However, in an unexpected result, we found that warmer temperatures (0 °C → room-temperature) actually led to cleaner reactions, thereby facilitating the selective formation of aldehyde **105**, which could be isolated in 85% yield.[58] Several features regarding this transformation should be noted: (a) only the desired diastereomer (i.e., **105**) is observed under the reaction conditions, as determined by ^1H NMR analysis of the crude reaction products; (b) the cyclization is fast, with the starting material being consumed upon addition of BCl_3 at 0 °C; and (c) these optimal conditions could be used to reliably prepare gram quantities of key intermediate **105**.

(52) For pertinent reviews, see: (a) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3363−3446. (b) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517−536.
(53) Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195−203.
(54) *p*-Toluenesulfonamides can be deprotonated at the methyl group by bases as weak as LDA. For a discussion, see: MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662−3670.
(55) On the basis of Weinreb's RCM studies on related compounds, a 5-carbon C3 substituent was thought to be suitable; see reference 15c.
(56) Direct synthesis of enoxysilanes through a Wittig reaction remains an unsolved problem in organic synthesis. For a pertinent discussion, see: (a) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847−4852. For a review regarding one-carbon homologations of ketones, see: (b) Badham, N. F. *Tetrahedron* **2004**, *60*, 11−42.
(57) Schönauer, K.; Zbiral, E. *Tetrahedron Lett.* **1983**, *24*, 573−576.
(58) Reaction of the corresponding TMSE enol ether of **104** (see Scheme 20) under the identical conditions also led to the formation of aldehyde **105**, albeit only in 55% yield.

Scheme 21



Scheme 22



Origin of Diastereoselectivity in the Enoxysilane-*N*-Sulfonyliminium Ion Cyclization. Intrigued by the results obtained during optimization of the enoxysilane-*N*-sulfonyliminium ion cyclization of substrate **104**, we sought an explanation for the improvements in yield and stereoselectivity at higher reaction temperatures. Because the undesired epimer of product was not observed under these conditions and isolated yields were not quantitative, we questioned the stability of the undesired C3 aldehyde epimer **106** to our new reaction conditions (Scheme 21). It was plausible that this epimer would be less stable under the reaction conditions than epimer **105**, because the aldehyde group of **106** would be easier to activate for subsequent transformations as it is in a much less congested environment. When a sample of aldehyde **106** was subjected to BCl_3 and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 at 0 °C, then warmed to room-temperature, indeed rapid decomposition took place. Thus, the high levels of diastereoselectivity can partially be attributed to byproduct instability. As we believed the decomposition of aldehyde **106** occurred through Prins cyclization pathways involving the terminal alkene, an alternative cyclization substrate bearing a saturated side chain was desired for further studies. The appropriate substrate **107** was readily obtained by catalytic hydrogenation of alkene **103**, followed by formation of the silyl enol ether.

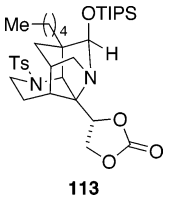


Figure 5. TIPS-*N*,*O*-acetal **113** is observed in cyclization reactions.

Some mechanistic insight was gleaned by examining saturated substrate **107** in the enoxysilane-*N*-sulfonyliminium ion cyclization (Scheme 22). Under the optimal cyclization conditions (0 °C → room-temperature), a 9:1 mixture of aldehyde **108** and its epimer **109** was observed (entry 1). The fact that epimer **109** was isolated supports the notion that the corresponding undesired product (i.e., **106)** in the real system likely decomposes by Prins pathways (see Scheme 21).

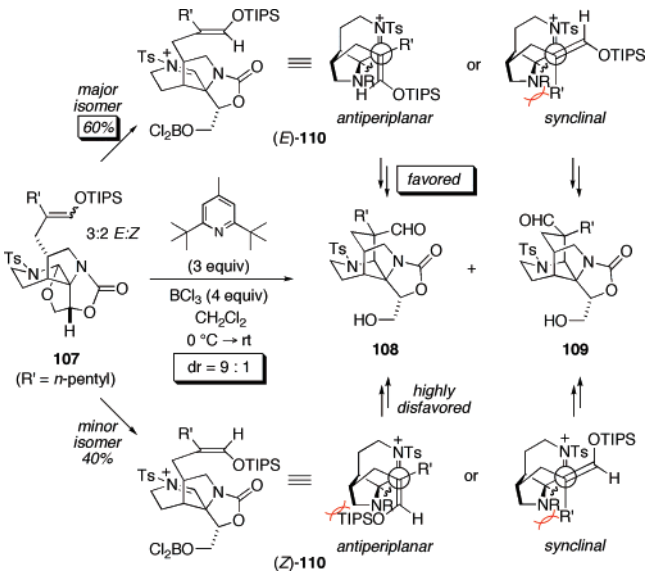
One hypothesis to explain the high (9:1) stereoselectivity observed in the enoxysilane-*N*-sulfonyliminium ion cyclization of substrate **107** is that the cyclization process is reversible and the products are thereby formed under thermodynamic control. In this scenario, *N*-tosyliminium ion **110** could cyclize to afford oxocarbenium intermediate **111** or epimer **112**. The pyridine buffer could serve to prevent O−Si bond cleavage of these newly formed TIPS−oxocarbenium intermediates, thereby allowing thermodynamic equilibrium to be reached. Of the two potential intermediates, **111** should be thermodynamically favored as it places the smaller of the two C3 substituents in juxtaposition with C6 of the pyrrolidine ring, thereby minimizing a *syn*-pentane interaction.[59] This reversible pathway would favor formation of aldehyde **108**, rather than C3 epimer **109**, in accord with empirical observations and theoretical calculations.[60]

To probe this reversibility hypothesis, two experiments were carried out. First, at −78 °C, the reaction was found to proceed with much lower levels of diastereoselectivity (dr 2.6:1). In a second experiment, the cyclization was initiated at −78 °C, and the reaction was then allowed to warm to room-temperature. A low diastereomeric ratio of 2.8:1 was observed, close to that obtained at −78 °C. Thus, the cyclization is likely not reversible, as warming the reaction mixture from −78 °C to room-temperature prior to quenching did not lead to enhanced diastereoselectivity. It should be noted that, in all cases, we observed the formation of TIPS-*N*,*O*-acetal **113** (Figure 5),[61] which suggests that cyclization of substrate **107** proceeds through the TIPS-enoxysilane rather than a boron enolate or enol.

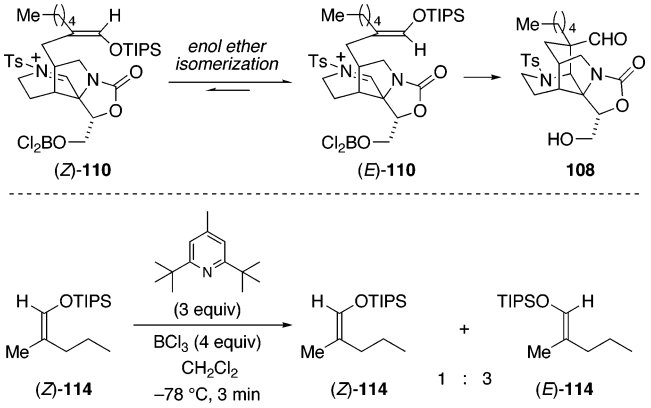
Having shed doubt on the reversibility hypothesis, we considered alternative explanations for the high levels of diastereoselectivity observed in the enoxysilane-*N*-sulfonyliminium ion cyclization carried out at 0 °C to room-temperature. An analysis of the four likely transition structures that would lead to the observed products **108** and **109** is presented in Scheme 23. As the cyclization experiments are typically carried out with a mixture of enoxysilane isomers (3:2, *E*:*Z*), two *N*-sulfonyliminium ion species are thought to form initially, namely, (*E*)-**110** and (*Z*)-**110**. Whereas cyclization of either of these intermediates in an antiperiplanar fashion would deliver

(59) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.
(60) Epimer **109** was calculated to be approximately 7.6 kcal/mol higher in energy than the desired product **108**; see Scheme 10.
(61) The isolation of *N*,*O*-acetal **113** is somewhat dependent on reactions times and quenching methods.

Scheme 23

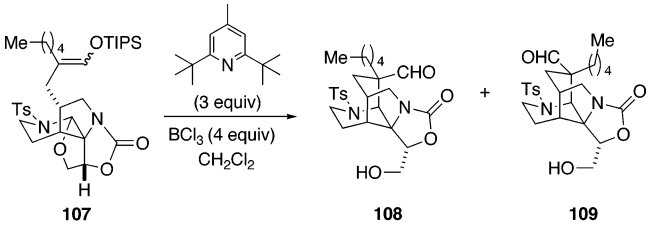


Scheme 24



desired aldehyde **108**, the corresponding synclinal cyclization pathway would afford epimeric product **109**. Neither of the two synclinal transition structures appear particularly favorable, as both would suffer from destabilizing interactions between the *n*-pentyl side chain (i.e., R′) and the pyrrolidine ring. In considering the antiperiplanar transition structures, cyclization of major isomer (*E*)-**110** to form aldehyde epimer **108** appears quite favorable. In contrast, it is unlikely that **108** could arise from minor isomer (*Z*)-**110** because of the highly disfavorable interaction that would exist between the bulky TIPS group and pyrrolidine ring. According to this analysis, the maximum yield of desired product **108** that should be obtained in a cyclization reaction should be approximately 60%, corresponding to the amount of *E* enoxysilane present in the starting material.

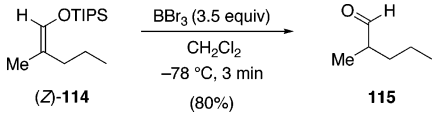
As the observed yields of desired aldehyde **108** were higher than 60%, and we believed the reversibility hypothesis to be untrue, we speculated that stereoisomers (*E*)- and (*Z*)-**110** could potentially interconvert under the reaction conditions, likely via neutral precursors such as **107**.[62] This interconversion would funnel the unproductive *Z* enoxysilane stereoisomer through the productive cyclization pathway (Scheme 24, (*Z*)-**110** → (*E*)-**110** → **108**). To probe this isomerization hypothesis, a simple model system was studied. (*Z*)-Enoxysilane **114**, prepared in one step from commercially available 2-methylpentanal,[43] was exposed to typical buffered-BCl_3 reaction conditions at −78 °C.



olefin isomer	temperature	108:109
(*E*)-**107**	–78 °C	>>20:1
(*E*)-**107**	0 °C → rt	>>20:1
(*Z*)-**107**	–78 °C	2:3
(*Z*)-**107**	0 °C → rt	3:1

Figure 6. Impact of enol ether geometry in the enoxysilane-*N*-sulfonyliminium ion cyclization.

Scheme 25



After just 3 min, the reaction mixture was quenched with Et_3N, followed by MeOH. As determined by ^1H NMR analysis of the resulting mixture, a 1:3 mixture of (*Z*)- and (*E*)-enoxysilanes **114** was obtained, thus supporting the notion that our optimal reaction conditions would promote rapid isomerization of the TIPS enoxysilane intermediates.[63]

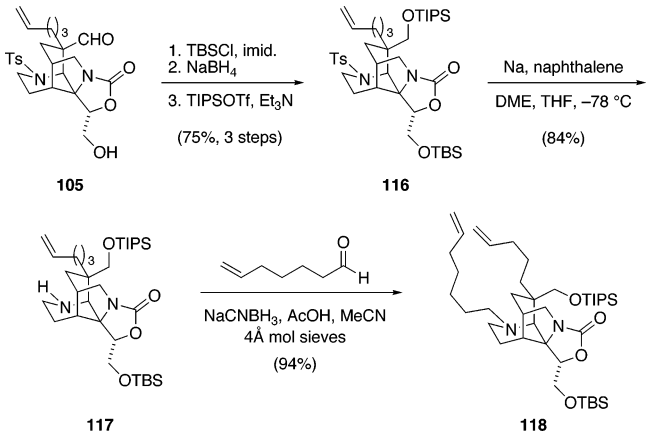
To further investigate the enol ether isomerization hypothesis, the *E* and *Z* stereoisomers of **107** were carefully separated using preparative HPLC, then individually studied in the enoxysilane-*N*-sulfonyliminium ion cyclization. As summarized in Figure 6, the *E* and *Z* isomers behaved very differently from one another, thus confirming the importance of enol ether geometry in the cyclization outcome. Whereas excellent diastereoselectivity (dr ≫ 20:1) was observed in forming tetracyclic aldehydes **108** and **109** when (*E*)-**107** was employed, use of (*Z*)-enoxysilane **107** led to these products in much lower diastereomeric ratios. Moreover, in the case of (*Z*)-**107**, variations in temperature significantly influenced the product distribution, with lower temperatures leading to lower levels of diastereoselectivity. These results are consistent with a scenario in which the rate of double bond isomerization (i.e., (*Z*)-**110** → (*E*)-**110**, Scheme 24) increases with a higher temperature, where upon it becomes competitive with cyclization.

Having gained an understanding of the factors that govern selectivity under the optimal buffered-BCl_3 enoxysilane-*N*-sulfonyliminium ion cyclization conditions, we questioned what was happening under the reaction conditions (i.e., BBr_3, −78 °C to room-temperature) employed in our early model studies (see Scheme 9, **48** → **49** + **50**). To probe this issue, (*Z*)-enol ether **114** was treated with excess BBr_3 at −78 °C for 3 min (Scheme 25). After quenching with Et_3N, then MeOH, approximately 80% of the material had undergone cleavage of

(62) For the isomerization of enoxysilanes, see: (a) Deyine, A.; Dujardin, G.; Mammeri, M.; Poirier, J.-M. *Synth. Commun.* **1998**, *28*, 1817−1821. (b) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444−6445. (c) Denmark, S. E.; Pham, S. M. *J. Org. Chem.* **2003**, *68*, 5045−5055.

(63) It is plausible that enol ether isomerization occurs by protonation of the enoxysilane, followed by rapid deprotonation. The proton source is presumed to be a pyridinium salt of the 2,6-di-*tert*-butyl-4-methylpyridine buffer, which would form in the presence of adventitious HCl.

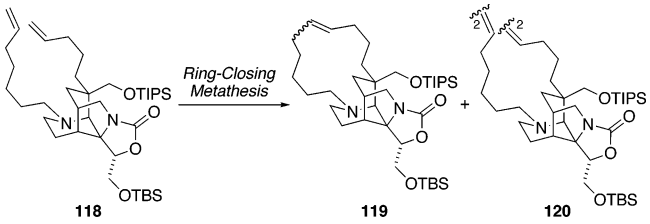
Scheme 26



the TIPS group to afford aldehyde **115**, as determined by ^{1}H NMR analysis of the crude products. Thus, it is likely that when enoxysilane-*N*-sulfonyliminium ion cyclizations are caried out with BBr_3 in the absence of an amine buffer, desilylation takes place at a rate competitive to cyclization. The distribution of products in this case would be the result of iminium ion cyclization occurring by pathways that involve potentially three different nucleophiles: enoxysilanes, boron enolates, and enols. According to the analysis summarized in Scheme 23, the latter two could well react with lower stereoselectivity. The fact that the BBr_3-promoted cyclization (BBr_3 used in excess) is initially fast, but ultimately requires long reaction times for complete conversion (approximately 24 h at room-temperature), further supports this notion.

Assembly of the 13-Membered Macrocycle by a Ring-Closing Metathesis and Subsequent Elaboration Toward Sarain A. With a reliable, high-yielding route to the diazatricycloundecane core and C3 quaternary carbon stereocenter of sarain A developed, attention was focused on assembling the saturated macrocycle by an optimized ring-closing metathesis strategy. The sequence ultimately developed for elaborating aldehyde **105** to RCM precursor **118** is highlighted in Scheme 26. Following TBS-protection of the primary alcohol, the aldehyde was reduced, and the resulting alcohol was silylated to provide TIPS ether **116** in 75% yield over three steps. Next, the tosyl group of intermediate **116** was removed with sodium naphthalenide to furnish amine **117**.[64] To arrive at the desired RCM substrate, several options were considered for functionalizing the secondary amine, such as amidation, alkylation, and reductive amination. As amidation would require later manipulations, and efforts to alkylate the secondary amine with 1-iodo-6-heptene[65] were unsuccessful, we settled on a reductive amination procedure. Under optimal conditions, reaction of amine **117** with 6-hepten-1-al,[66] 4 Å molecular sieves, and AcOH in MeCN, followed by addition of $NaBH_3CN$, afforded tertiary amine **118** in 94% yield.

Having established a route to diene **118**, we turned to execute a ring-closing metathesis reaction to construct the 13-membered macrocycle. Although not unprecedented,[67] the ability to perform ring-closing metathesis reactions in the presence of a basic tertiary amine was expected to be a significant challenge,[48,67]



Conditions		Isolated Yields	
		119	120
MesN NMes, Cl, Ru=CHPh, Cl, PCy_3 **81**	15 mol% cat. AcOH (2 equiv) CH_2Cl_2 (3 mM) reflux	*17%*	*61%*
Cy_3P, Cl, Ru=CHPh, Cl, PCy_3 **121**	5 mol% cat. CH_2Cl_2 (0.25 mM) reflux	*75–85%*	*not observed*

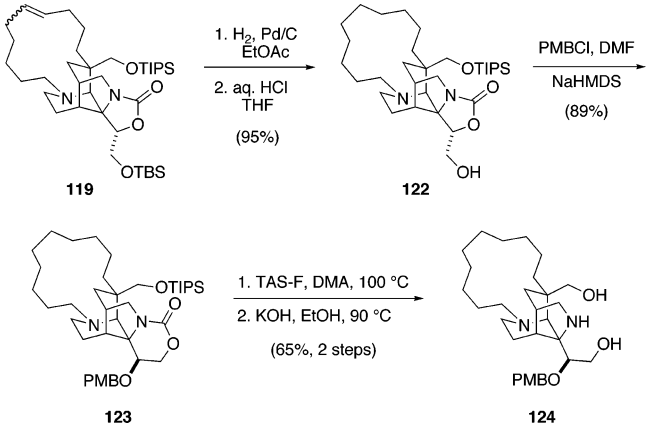
Figure 7. Ring-closing metathesis of diene **118**.

especially considering the overall complexity of our synthetic intermediates. As shown in Figure 7, we initially explored the use of Grubbs' second generation catalyst **81**, because this catalyst had been used in our previous macrocyclization experiments (see Scheme 15). Although it was possible to obtain macrocycle **119** using these conditions, multiple byproducts were observed, with the bulk of material corresponding to dimeric products **120**. The use of Grubbs' first generation catalyst **121** to form the desired macrocycle was also examined. This catalyst was generally considered advantageous since it probably would not require an acidic additive (i.e., AcOH),[67f,68] and would be less likely to lead to thermodynamic mixtures of products.[69] In fact, the use of catalyst **121** improved the yields of desired monomer **119**. After substantial optimization, which involved lowering the catalyst loading to 5 mol %, carrying out the transformation at high dilution, and rigorously excluding O_2, dimer **120** could be avoided and desired product **119** was isolated in 75−85% yield.

Macrocycle **119** was further elaborated toward sarain A as shown in Scheme 27. Hydrogenation with Pd/C completed installation of the saturated macrocycle, which upon exposure to HCl afforded alcohol **122**. Reaction of alcohol **122** with NaHMDS and para-methoxybenzyl chloride (PMBCl) led to rearrangement of the 5-hydroxymethyl oxazolidinone to the corresponding 5-hydroxy-[1,3]oxazinan-2-one,[70] with concurrent

(64) Sungchul, J.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312.
(65) Cossy, J.; Aclinou, P. *Tetrahedron Lett.* **1990**, *31*, 7615−7618.
(66) Lin, Y-. T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2517−2520.
(67) (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Tetrahedron Lett.* **2004**, *45*, 719−722. (b) Dhavale, D. D.; Jachak, S. M.; Karche, N. P.; Trombini, C. *Synlett* **2004**, 1549−1552. (c) Bernarki, L.; Bonini, B. F.; Capitò, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778−1782. (d) Wipf, P.; Rector, S. R.; Takahasi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848−14849. (e) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146−1148. (f) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hiller, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867.
(68) AcOH is required for catalyst turnover; it is thought that AcOH protonates the tertiary amine, thereby preventing catalyst deactivation that would occur otherwise.
(69) The mixture of monomeric and dimeric products obtained from use of Grubbs' 2nd generation catalyst is believed to reflect a thermodynamic distribution of products, because individually subjecting either monomer **119** or dimer **120** to the identical reaction conditions led to similar 1:3−4 ratio of the monomeric and dimeric adducts.
(70) For a related rearrangement that proceeds through an isocyanate, see: (a) Tadanier, J.; Martin, J. R.; Hallas, R.; Rasmussen, R.; Grampovnik, D.; Rosenbrook, W., Jr.; Arnold, W.; Schuber, E. *Carbohydr. Res.* **1981**, *98*, 11−23. Oxazinanone could be thermodynamically preferred to the corresponding oxazolidinone; see: (b) Sadybakasov, B. K.; Ashirmatov, M. A.; Afanas'ev, V. A.; Yu. Struchkov, T. *Zh. Strukt. Khim.* **1989**, *30*, 645−650.

Scheme 27



protection of the secondary hydroxyl, to provide PMB ether **123** in 89% yield. Next, considerable experimentation was carried out to optimize removal of the TIPS protective group. Although conditions employing TBAF or HF were unsuccessful, reaction of silyl ether **123** with TAS-F[71] in DMA at 100 °C led to clean desilylation. The tetrahydrooxazinone fragment of the resulting intermediate was cleaved with KOH in EtOH at 90 °C to provide diamine diol **124** in 65% yield over the two steps.

Toward the Unsaturated Macrocycle of Sarain A: An Unanticipated Skeletal Rearrangement. With diamine diol **124** in hand, we considered a number of strategies to address the next roadblock en route to sarain A, namely, installation of the skipped-triene containing macrocycle (**124** → **125**). Although attempts to prepare the unsaturated macrocycle in simple model systems had been described by Heathcock,[16c] no related studies involving advanced synthetic intermediates bearing the sarain A core skeleton or saturated macrocycle had been reported. Of the many methods considered, the most attractive involved Nozaki−Hiyama−Kishi,[72] Stille,[73] or Sonogashira[74] macrocyclizations. Several potential substrates for these strategies are depicted in Figure 8 (**126**, **127**, and **128**, respectively). As an sp^2-sp^2 cross-coupling approach to the unsaturated macrocycle of sarain A would be quite direct, and the use of intramolecular Stille couplings to form macrocycles is well precedented,[73] we opted to pursue the synthesis of stannane **127** as the primary objective.

Our initial efforts toward a Stille macrocyclization precursor are shown in Scheme 28. Diamine diol **124** was allowed to react with aldehyde **129**[43] in refluxing PhH to afford *N*,*O*-acetal **130** as a single stereoisomer.[75] Although we had anticipated the formation of a 6-membered oxazinane product, the structure of oxazocane **130** was confirmed by 2-dimensional NMR studies.[43] This result was thought to be inconsequential, since in the next step, we hoped to reduce the *N*,*O*-acetal to deliver an *N*-alkylated product.

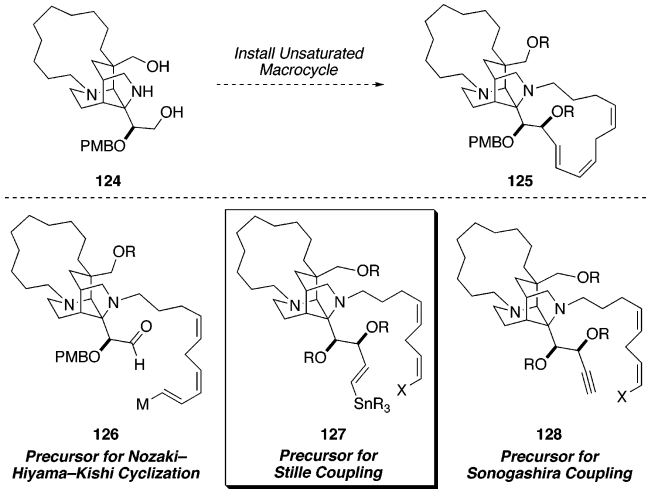
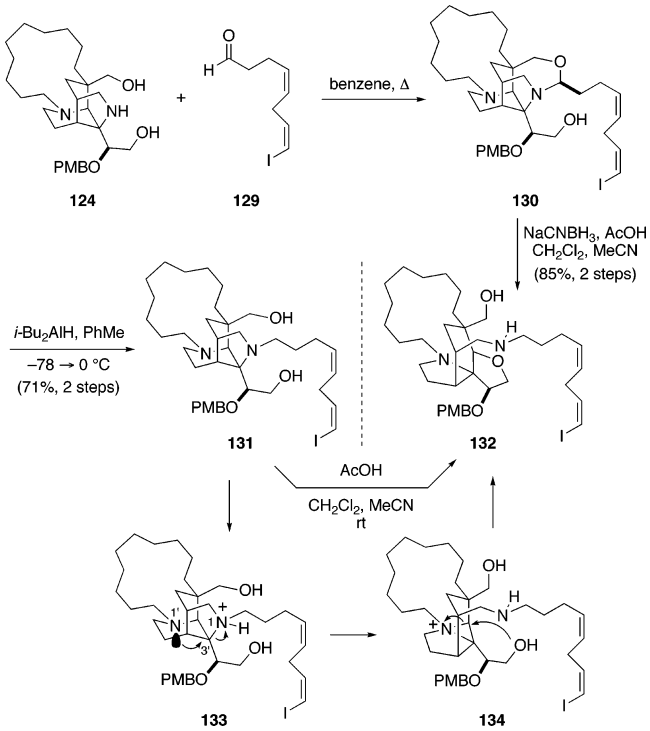


Figure 8. Strategies to fashion the skipped-triene containing macrocycle of sarain A.

Scheme 28

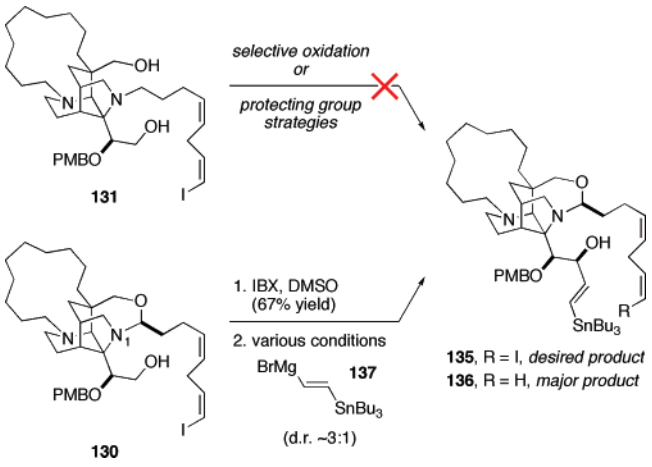


In our first attempt to carry out the proposed reduction, *N*,*O*-acetal **130** was allowed to react with $NaCNBH_3$ and AcOH at room-temperature. Although a reduction product was obtained, detailed NMR investigation[14c,d] established that extensive skeletal rearrangement had taken place to afford tetracycle **132**. Fortunately, the desired reduction could be accomplished with *i*-Bu_2AlH, providing the *N*-alkylated product **131** in 71% yield from secondary amine **124**.

To probe the mechanism of this intricate skeletal rearrangement, diol **131** was treated with AcOH in a mixture of CH_2Cl_2 and MeCN at ambient temperatures. Under these relatively mild conditions, designed to mimic those that caused rearrangement but in the absence of a reducing agent, the identical tetracyclic product **132** formed quantitatively.[76] Cognizant that the rear-

(71) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.
(72) For reviews of Nozaki−Hiyama−Kishi reactions, see: (a) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Soc. Rev.* **1999**, *28*, 169−177. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045. (c) Cintas, P. *Synthesis* **1992**, 238−257.
(73) For reviews of the intramolecular Stille coupling, see: (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235−1246. (b) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261−268.
(74) For a recent review, see: Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874−922.
(75) Relative configuration at the aminal stereocenter was determined by $^1H-^1H$ NOESY experiments.
(76) In the presence of AcOH, sarain A (**1**) does not undergo the analogous skeletal rearrangement.

Scheme 29



rangement is acid-catalyzed, we postulate that the process occurs by protonation of the pyrrolidine nitrogen (**131** → **133**), followed by formation of intermediate aziridinium ion **134**. Subsequent attack of the primary alcohol would lead to tetrahydrofuran ring formation, giving the observed rearranged product, **132**. Although aziridinium ion rearrangements are known,[77] to the best of our knowledge, this is the first example of an aziridinium ion rearrangement in which the leaving group is a tertiary amine.[78] The facility with which aziridium ion **134** is generated from diamine **133** stands in marked contrast to the rate at which half-neutralized *N*,*N*′-dimethylpropanediamine exchanges methyl groups in H_2O by displacement of an ammonium salt by an amine ($t_{1/2} = 1.6 \times 10^6$ days, at room-temperature).[78b] The near perfect alignment of the nonbonded electron pair of tertiary amine N1′ with the σ^* orbital of the C3′−N1 bond in **133**, is undoubtedly responsible for the ease of the observed rearrangement.

Successful Construction of the Unsaturated Macrocycle. Aware that our late-stage intermediates could be prone to skeletal rearrangement, particularly under acidic conditions, we returned to the difficult task of assembling the skipped triene-containing macrocycle of sarain A. Preliminary efforts to elaborate *N*-alkylated diol **131** toward Stille macrocyclization precursor **135** by selective alcohol oxidation methods or various protecting group strategies were unfruitful (Scheme 29). As an alternative, we reasoned that it could be advantageous to carry *N*,*O*-acetal **130** forward in the synthesis, then defer its reduction to a later stage. This strategy was attractive because N1 of *N*,*O*-acetal **130** would be less basic, and thus less prone to skeletal rearrangement under acidic conditions. Moreover, on an intermediate such as **130**, the two alcohols of precursor **124** would be differentiated. Attempts to oxidize alcohol **130** to the corresponding aldehyde, using oxidants thought to be compatible with the basic tertiary amines,[79] were initially met with substantial difficulty. However, it was found that oxidation of alcohol **130** with 2-iodoxybenzoic acid (IBX)[79a] in DMSO delivered the desired aldehyde in 67% yield. Subsequent reaction of the aldehyde with β-stannylvinylmagnesium bromide **137**[80] under a variety of conditions led to mixtures of products. After inspection, it became apparent that although stereocontrolled addition of the Grignard reagent had occurred to generate the syn β-alkoxy alcohol (dr ~3:1), the major product of this reaction (i.e., **136**) suffered from loss of the vinyl iodide functional group. In an effort to minimize the halogen-magnesium exchange that likely gave rise to des-iodide **136**, substantial experimentation was carried out. However, after exploring various solvents, nucleophiles (e.g., Li, Ce, and Zn reagents), and substrates (e.g., vinyl bromide instead of vinyl iodide), no substantial improvements were observed.

Given the difficulties encountered in our somewhat ambitious approaches to a Stille macrocyclization precursor,[81] we considered an alternative stepwise strategy that would ultimately provide access to the atomic skeleton of sarain A (Scheme 30). To initiate efforts, diamine diol **124** was condensed with butanal **138**[82] to afford oxazocane **139**.[75] With a simplified *N*,*O*-acetal side chain in place, it was now possible to introduce the vinyl stannane functional group by IBX oxidation,[79a] followed by addition of Grignard reagent **137** to provide **140** (dr 3−4:1). Although **140** formed as an inseparable mixture of epimers, it was presumed that the major adduct had the desired *S* configuration at C8′, which would arise from chelation-controlled addition of the Grignard reagent.[83] Reaction of the diastereomeric mixture with TBAF facilitated desilylation to provide diol **141**. Despite finding that selective oxidation of the primary alcohol of **141** was not possible, we could advance material by resorting to less attractive protective group manipulations. Thus, double TES-protection of diol **141** furnished silyl ether **142**. Fortuitously, at this stage, it was possible to separate the mixture of C8′ epimers by conventional column chromatography. Isomerically pure **142** was then allowed to react with K_2CO_3 in MeOH to selectively cleave the primary TES protective group. Dess−Martin oxidation of alcohol **143**,[84] followed by Wittig reaction with phosphonium salt **144**,[85] then delivered the

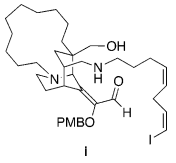
(77) Aziridinium ions are occasionally formed under S_N1-type conditions. (a) For an aziridinium ion that was generated by trapping of a secondary carbocation formed by Prins cyclization, see: Graham, M. A.; Wadsworth, A. H.; Thorton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966−967. (b) For an aziridium ion that was formed by trapping of a quinone methide intermediate, see: Shamma, M.; Nugent, J. F. *Tetrahedron* **1973**, *29*, 1265−1272.

(78) (a) Fragmentation of protonated 1,2-ethylenediamine to an aziridinium ion has been observed in the gas phase; see: Bouchoux, G.; Choret, N.; Penaud-Berruyer, P.; Flammang, R. *J. Phys. Chem. A* **2001**, *105*, 9166−9177. (b) *N*,*N*′-Dimethyl-1,3-propanediamine exchanges methyl groups slowly in water in the presence of acid; see: Callahan, B. P.; Wolfenden, R. *J. Am. Chem. Soc.* **2003**, *125*, 310−311.

(79) Oxidation in the presence of basic amines is not straightforward and often requires substantial experimentation before suitable conditions are discovered. Several oxidation procedures commonly employed in our studies are as follows. For a review of IBX oxidations, see: (a) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111−124. For a relevant example involving Swern oxidation, see: (b) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000−15001. For the Narasaka-Mukaiyama oxidation, see: (c) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773−2776. For Parikh-Doering oxidation, see: (d) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507. See also references 39 and 51a for Dess−Martin and TPAP/NMO oxidations, respectively.

(80) Grignard reagent **137** was prepared from the corresponding lithium reagent and $MgBr_2$. For the preparation of this lithium reagent, see: D. Seyferth, S. C. Vick, *J. Organomet. Chem.* **1978**, *144*, 1−12.

(81) In addition to skeletal rearrangement and loss of iodide, we have also observed fragmentation of the pyrrolidine ring (e.g., forming **i**), presumably through a β-elimination pathway.

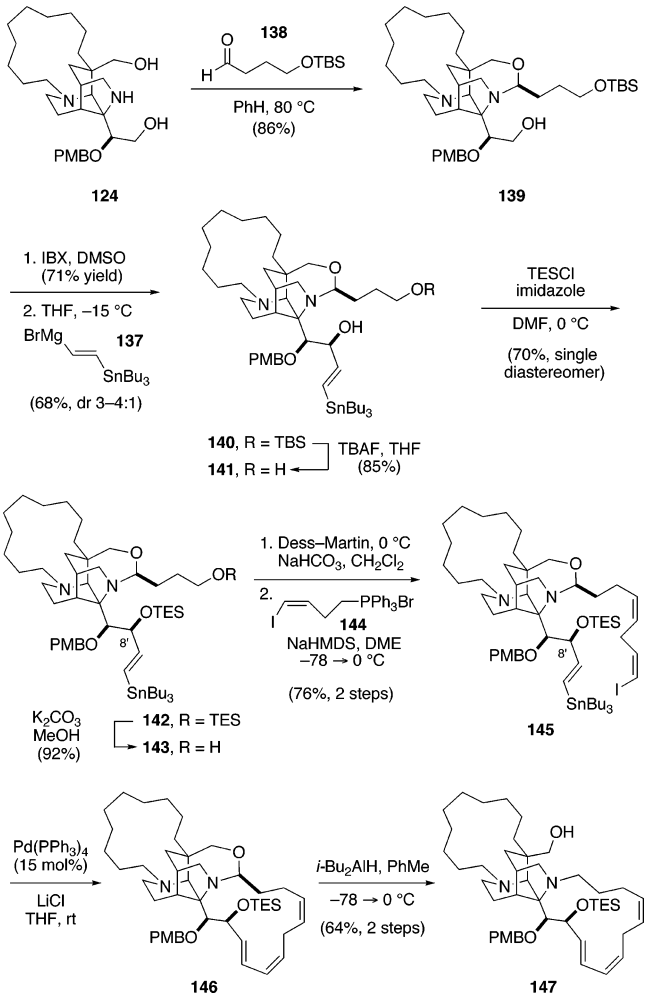


i

(82) Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097−2108.

(83) For a pertinent review, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

Scheme 30

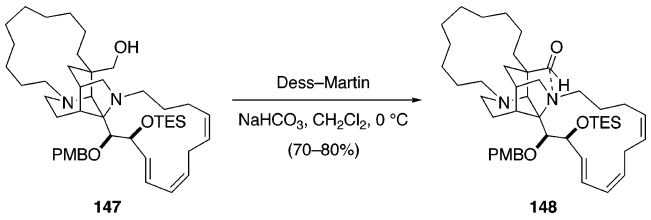


coveted Stille coupling substrate **145** in 76% yield over two steps. Gratifyingly, upon reaction of stannyl iodide **145** with catalytic $Pd(PPh_3)_4$ and excess LiCl[86] at ambient temperatures in THF, cyclization took place to assemble the 14-membered triene ring of product **146**.[87] Reduction of the *N*,*O*-acetal of **146** with *i*-Bu_2AlH delivered pentacyclic alcohol **147**, a compound that possesses the full skeleton of sarain A, in 64% yield from stannyl iodide **145**. It should be noted that alternative Stille coupling conditions employing copper additives[73] were examined, but found to be inferior in assembling the unsaturated macrocycle.

Installation of the Tertiary Amine−Aldehyde Proximity Interaction and Completion of the Total Synthesis of (−)-Sarain A. To complete the total synthesis of sarain A, two major tasks remained: installation of the tertiary amine−aldehyde functional group by oxidation of the C2 alcohol and cleavage of the two remaining protective groups to unmask the C7′,C8′-diol. We suspected that the former of these tasks would be exceptionally challenging considering: (a) the C2 alcohol is neopentylic and rests in a sterically encumbered environment, (b) the tertiary amine lies in close proximity to the C2 alcohol,[88]

(84) Attempts to achieve sequential deprotection of the primary triethylsilyl ether and oxidation by use of Swern oxidation conditions were unsuccessful; for this procedure, see: Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161−5164.
(85) Nicolaou, K. C.; Ramphal, J. Y.; Abe, Y. *Synthesis* **1989**, 898−901.
(86) For the use of LiCl in Stille couplings, see: Amator, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc*. **1993**, *115*, 9531−9541.

Scheme 31

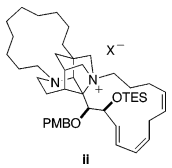


and (c) the desired zwitterionic product would likely be difficult to handle in the laboratory, as was the case for sarain A during its isolation.[2] Several mild oxidation procedures were examined,[79] which ultimately led to the identification of bicarbonate-buffered Dess−Martin periodinane[39,89] as the most effective oxidation conditions. In this way, diamine alcohol **147** was transformed to aldehyde **148** in 70−80% yield (Scheme 31). The crude oxidized product, which was stable to both aqueous workup and filtration through SiO_2, was used in subsequent transformations without scrupulous purification.

To complete the total synthesis of sarain A, we hypothesized that a global deprotection would be optimal, since it would minimize the handling and purification of sensitive late-stage compounds. Inspired by Danishefsky and co-workers who were able to remove three secondary PMB protecting groups simultaneously without disturbing a skipped triene,[90] we questioned if sarain A would be stable to excess TMSI.[91] Notably, when a sample of natural sarain A (**1**) was allowed to react with 50 equiv of TMSI in CH_2Cl_2 from 0 °C → room-temperature for short reaction times, it was possible to recover pure sarain A after SiO_2 chromatography (Scheme 32). However, when key synthetic intermediate **148** was exposed to the identical reaction conditions, protective group cleavage was sluggish. At longer reaction times, complex product mixtures were obtained, with decomposition being partially attributed to the sensitive nature of the skipped-triene, which was likely unstable to adventitious HI.[92]

We conceded that global deprotection to arrive at sarain A (**1**) could be exceptionally difficult, and in our first preparation of the natural product, stepwise removal of the TES and PMB protective groups would be acceptable. With the hope of removing the TES protecting group, late-stage intermediate **148** was allowed to react under mildly acidic conditions involving either AcOH, dilute HCl, or HF•pyr. Whereas the former two conditions led to recovery of starting material, HF•pyr readily promoted the desired deprotection in reaction times as short as

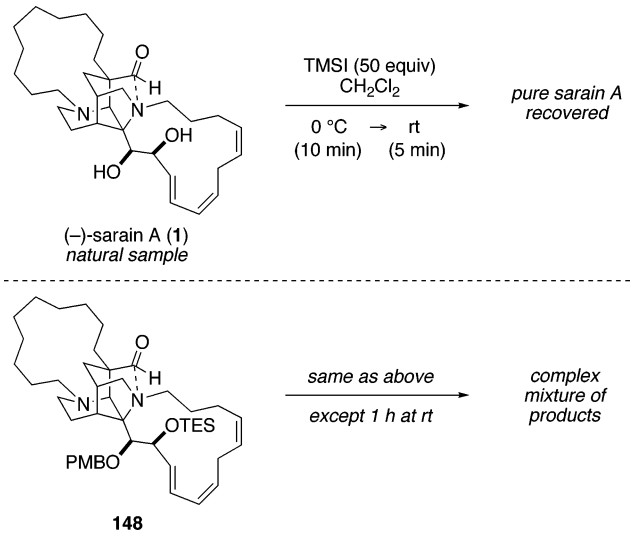
(87) Notably, the C8′ epimer of substrate **145** fails to cyclize under the identical reaction conditions.
(88) The proximal tertiary amine could intercept an activated alcohol derivative prior to oxidation to afford quaternary ammonium salt **ii**. We postulate that this ammonium salt formed during attempted Swern oxidation of alcohol **147**.



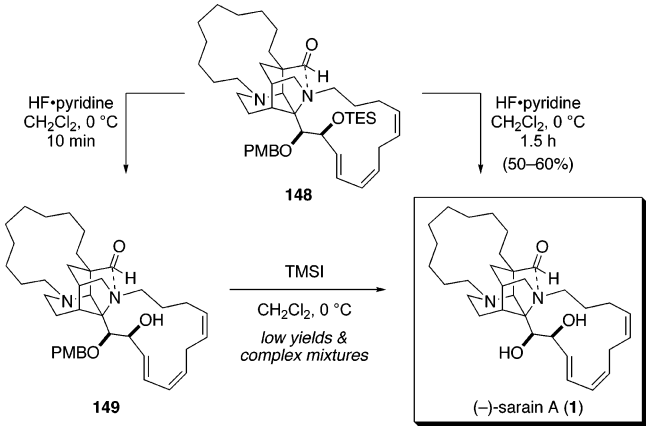
ii

(89) Dess−Martin periodinane was freshly prepared using Schreiber's procedure; see: Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.
(90) Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659−663.
(91) For the use of TMSI to remove benzylic protecting groups, see: Jung, M. E.; Lyster, M. A. *J. Org. Chem*. **1977**, *42*, 3761−3764.
(92) HI addition adducts were detected by ESI-MS.

Scheme 32



Scheme 33



10 min to furnish alcohol **149** (Scheme 33). Direct exposure of crude alcohol **149** to TMSI at 0 °C delivered the first synthetic sample of sarain A. Unfortunately, yields were low and the synthetic sarain A was contaminated with various byproducts, which proved inseparable by benchtop chromatography, HPLC, and SFC; indeed, purification of sarain A was not a trivial task as the isolation chemists had forewarned.[2] However, in a unanticipated discovery, it was noticed that extended reaction of intermediate **148** with HF•pyr led to the clean formation of a new product, immediately recognized as sarain A (**1**). After aqueous workup and purification on SiO_2, synthetic sarain A (**1**) was isolated in 50−60% yield and found to be indistinguishable from an authentic sample of the natural product by NMR, mass spectrometric, and chromatographic comparisons.[93] Furthermore, CD comparisons confirm that the absolute configuration of (−)-sarain A (**1**) is as depicted in Scheme 33, consistent with the proposal made by Cimino and co-workers.[2d]

Conclusion

In summary, the first total synthesis of the structurally unique alkaloid (−)-sarain A (**1**) has been achieved. The enantioselective route reported herein features a number of key steps, including: (a) an intermolecular Michael addition to build the C4′−C3′−C7′ stereotriad, (b) an enoxysilane-*N*-sulfonyliminium ion cyclization to assemble the diazatricycloundecance core and set the C3 quaternary carbon center simultaneously, (c) a high-yielding ring-closing metathesis reaction to construct the 13-membered macrocycle, (d) a Stille macrocyclization to forge the skipped triene-containing 14-membered ring, and (e) a late-stage installation of the tertiary amine-aldehyde proximity interaction. We hope this account of the various strategies conceived, setbacks encountered, and solutions developed en route to sarain A will showcase the challenges and excitement of complex molecule synthesis.

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Supporting Information Available: Experimental details and characterization data for select compounds, in addition to spectral comparison for synthetic and natural (−)-sarain A. This material is available free of charge via the Internet at http://pubs.acs.org.

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(93) Comparisons were made after adding CD_3CO_2D; see reference 2c.