Asymmetric Construction of the Diazatricyclic Core of the Marine Alkaloids Sarains A−C

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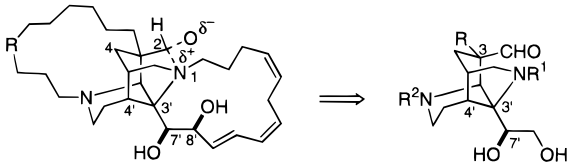
A breathtaking variety of structurally novel alkaloids are found in sponges.[2] Arguably the most remarkable are sarains A−C (**1**−**3**), which were isolated by Cimino and coworkers from the sponge *Reniera sarai* collected in the Bay of Naples.[3,4] The diazatricycloundecane core with its "proximity" interaction between the aldehyde substituent at C2 and N1[5] and the 14-membered ring containing a vicinal diol and three (two cis and one trans) double bonds is unprecedented, defining this class of marine alkaloids.[6] A preliminary survey of biological activity identified antibacterial, insecticidal, and antitumor activities with sarains A−C.[7] The fascinating structures of these alkaloids have stimulated several synthetic investigations in this area. Sisko and Weinreb reported the first assembly of the basic diazatricycloundecane core,[8] while notable progress toward sarain A has also been registered by the Heathcock group.[9] Herein, we report the first asymmetric construction of the diazatricycloundecane core of sarains A−C (**1**−**3**) by a strategy that deals effectively with the critical, fully substituted, C3′ center and relates this stereocenter to that of the proximal diol unit of the 14-membered ring.

Our analysis of the synthetic challenge presented by sarains A−C (**1**−**3**)

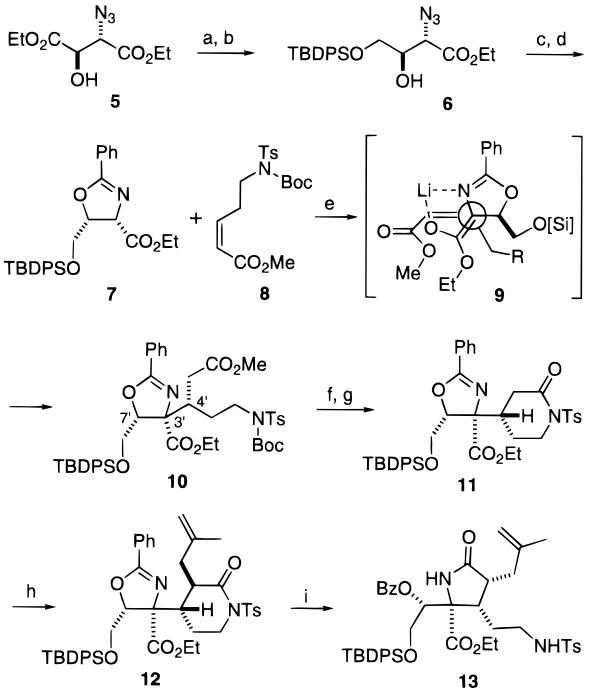


sarain A (**1**) R = CH_2
sarain B (**2**) R = –(*Z*)-CH=CH–
sarain C (**3**) R = –(*Z*)-CH=CHCH_2–

4

identified diazatricycle **4** as a particularly attractive subgoal, since this intermediate contains all the key elements of the diazatricycloundecane core of sarains A−C and sufficient functionality in the side chain for potential future elaboration of the 14-membered dihydroxy-skipped triene ring. Our strategy was to fashion early on the C4′−C3′−C7′ stereotriad as well as assemble most of the carbon framework of **4** with an intermolecular Michael reaction (Scheme 1). Since diethyl tartarate was to be the starting enantiopure building block, our initial investigations employed the less expensive L enantiomer and targeted *ent*-**1**−**3**.[10] The carbonyl group of the α-hydroxy ester unit of diester **5**[11] was selectively reduced with borane in the presence of catalytic $NaBH_4$ to provide the corresponding diol in 54% yield.[12] Protection of the primary alcohol as a *tert*-butyldiphenylsilyl (TBDPS) ether generated ester **6** in 82% yield.[13] After hydrogenation of the azide group of **6**, the resulting vicinal amino alcohol was converted to oxazoline **7** in 73% overall yield.[14] This intermediate was deprotonated with lithium hexamethyldisilazane (LHMDS) at −78 °C, and the resulting lithium enolate was condensed with (*Z*)-enoate **8**[15−17] under carefully optimized conditions (−78 °C in a 2:1 mixture of DME−THF) to provide Michael adduct **10** as a single stereoisomer in 71% yield.[18] The stereochemical outcome of this key Michael reaction is in accord with transition-state assembly **9**.[19,20]

Scheme 1[a]



[a] Reagents: (a) BH_3·DMS, THF, cat. $NaBH_4$, 54%; (b) TBDPSCl, imid., THF, 82%; (c) H_2, Pd/C, EtOAc; (d) methyl benzimidate hydrochloride, CH_2Cl_2, 73% over two steps; (e) LHMDS, THF, DME, −78 °C, 71%; (f) DMSO, 180 °C, 69%; (g) Me_3Al, PhMe, 91%; (h) LHMDS, THF, DMPU, 3-bromo-2-methylpropene, −78 °C, 79%; (i) THF, 2 N HCl 75%. DMPU = *N*,*N*-dimethylpropylene urea.

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(2) For reviews, see: (a) Kobayashi, J.; Ishibashi, M. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1992; Vol. 41, Chapter 2. (b) Faulkner, D. J. *Natl. Prod. Rep.* **1998**, *15*, 113 and previous reviews in this series.

(3) Both the names sarain and saraine have been employed to describe these alkaloids.[4,6]

(4) Cimino, G.; De Stefano, S.; Scognamiglio, G.; Trivellone, E. *Bull. Soc. Chim. Belg.* **1986**, *95*, 783.

(5) Leonard, N. J.; Oki, M.; Chiavarelli, S.*J. Am. Chem. Soc.* **1955**, *77*, 6234 and references cited therin.

(6) (a) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Pulti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863. (b) Cimino, G.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Pure Appl. Chem.* **1989**, *61*, 535. (c) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519. (d) Guo, Y.-W.; Madaio, A.; Scognamiglio, G.; Trivellone, E.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341.

(7) Caprioli, V.; Cimino, G.; DeGuilio, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. *Comp. Biochem. Physiol.* **1992**, *103B*, 293.

(8) Sisko, J.; Henry, J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945.

(9) (a) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. *Synlett* **1995**, 467. (b) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *Abstracts of Papers*, 216th National Meeting of the American Chemical Society, Boston, MA; American Chemical Society: Washington, DC, 1998; ORGN 526.

(10) Since D-diethyl tartrate is also commercially available, our strategy can just as well be directed at the natural alkaloids.

(11) Saito, S.; Komada, K.; Moriwake, T. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, p 220.

(12) Sauret-Cladiere, S.; Jeminet, G. *Tetrahedron: Asymmetry* **1997**, *8*, 417.

(13) Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975.

(14) For a comprehensive review of the chemistry of oxazolines, see: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.

(15) Prepared in three standard steps and 55% overall yield from 3-butyn-1-ol: (a) (Boc)NHTs, Ph_3P, DEAD, THF;[16] (b) *n*−BuLi, MeOCOCl, Et_2O; (c) H_2, $Pd/CaCO_3$/Pb, MePh.[17]

(16) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(17) Taschner, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1986**, *64*, 108.

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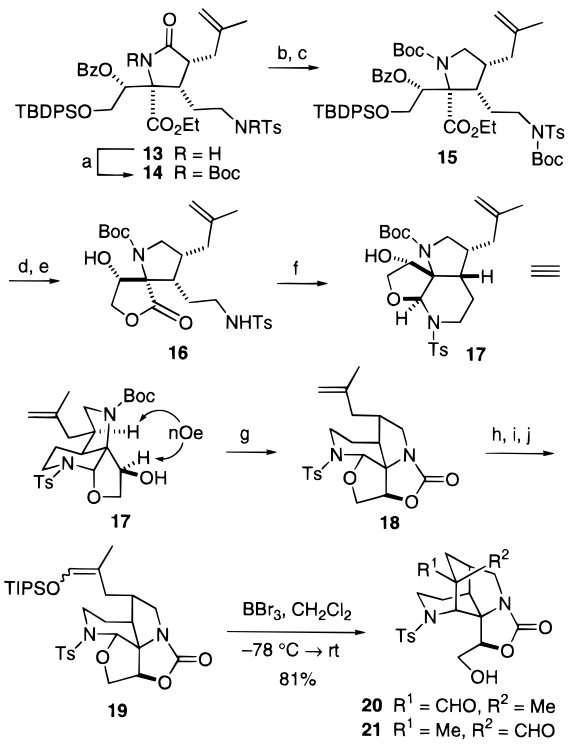
Scheme 2[a]



[a] Reagent: (a) $(Boc)_2O$, CH_3CN, cat. DMAP, 98%; (b) DIBALH, CH_2Cl_2, −78 °C; (c) $NaCNBH_3$, HOAc, 67% over two steps; (d) TBAF, THF; (e) K_2CO_3, MeOH, 79% over two steps; (f) DIBALH, CH_2Cl_2, −78 °C; 2 N HCl, 78%; (g) NaHMDS, THF, −78 to 0 °C, 90%; (h) BH_3·THF, THF, 0 °C; EtOH, 4 N NaOH, 30% H_2O_2; (i) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 69% over two steps; (j) TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 77%.

The remaining carbons of the diazatricyclic core were incorporated using lactam derivative **11**, since attempts to alkylate **10**, or directly trap the lithium enolate produced from the Michael reaction, were unsuccessful. Lactam **11** was accessed in 63% yield by thermal cleavage of the *tert*-butoxycarbonyl (Boc) group of **10**,[16] followed by cyclization of the resulting amino ester with Me_3Al.[21] Deprotonation of **11** with LHMDS and alkylation with 3.5 equiv of 3-bromo-2-methylpropene at −78 °C resulted in the formation of **12** as a single stereoisomer in 79% yield. The stereochemical assignment for **12** was made initially on the expectation that allylation would proceed preferentially from the enolate face opposite the oxazoline side chain. Finally, exposure of **12** to dilute HCl cleaved the oxazoline ring[22] and promoted translactamization to provide pyrrolidinone **13** in 75% yield.

Elaboration of **13** to arrive at Mannich cyclization precursor **19** was initiated by protection of both nitrogens with Boc groups[23] to yield **14** (Scheme 2). Selective reduction of the pyrrolidinone carbonyl group of this intermediate with DIBALH at −78 °C provided a 3:2 mixture of hemiaminals,[24] which was immediately reduced with $NaCNBH_3$[25] to furnish pyrrolidine **15** in 67% overall yield. The silyl ether of **15** was next discharged with TBAF. The liberated primary alcohol was allowed to react with K_2CO_3 in MeOH, which cleaved the benzoate and sulfonamide Boc protecting groups and promoted lactonization to provide **16** in 79% yield. This spirolactone was then treated with 4 equiv of DIBALH at −78 °C, followed by quenching with aqueous HCl to generate tricyclic aminal **17** in 78% yield. At this point, the stereochemistry of the methallyl group was readily confirmed by ^1H NMR NOESY studies. Exposure of **17** to sodium hexamethyldisilazane (NaHMDS) promoted cyclization to generate oxazolidinone **18** (90%), which was hydroborated and oxidized to yield a 1:1 mixture of primary alcohols. Oxidation of this mixture with Dess−Martin periodinane[26] and reaction of the resulting aldehyde epimers with triisopropylsilyl triflate provided an inseparable 1.5:1.0 mixture of enoxysilane stereoisomers **19** in 53% overall yield from **18**.[27]

With the synthesis of **19** in hand, we turned to the crucial *N*-tosyliminium ion−enoxysilane cyclization, which derives some precedent from Sisko and Weinreb's earlier assembly of a simpler sarain A core using an *N*-tosyliminium ion-allylsilane cyclization.[8,28] Attempts to promote Mannich cyclization of **19** with $SnCl_4$, BF_3·OEt_2, or Me_3Al proved unsuccessful and typically returned the aldehyde precursors of **19**. However, the desired cyclization was successfully realized when **19** was exposed to 3.5 equiv of BBr_3 in CH_2Cl_2 at −78 °C to room temperature, which produced the diazatricycloundecanes **20** and **21** in a 3:1 ratio and 81% combined yield.[29] The structure of the major isomer **20** (mp 214−216 °C) was confirmed by single-crystal X-ray diffraction analysis.[30]

In summary, an enantioselective total synthesis of the core of sarains A−C (**1**−**3**) has been developed. Our strategy integrates generation of the diazatricycloundecane core of these alkaloids with formation of a side chain containing the C7′ alcohol stereocenter, the latter of which provides a convenient handle for further elaboration of the 14-membered dihydroxy-skipped triene ring.[31] A stereoselective bimolecular Michael reaction of a tartrate-derived oxazoline and a (*Z*)-enoate to set the C4′−C3′−C7′ stereocenters and the first example of an intramolecular *N*-tosyliminium ion−enoxysilane condensation are the central strategic steps of this sequence.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for compounds **5**−**21** and NOESY data for **17** (13 pages).

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(18) For seminal contributions to the use of enantiopure oxazolidines in asymmetric synthesis, see: (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311. (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.

(19) Optimization of this condensation and definition of its stereochemistry was initially accomplished with a related threonine-derived oxazolidine.[20]

(20) Jaroch, S.; Matsuoka, R.; Overman, L. E. Manuscript in preparation.

(21) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(22) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(23) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510.

(24) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(25) Lenz, G. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 33.

(26) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(27) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(28) For a recent review of *N*-sulfonyliminium ion chemistry, see: Weinreb, S. M. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1997; Vol. 190, p 131.

(29) When the reaction was conducted at lower temperature (−78 °C → −40 °C), product formation was sluggish (40% conversion after 48 h at −40 °C) and the ratio of **20** to **21** was unchanged.

(30) The authors have deposited coordinates for compound **20** with the Cambridge Crystallographic Data Centre.

(31) The formation of the undesired stereochemistry at C3 as the major product from cyclization of **19** is anticipated to be of little significance in extending this chemistry toward the natural products themselves if the saturated macrocyclic ring of sarain A (or the corresponding unsaturated rings of sarain B or C) is present prior to Mannich cyclization.