Alkaloids

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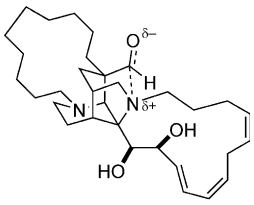
Formal Synthesis of Sarain A: Intramolecular Cycloaddition of an Eight-Membered Cyclic Nitrone to Construct the 2-Azabicyclo-[3.3.1]nonane Framework**

Takuya Higo, Tomoya Ukegawa, Satoshi Yokoshima, and Tohru Fukuyama**

Abstract: *An enantioselective route to the tetracyclic skeleton of sarain A has been developed. Asymmetric reduction of an ynone introduced a chiral center which was transferred to the contiguous tertiary stereogenic centers through an Ireland–Claisen rearrangement. The 2-azabicyclo[3.3.1]nonane framework was constructed by an unprecedented intramolecular cycloaddition of an eight-membered cyclic nitrone. Using the steric bias of the bicyclic system, the quaternary carbon atom was constructed by a stereoselective aldol reaction. Further ring formations were performed by ring-closing metathesis for the 13-membered ring and an iodoamidation reaction for the pyrrolidine ring. The present synthesis has successfully provided an alternative route to the late-stage intermediate of Overman's synthesis.*

Sarain A (**1**; Figure 1) is a marine alkaloid isolated from the sponge *Reniera sarai* in 1986 by Cimino and co-workers.[1] This alkaloid shows antitumor, antibacterial, and insecticidal activities.[2] X-ray crystallography of the corresponding diacetate[3] and NMR techniques[4] have revealed that sarain A is a pentacyclic compound which contains 13- and 14-membered macrocyclic rings and a 2-azabicyclo[3.3.1]nonane framework fused with a pyrrolidine ring to form a 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane core. Sarain A has seven stereogenic centers, including a quaternary carbon atom, and the 14-membered ring has a vicinal diol and skipped triene moieties. The tertiary amine and aldehyde moieties on the diazatricycloundecane core form a proximity interaction,[5] which is sensitive to the pH and solvent environment.[6] Because of these structural features and its biological activities, sarain A has attracted much attention in the synthetic community. In fact, a variety of synthetic studies have been reported to date,[7–11] and Overman and co-workers accomplished the first and only total synthesis of sarain A.[12]



sarain A (**1**)

Figure 1. Structure of sarain A.

Obviously, a major point of interest is the construction of the characteristic 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane core. The synthetic strategies reported to date involve intramolecular reactions by either the Mannich reaction,[10c,12] the Michael reaction,[8c,9a,11b] or the addition of allylsilane to the N-sulfonyliminium ion.[7,10b] Both cycloaddition reactions of azomethine ylides[7,8] and a 3-oxidopyridinium betaine[9a] have also been explored to prepare the fused heterocycles. Herein we disclose a novel enantioselective construction of the core structure of sarain A, and it features an intramolecular cycloaddition of an eight-membered cyclic nitrone and an iodoamidation reaction. Our synthesis provides an alternative route to Overman's synthetic intermediate.

Scheme 1 depicts our retrosynthesis. We envisioned that the highly functionalized 14-membered ring would be formed at a later stage of the synthesis and the removal of the C9′–C18′ bridge would lead to the tetracyclic compound **2**, which is an equivalent of Overman's intermediate.[12] Cleavage of the N–C bonds at N1–C3′ and N1′–C16, and further simplification generates the 2-azabicyclo[3.3.1]nonane **3**.[13] The quaternary stereogenic center at C3 could be stereoselectively installed by means of the steric bias of the bicyclic system.[14] The 2-azabicyclo[3.3.1]nonane framework could be constructed by the intramolecular cycloaddition of the eight-membered cyclic nitrone **4** in an unprecedented manner.[15] The nitrone then would be derived from the aldehyde **5**. The contiguous stereogenic centers in **5** could in turn be constructed through an Ireland–Claisen rearrangement of **6**.[16]

Our synthesis commenced with asymmetric synthesis of the substrate for the Ireland–Claisen rearrangement (**9**; Scheme 2). A reaction between an anion derived from the terminal alkyne **7** and amide **15** afforded a ketone, which was subsequently subjected to asymmetric reduction[17] to give the propargyl alcohol **8** in 92% yield and 98% *ee*. Reduction of **8** with Red-Al followed by acylation using **17** furnished the requisite substrate **9**. The crucial Ireland–Claisen rearrangement of **9** was carried out by treatment with LHMDS in the

[*] Dr. T. Higo, Dr. S. Yokoshima, Prof. T. Fukuyama
Graduate School of Pharmaceutical Sciences, Nagoya University
Furo-cho, Chikusa-ku, Nagoya 464-8601 (Japan)
E-mail: yokosima@ps.nagoya-u.ac.jp
fukuyama@ps.nagoya-u.ac.jp
Dr. T. Higo, T. Ukegawa
Graduate School of Pharmaceutical Sciences, University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

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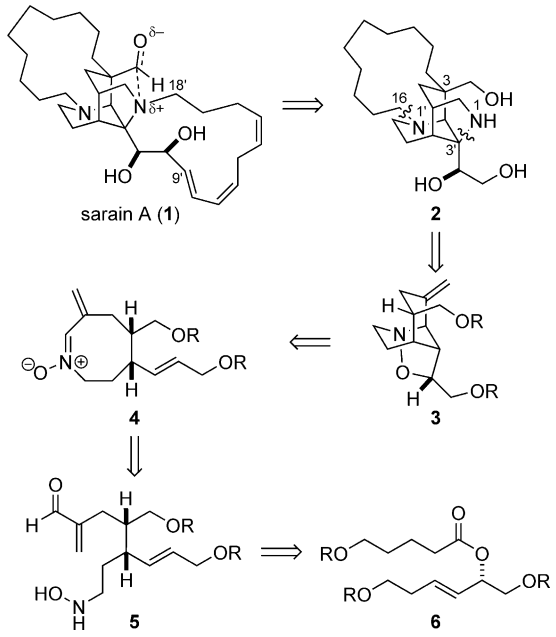
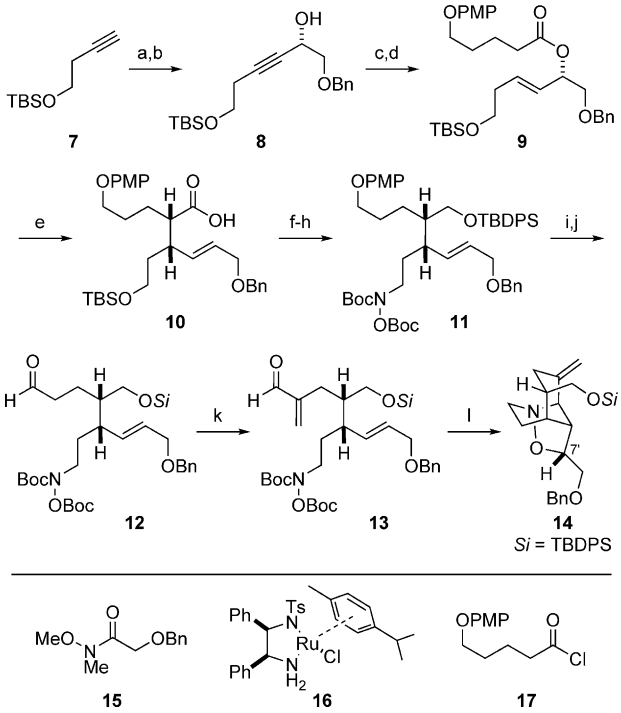


Scheme 1. Retrosynthesis.



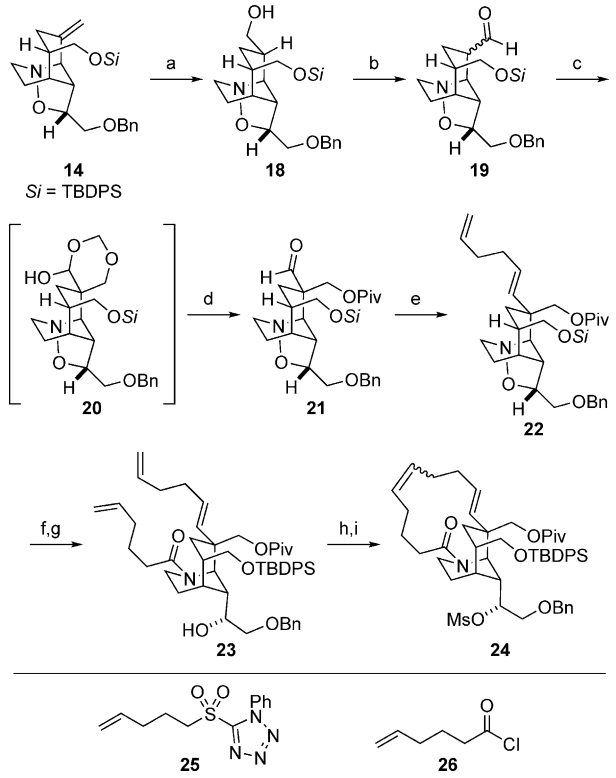
Scheme 2. Intramolecular cycloaddition of a cyclic nitrone. a) *n*BuLi, THF, −78 °C; **15**, 0 °C, 99%; b) **16** (2 mol%), HCO_2H-Et_3N (1:1), CH_2Cl_2, −78 to 0 °C, 92%, 98% *ee*; c) Red-Al, toluene, RT, 97%; d) **17**, pyridine, CH_2Cl_2, 0 °C, 89%; e) LHMDS, TMSCl, Et_2O/THF (5:2), −78 to 0 °C, 89%, d.r. > 20:1; recrystallization, 81%, > 99% *ee*; f) $ClCO_2Et$, Et_3N, THF, 0 °C; $NaBH_4$, H_2O, 0 °C to RT, 98%; g) TBDPSCl, imidazole, DMF, RT; TFA, H_2O; h) BocNHOBoc, DEAD, Ph_3P, toluene, RT; i) CAN, $NaHCO_3$, MeCN-H_2O, 0 °C, 89% (two steps); j) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 0 °C, 97%; k) $H_2C{=}NMe_2^+I^-$, *i*Pr_2NEt, CH_2Cl_2, reflux; MeI, RT, 76%; l) TFA, CH_2Cl_2, 40 °C; pyridine, 40 °C, 79%. Boc = *tert*-butoxycarbonyl, CAN = ceric ammonium nitrate, DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, LHMDS = lithium hexamethyldisilazide, PMP = *p*-methoxyphenyl, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

presence of TMSCl to give the carboxylic acid **10** in 89% yield with high diastereoselectivity (d.r. > 20:1).

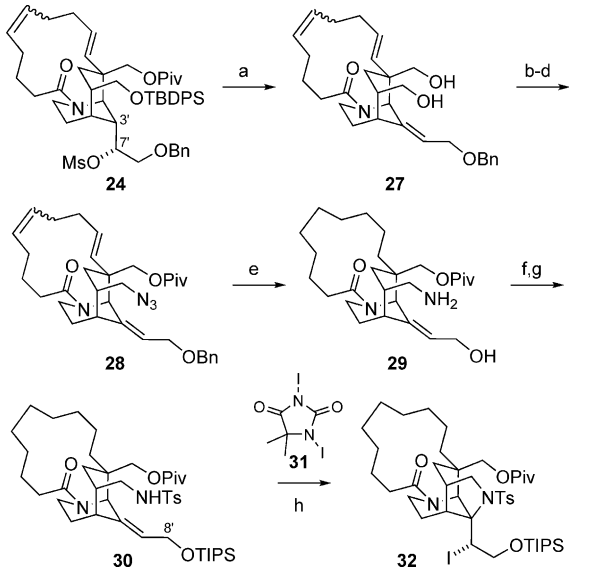
After successfully constructing the contiguous stereogenic centers by the Ireland–Claisen rearrangement, we turned our attention to the intramolecular cycloaddition of the cyclic nitrone (Scheme 2). The carboxylic acid moiety in **10** was reduced through a mixed anhydride, and the resulting alcohol was protected with a TBDPS group. After one-pot cleavage of the TBS ether under acidic conditions, the hydroxylamine moiety was installed by means of a Mitsunobu reaction with *N*,*O*-bis-Boc-hydroxylamine.[18] Cleavage of the PMP group in **11** and subsequent Swern oxidation afforded the aldehyde **12**, which was reacted with Eschenmoser's salt[19] followed by N-methylation with iodomethane to furnish the enal **13** in 76% yield. Deprotection of the hydroxylamine moiety in **13** with TFA at 40 °C and subsequent neutralization with pyridine produced the cyclic nitrone, which underwent an intramolecular cycloaddition to give the 2-azabicyclo-[3.3.1]nonane **14** in good yield. The distinct advantage of our novel synthesis of the 2-azabicyclo[3.3.1]nonane skeleton is the stereoselective introduction of the oxygen functionality at C7′.[20,21]

With the requisite intermediate containing the 2-azabicyclo[3.3.1]nonane framework in hand, we then focused on construction of the quaternary stereogenic center and the 13-membered ring (Scheme 3). Hydroboration of the *exo*-methylene moiety from the less hindered face followed by oxidative workup afforded the alcohol **18** as a single diastereomer, which was subjected to Swern oxidation to give the aldehyde **19**.[22] Treatment of **19** with formalin in the presence of potassium carbonate in 1,4-dioxane caused a stereoselective aldol reaction and trapping by formaldehyde to furnish the isolable hemiacetal **20**.[23] Heating **20** in toluene at 100 °C liberated the aldol product, which was protected with a pivaloyl group to afford **21** in 58% yield (two steps). To construct the 13-membered ring, an olefin unit was installed onto the aldehyde moiety in **21** by means of a Julia–Kocienski olefination using **25**.[24] Reductive cleavage of the N−O bond followed by acylation of the resulting secondary amine with **26** yielded **23**. After mesylation of the hydroxy group in **23**,[25] the resulting compound underwent a facile ring-closing metathesis upon treatment with the second-generation Grubbs catalyst in dichloromethane at room temperature, thus giving the desired product **24** with a 13-membered ring.[26]

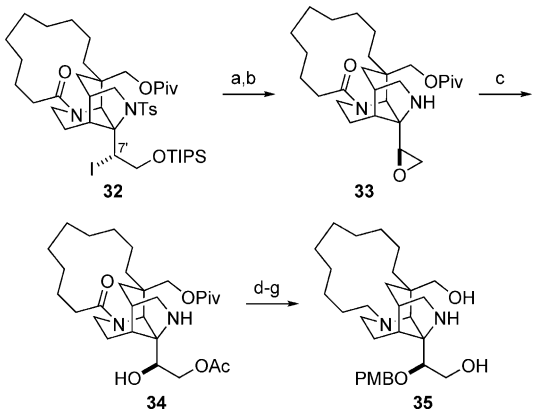
We next tried to construct the pyrrolidine ring using the oxygen functionalities in **24** (Scheme 4). Our initial attempts involved an intramolecular C−H amination reaction at the C3′ position.[27] However, the reaction did not proceed, perhaps because of the steric hindrance around the C3′ position (data not shown). After extensive investigations, we eventually realized that iodoamidation of the double bond formed between C3′ and C7′ effectively constructed the pyrrolidine ring as described below.



Scheme 3. Construction of the quaternary stereogenic center and the 13-membered ring. a) 9-BBN, THF, RT; aq. NaOH, aq. H_2O_2, RT, 89%; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 0 °C, 90%; c) aq. HCHO, K_2CO_3, 1,4-dioxane, RT; d) toluene, 100 °C; PivCl, pyridine, DMAP, 100 °C, 58% (two steps); e) **25**, LHMDS, THF, −78 to 0 °C, 95%; f) Zn, AcOH-Et_2O (1:2), RT; g) **26**, aq. $NaHCO_3$, CH_2Cl_2, 0 °C, 93% (two steps); h) MsCl, $Me_2N(CH_2)_3NMe_2$, CH_2Cl_2, 0 °C to RT, 99%; i) Grubbs II, CH_2Cl_2, RT, 96%. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = 4-(dimethylamino)pyridine, Ms = methanesulfonyl, Piv = pivaloyl, THF = tetrahydrofuran.



Scheme 4. Construction of the pyrrolidine ring. a) TBAF, THF, RT; *t*BuOK, 93%; b) MsCl, iPr_2NEt, CH_2Cl_2, 0 °C; TESOTf; c) NaN_3, DMSO, 90 °C; TBAF, 60 °C, 86% (two steps); d) PivCl, pyridine, DMAP, toluene, 100 °C, 89%; e) H_2 (1 atm), $Pd(OH)_2/C$, AcOH/MeOH (1:19), RT; f) TsCl, aq. $NaHCO_3$, CH_2Cl_2, RT, 90% (two steps); g) TIPSOTf, iPr_2NEt, CH_2Cl_2, 0 °C, 83%; h) **31**, I_2, Cs_2CO_3, CH_2Cl_2, RT, 62%. TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.



Scheme 5. Conversion into Overman's intermediate. a) TBAF, THF, RT, 88%; b) lithium naphthalenide, THF, −78 °C, 91%; c) AcOH, 50 °C; d) TFAA, pyridine, THF, 0 °C; aq. $NaHCO_3$, RT, 79% (two steps); e) PMBOC(=NH)CCl_3, TfOH, CH_2Cl_2, 0 °C, 72%; f) $LiBH_4$, MeOH, THF, 50 °C; g) $LiAlH_4$, $AlCl_3$, Et_2O/THF (14:1), 0 °C to RT, 76% (two steps). PMB = *p*-methoxybenzyl, TFAA = trifluoroacetic anhydride.

Cleavage of the TBDPS group in **24** and subsequent treatment with *t*BuOK induced regio- and stereoselective elimination of the mesyloxy group to form the double bond between C3′ and C7′ position.[28] Under these reaction conditions, the pivaloyl ester was also cleaved to give the diol **27**. Selective introduction of an azide group to the less hindered alcohol and protection of the other alcohol with a pivaloyl group were realized through a three-step sequence. Hydrogenation of **28** over Pearlman's catalyst induced selective saturation of the two disubstituted double bonds, hydrogenolysis of the benzyl group, and reduction of the azide group, to give the amine **29**. Sequential introduction of a tosyl group to the amino group and a TIPS group to the hydroxy group afforded **30**.[29] Upon treatment with 1,3-diiodo-5,5-dimethylhydantoin (**31**) and iodine in the presence of cesium carbonate in dichloromethane at room temperature, 5-*exo* cyclization proceeded stereoselectively to give **32** in 62% yield.[30]

Removal of the TIPS group in **32** with TBAF induced an inversion at C7′ to form an oxirane ring (Scheme 5). After reductive removal of the tosyl group using lithium naphthalenide, the epoxide was cleaved from the less hindered side by heating in acetic acid to give **34**. Thus, the secondary hydroxy group at the C7′ position was stereoselectively introduced. Finally, **34** was converted into Overman's intermediate **35** as follows. Protection of the secondary amine with a trifluoroacetyl group was followed by introduction of a PMB group to the C7′ hydroxy group. After reductive cleavage of the three acyl protective groups, the lactam moiety was reduced with aluminum hydride to furnish **35**. The spectroscopic data of the synthetic sample were identical to those reported.[12c]

In conclusion, we have developed an efficient synthetic route to the tetracyclic skeleton of sarain A, and it features an

intramolecular cycloaddition of an eight-membered cyclic nitrone to construct the 2-azabicyclo[3.3.1]nonane framework and an iodoamidation reaction to form the pyrrolidine ring. This synthesis provides an alternative route to the intermediate in Overman's synthesis of sarain A.

Keywords: alkaloids · cycloaddition · heterocycles · metathesis · natural products

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Angew. Chem. **2015**, *127*, 7475 – 7478

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[20] We initially planned inversion of the stereochemistry at C7′ at a later stage to match that of the natural product.

[21] The isoxazolidine ring formed in the key cycloaddition reaction was strategically left to increase the steric bias for the ensuing formation of the quaternary stereogenic center.

[22] The resulting aldehyde tended to epimerize during purification.

[23] The formation of hemiacetal **20** effectively prevented the Cannizzaro reaction of the aldol product.

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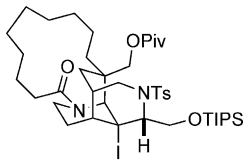
[28] The hydroxy group was likely to work as an internal base to assist the regioselective elimination.

[29] Bulky protecting groups introduced on the hydroxy group at the C8′ position improved the selectivity between 5-*exo* and 6-*endo* cyclization. This might be attributed to the steric repulsion between the amino group and the bulky protecting group on the hydroxy group.

[30] 6-*Endo* cyclization concomitantly occurred to give **36** in 17% yield. The undesired product **36** could be converted back into **30** by treatment with *t*BuLi in THF at −78 °C.



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