Synthesis of the Tricyclic Core of Sarain A. Use of Formaldehyde in an Intramolecular Grigg Azomethine Ylide Cyclization

Derek J. Denhart, David A. Griffith, and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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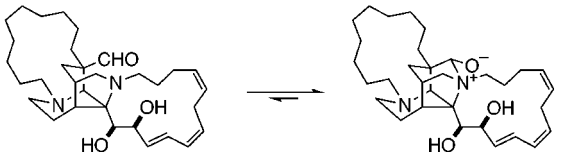
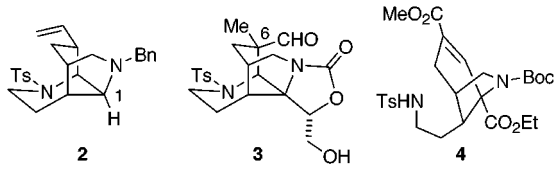
Sarain A (**1**) is an alkaloid first isolated by Cimino and co-workers from a sponge collected in the Bay of Naples.[1] In subsequent work, two congeners having one or two more carbons and a *Z*-double bond in the macrocyclic ring (sarains B and C) were isolated from the same source.[2] The bizarre structure of sarain A has elicited considerable synthetic attention, and two syntheses of the tricyclic core have been recorded, a synthesis of (±)-**2** by Weinreb and co-workers[3] and a recently communicated synthesis of **3** by Overman and co-workers.[4] Our own initial efforts in this direction, previously summarized,[5] reached the stage of intermediate **4**, but we were unable to remove the *N*-tosyl group or cause the nitrogen atom of the sulfonamide to add to the α,β-unsaturated ester. In this paper, we report a revised route that solves these problems.





As shown in Scheme 1, unsaturated amine **7** was prepared by Wittig reaction of phosphorane **5** and aldehyde **6**.[6] This amine was converted into the mixed anhydride with pivalic acid, which was coupled with the *tert*-butylcarbamate derived from monoethyl malonate (**10**), prepared in a straightforward manner from the commercially available diethyl aminomalonate (**8**).[7] The resulting amide **11** was treated with trifluoroacetic acid to remove the *tert*-butoxycarbonyl group and provide primary amine **12**.

In our previous approach to the sarain core, we constructed the 3,9-diazabicyclo[4.3.0]nonane by an intramolecular azomethine ylide cyclization, generating the azomethine ylide by flash vacuum pyrolysis of an aziridine activated by ester and amide carbonyl groups.[4] However, the steps leading to the required aziridine were relatively low-yielding and the flash-vacuum pyrolysis procedure seriously limited throughput. As a result, the previous approach was not ideal for an early step in a lengthy total synthesis. Therefore, we turned to the procedure of Grigg and co-workers,[8] whereby the azomethine ylide is generated by condensation of an α-amino acid derivative with an aldehyde. To this end, amine **12** was treated with paraformaldehyde in refluxing toluene to obtain the bicyclic heterocycle **13** in good yield. For the cyclization, yields of up to 97% have been observed on a small scale, but larger scale seems to result in lower yields. The current best result is 78% on a scale of 7.6 g of starting amine. In all cases, the remainder of the material is a mixture of less polar, olefin-containing products that is presumed to be polymer.

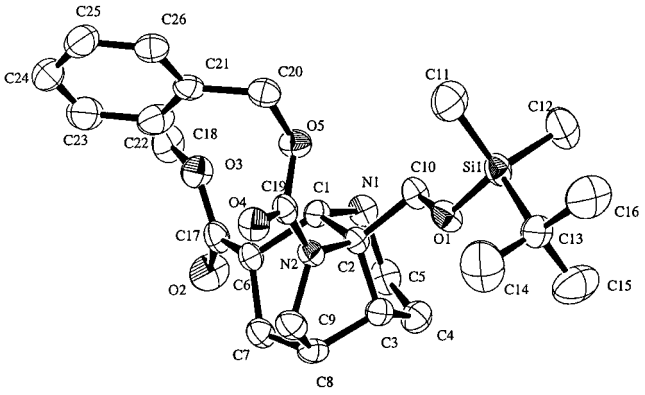


Figure 1. ORTEP structure of compound **23**.

The pyrrolidine nitrogen was benzylated by reaction with benzyl bromide and sodium carbonate, and the angular ester function was then reduced in a two-step process employing diisobutylaluminum hydride, followed by sodium borohydride. The resulting primary alcohol was protected as the *tert*-butyldimethylsilyl ether (**14**). Treatment of **14** with sodium and *tert*-butyl alcohol in liquid ammonia cleanly removed the benzyl groups from the lactam and primary alcohol, leaving the *N*-benzylamine intact. Reaction of this product with triethylsilyl chloride gave **15** in excellent yield. To avoid a previously observed rearrangement,[9] it was necessary to change the pyrrolidine nitrogen protecting group at this point. To this end, the *N*-benzylamine was then cleaved by catalytic hydrogenolysis and the resulting amine was protected as the benzyloxycarbonyl derivative (**16**).

Treatment of lactam **16** with lithium hexamethyldisilazane, followed by *p*-nitrobenzenesulfonyl chloride ("nosyl" chloride), gave the *N*-nosyl derivative. The triethylsilyl group was removed by reaction with camphorsulfonic acid to provide primary alcohol **17**. Methyl ester **18** was prepared by a three-stage process consisting of Moffatt−Swern oxidation,[10] oxidation of the resulting aldehyde with sodium chlorite,[11] and treatment of the resulting carboxylic acid with methyl iodide and potassium carbonate. Treatment of this material with lithium hexamethyldisilazane resulted in clean isomerization to β-keto ester **19**.

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(2) (a) Cimino, G.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *J. Nat. Prod.* **1990**, *53*, 1519. (b) Guo, Y.-W.; Madaio, A.; Scognamiglio, G.; Trivellone, E.; Cimino, G. *Tetrahedron* **1996**, *52*, 8341.

(3) (a) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 3210. (b) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945.

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(5) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. *Synlett* **1995**, 467.

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(8) (a) For a comprehensive review, see: Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. (b) For a similar reaction of a formaldehyde imine, see: Husinec, S.; Savic, V.; Porter, A. E. A. *Tetrahedron Lett.* **1988**, *29*, 6649.

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(10) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

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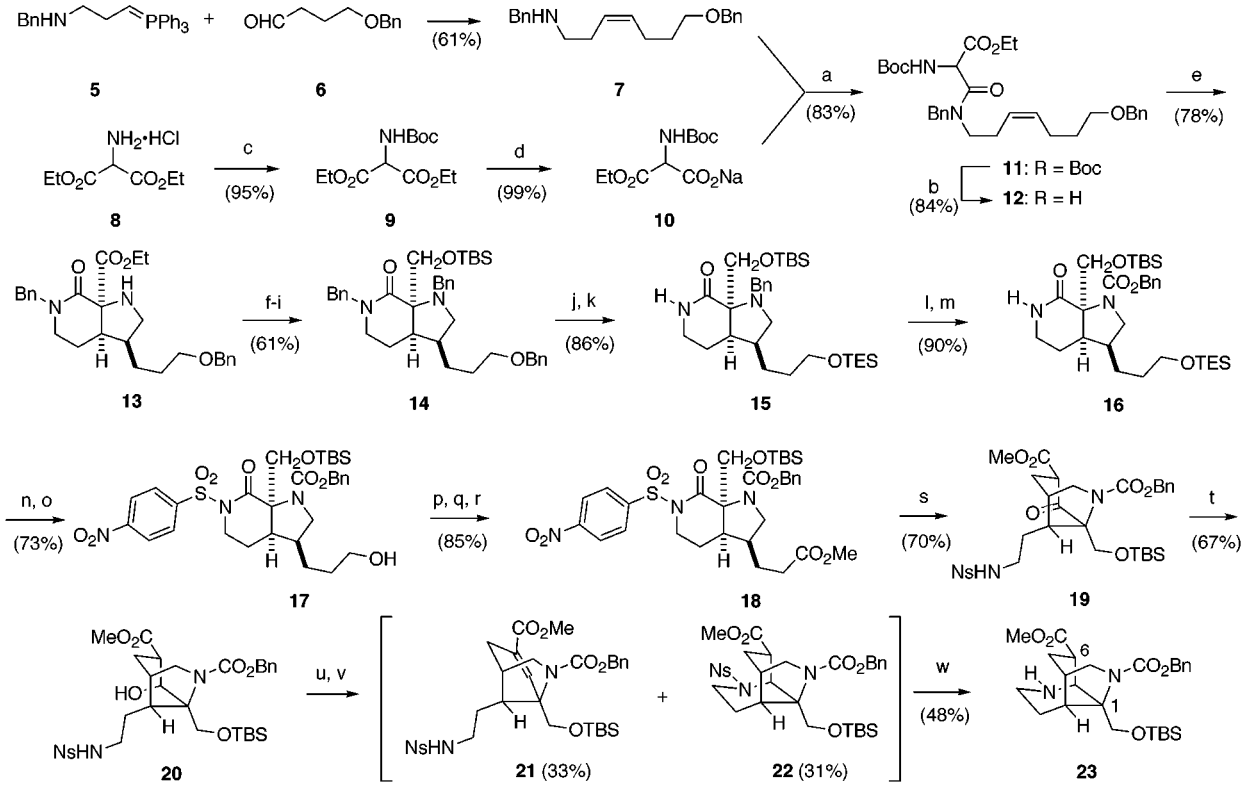
Scheme 1[a]



[a] Key: (a) (i) **10**, pivaloyl chloride, (ii) Et_3N, (iii) **7**; (b) CF_3CO_2H; (c) $(Boc)_2O$; (d) NaOH, EtOH; (e) paraformaldehyde, toluene, reflux; (f) $PhCH_2Br$, Na_2CO_3, CH_2Cl_2, H_2O, EtOH; (g) diisobutylaluminum hydride; (h) $NaBH_4$; (i) TBSCl; (j) Na, *t*-BuOH, NH_3; (k) TESCl; (l) H_2/Pd(OH)$_2$, THF; (m) $PhCH_2O_2CCl$; (n) (i) LiHMDS, THF, (ii) *p*-$NO_2C_6H_4SO_2Cl$; (o) camphorsulfonic acid, H_2O, THF; (p) Moffatt−Swern; (q) $NaClO_2$; (r) MeI, K_2CO_3; (s) LiHMDS, THF; (t) $NaBH_4$, MeOH, CH_2Cl_2; (u) TFAA, pyridine; (v) DBU; (w) PhSH, K_2CO_3, DMF.

Reduction of the ketonic carbonyl was accomplished by reaction with sodium borohydride in methanol−methylene chloride, and the resulting axial secondary alcohol was dehydrated by conversion into the trifluoroacetate, which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to accomplish elimination. This treatment led to an approximately equal mixture of the α,β-unsaturated ester **21**, the desired cyclization product **22**, and alcohol **20**. Treatment of the mixture of **21** and **22** with thiophenol and potassium carbonate in dimethylformamide removed the nosyl group, providing the sarain core, **23**. The structure of **23** was established by single-crystal X-ray analysis (Figure 1).

In summary, we have developed a viable route to the characteristic 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane skeleton of the sarains. Our route is relatively long (22 steps, 1.4% overall yield) and requires rather more protecting group manipulation than we would like.[12] However, the route does have some virtues compared to the previous syntheses of the sarain core. The Weinreb route, similar to ours in accessing the 3,9-diazabicyclo[4.3.0]nonane by an intramolecular azomethine ylide cyclization, provides an intermediate that is not functionalized at C1.[13] The Overman route, which uses a completely different strategy, gives an enantiomerically pure product, but it is a 3:1 mixture at C6, with the undesired diastereomer predominating. We are currently developing a modified route that should deal with the protecting group problems. Our plan is to introduce the less complicated macrocycle by alkylation of the ester enolate, and moledular models suggest that the ester enolate should alkylate exclusively from one face and yield the desired configuration at C5.[14]

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Supporting Information Available: Experimental procedures and spectral data for all compounds and X-ray crystallographic data for compound **23** (26 pages).

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(12) Our route diverges from the Weinreb route in the way that bicyclic lactam **17** is transformed into the tricyclic structure of **23**. In our approach, the six-membered lactam ring is opened by a sort of Dieckman reaction to give the β keto ester **19**. After modification of the functionality, the original six-membered ring is reformed by Michael addition of the pendant aminoethyl group, giving **23**. In the Weinreb approach, construction of the tricyclic system is accomplished directly by addition of a pendant allylsilane to an immonium ion, derived by partial reduction of the lactam carbonyl. In early work we did explore a similar strategy using an aldehyde and the corresponding dioxolane in place of the allylsilane. However, as has been described in ref 5, these attempts failed. It should be noted that the modified approach reported here, although more complicated, is not significantly less efficient—requiring only five steps to convert **18** into ester **23**.

(13) However, in recently completed work, the Weinreb group have succeeded in introducing a one-carbon unit at C1: Irie, O.; Henry, J.; Samizu, K.; Weinreb, S. M. *J. Org. Chem.*, in press.

(14) This anticipation has now been confirmed by Weinreb and coworkers; ref 13.