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Facile Synthesis of the Tricyclic Core of Sarain A. 3-Oxidopyridinium Betaine Cycloaddition Approach[1]

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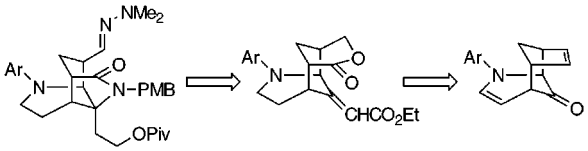
ABSTRACT



A new approach to a suitably functionalized tricyclic core of sarains has been developed by means of Katritzky's cycloaddition using 3-oxidopyridinium betaines. A key step was the regioselective differentiation of the two nearly identical hydroxy groups derived from oxidative cleavage of the double bond in 8 to afford 14. A stereocontrolled construction of the tricyclic core 20 of sarains containing the requisite side chain at C-3′ was achieved by an intramolecular conjugate addition.

A fascinating array of structurally unusual alkaloids is found in marine sponges. Among them are sarains A−C (**1**−**3**), which were isolated by Cimino and co-workers from the sponge *Reniera sarai*.[2a,b] They were reported to exhibit antitumor, antibacterial, and insecticidal activity.[2c] The extraordinary architecture of sarains has attracted considerable synthetic interest.[3] To date, three innovative syntheses of the tricyclic core have been described, along with approaches for attachment of the two macrocyclic rings onto the common 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane nucleus: these previous syntheses involve two independent examples of an intramolecular azomethine ylide cyclization by Weinreb[4] and Heathcock,[5] and also an intramolecular iminium ion cyclization by Overman.[6] Herein we report a concise, stereocontrolled construction of the tricyclic core **2** of sarains containing the requisite side chain at C-3′.

The cornerstone of our synthetic plan was a quick assembly of the central azabicycle of sarains by the [4 + 3] cycloaddition of the six-membered cyclic oxyallyl **6** with cyclopentadiene (Scheme 1). We have previously demonstrated that use of cyclic oxyallyls, i.e., oxyallyls embedded within rings, provides convenient access to medium-sized carbocycles and heterocycles by virtue of the spectator rings.[1d] Particularly attractive is diastereoselective formation of the endo-like cycloadduct **5** which provides a suitable scaffold bearing functionalities necessary for installing the pyrrolidine ring, as well as the side chains at C-3 and C-3′. Central to the successful implementation of the oxyallyl cycloaddition approach toward sarains was the regioselective differentiation of the two nearly identical hydroxy groups in **4** to furnish **3**. An intramolecular conjugate addition

(1) Part 11 in the series of synthetic studies on [4 + 3] cycloadditions of oxyallyls. See the following. (a) Part 10: Lee, K.; Cha, J. K. *Org. Lett.* **1999**, *1*, 523. (b) Part 9: Cho, S. Y.; Lee, J. C.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 3394. (c) Part 8: Lee, J. C.; Jin, S.-j.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804. (d) Part 7: Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217. (e) Part 6: Jin, S.-j.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 10914.

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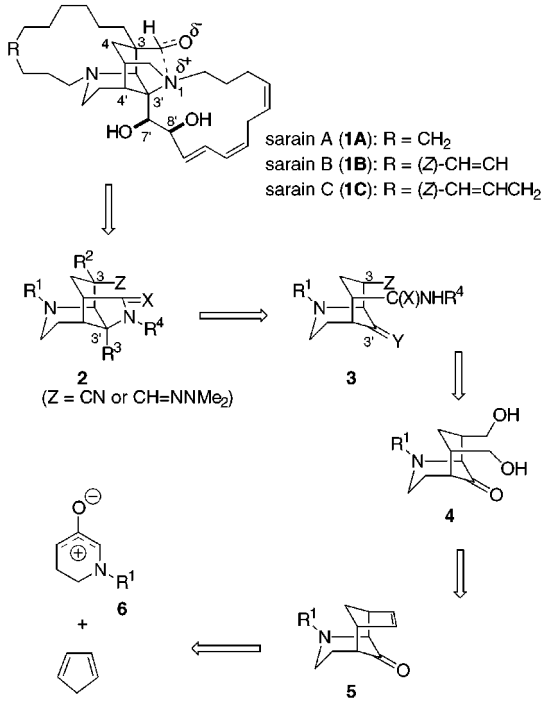
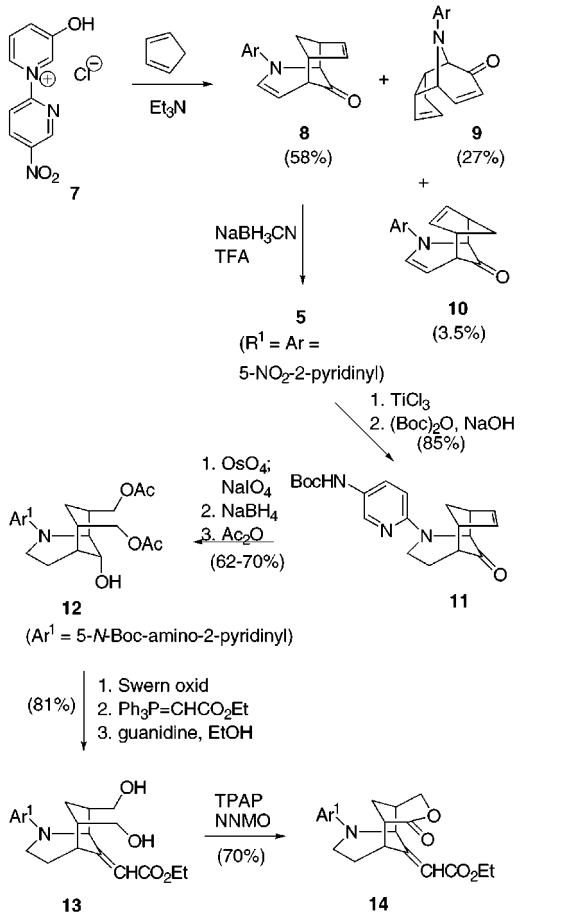
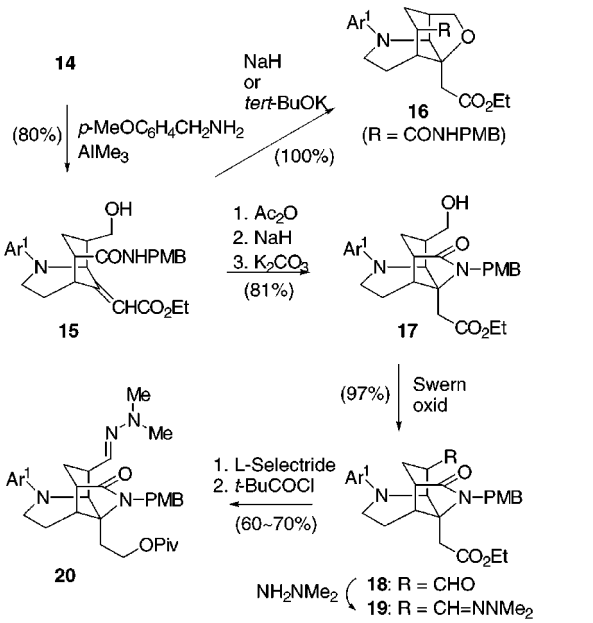
Scheme 1



Scheme 2



Scheme 3



(where Y = α,β-unsaturated ester) or silver(I)-promoted ω-aminoallene cyclization[7] (where X = H_2; Y = allene) of **3** was envisaged for the requisite construction of the pyrrolidine ring.

An ideal starting material was found in the known yet little-explored cycloadduct **8**, which was prepared in large quantities by a slight modification of Katritzky's method using 3-oxidopyridinium betaines (Scheme 2).[8,9] Reduction of **8** with $NaBH_3CN$ gave tricyclic amine **5** in 70% yield. Since 5-nitro-2-pyridine-substituted compounds were found to have poor solubilities in typical organic solvents, the nitro group was first converted to *N*-*tert*-butoxycarbamate **11** (85%), although parallel results were obtained for the corresponding nitro derivatives. By straightforward manipulation of functional groups (i.e., oxidative cleavage of the olefin, followed by reduction with $NaBH_4$ and acetylation) bisacetate **12** was obtained in 62−70% overall yield.[10] Swern oxidation, subsequent Wittig olefination, and deacetylation (guanidine, EtOH) then afforded α,β-unsatured ester **13** in 81% yield. While inconsequential for subsequent transformations, it is interesting to note that the Wittig olefination gave only a single geometrical isomer. Oxidation with TPAP[11]

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(9) By slow addition (via syringe pump) of triethylamine into a mixture of **7** and cyclopentadiene at room temperature, [2π + 4π] endo cycloadduct **8** was obtained in 58% yield, in addition to [4π + 2π] cycloadduct **9** (27%) and [2π + 4π] exo cycloadduct **10** (3.5%). We decided to defer the ultimate regiocontrol to later study.

(10) For convenience, the cyclohexane ring in these bicyclic compounds is drawn in the chair conformation. However, the boat conformer is expected to be most stable, in which the two alkyl groups are equatorial.

afforded lactone **14** (70%) as a single regioisomer; the unequivocal structural determination was secured by ^{1}H−^{1}H COSY (vide infra). Thus, TPAP oxidation provided an excellent means of differentiating the two nearly identical hydroxy groups.[12]

Toward assembly of the pyrrolidine ring (Scheme 3), lactone **14** was converted smoothly to *N*-*p*-methoxybenzyl amide **15** (80%).[13] Treatment of **15** with NaH or potassium *tert*-butoxide resulted in exclusive formation of **16** (quantitative yield); its COSY spectrum clearly shows connectivity of the methine proton at C-2′ (δ 4.63 ppm, J = 4.3 Hz) to the proton (δ 2.62) at C-3, which is in turn coupled to one of −CH_2O− [δ 3.91 (dd) and 3.56 (d)].[12b] Protection of the primary alcohol in **15** as the acetate, followed by treatment with NaH and subsequent deacetylation, afforded the desired pyrrolidinone **17** in 81% yield. *N*,*N*-Dimethylhydrazones **19** and **20** were then prepared in excellent yield via aldehyde **18** by standard methods.

In summary, we have developed a new synthetic approach to a suitably functionalized tricyclic core of sarains by means of Katritzky's cycloaddition using 3-oxidopyridinium betaines. Construction of the western macrocyclic ring involving introduction of the C-3 side chain and also removal of the pyridine moiety is currently underway and will be reported in due course.

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(12) (a) Elucidation of the origin of the observed regiocontrol in TPAP oxidation must await further study. (b) Thus, the alternative regioisomer of **14** was unequivocally excluded as the TPAP oxidation product of **13**.

(13) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 492.