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Studies Towards a Total Synthesis of Sarains A–C. Stereospecific Condensation of α,β-Unsaturated Esters With the Phenyl Oxazoline Derivative of Threonine

Stefan Jaroch[1], Richard T. Matsuoka[2] and Larry E. Overman*

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, CA 92697-2025

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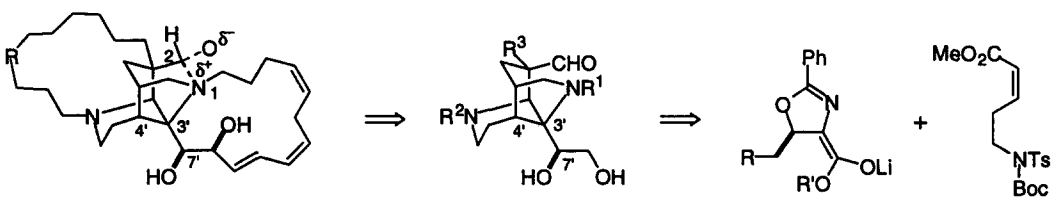
Abstract: Michael addition of oxazoline lithium enolate **5** to *E* and *Z* α,β-unsaturated esters proceeds with high enoate facial selectivity to yield enantiopure oxazoline derivatives of disubstituted glutamic acids. When a *Z* enoate is employed, the C4'–C3'–C7' stereotriad of sarains A–C can be generated.

In 1989, Cimino and coworkers isolated the unusual alkaloid sarain A (**1**) from the Mediterranean sponge *Reniera sarai*.[3] Its most intriguing structural feature is the unique diazatricycloundecane core which has a partial bonding interaction between the C2 aldehyde and N1. Sarain A and congeneric alkaloids **2** and **3** are challenging targets for total synthesis.[4] The first syntheses of the tricyclic core were published by Weinreb[5] and Heathcock[6] who independently used an intramolecular [3+2] azomethine ylide cycloaddition to access a diazabicyclo[4.3.0]nonane precursor. We recently described a quite different strategy which for the first time provided the diazatricycloundecane core of sarains A–C in enantiopure form.[7,8] A salient feature of our approach is to fashion the C4'–C3'–C7' stereotriad, and assemble nearly all of the carbons of core structure **4**, by a bimolecular Michael reaction of an enantiopure oxazoline nucleophile **5** (R = TBDPSO) with (*Z*)-enoate **6**.[7] We describe herein our initial investigations of the Michael reaction of threonine-derived oxazoline salt *ent*-**5** (R = H)[9] with α,β-unsaturated esters which provided the foundation of our approach to **1–3** and also led to a convenient enantiocontrolled synthesis of glutamic acid derivatives bearing side chains at C2 and C3.

Scheme 1



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

4 **5** **6**

The 1,4-addition of threonine-derived oxazoline anion *ent*-**5** (R = H) to conjugated nitroalkenes has been extensively developed by Seebach and co-workers.[9] To access the C4'–C3'–C7' stereotriad of sarains A–C, we investigated extending this Michael addition chemistry to enoate electrophiles.[10] Our initial studies employed α,β-unsaturated esters **8** and **9**, which were readily prepared using standard chemistry (Scheme 2).[11] Addition of the lithium salt of oxazoline **7**[12] to these enoates was efficient and highly diastereoselective (ds > 95:5)[13] when the reaction was carried out in DME at –75 to –65 °C. High diastereoselectivity was also realized

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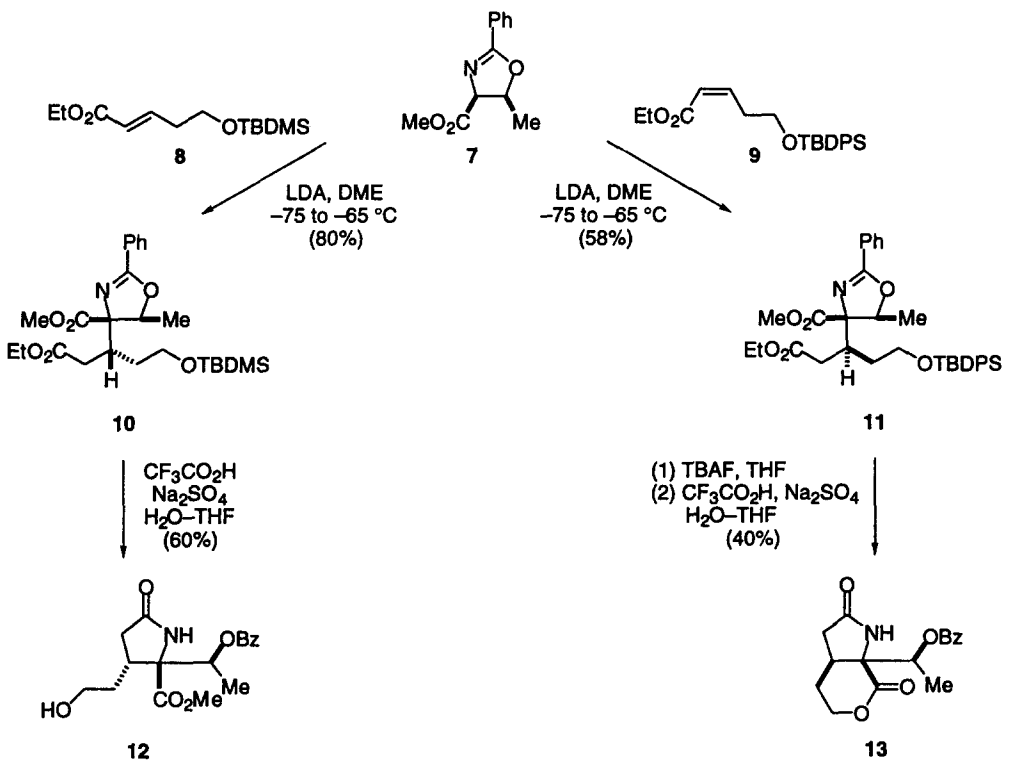
in diethyl ether, however, yields of the Michael addition products were much lower. Acidic hydrolysis[14] of adduct **11**, which was derived from *(Z)*-enoate **9**, gave oxazabicyclononadione **13**; whereas adduct **10** was transformed under identical conditions into pyrrolindinone **12**, which failed to cyclize to a δ-lactone. Since the 2-pyrrolidinone intermediate having a cis relationship of the β-hydroxyethyl and ester functionalities should lactonize more readily than **12**, this disparate behavior upon acid hydrolysis allowed the stereostructures of **10** and **11** to be assigned.[15]

Scheme 2

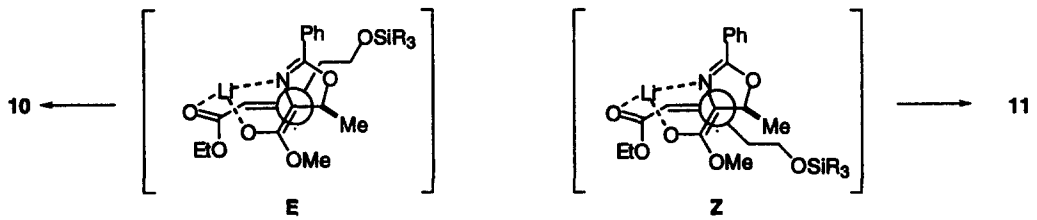


The stereochemical outcome of the 1,4-addition of the lithium salt of **7** with enoates **8** and **9** can be rationalized by considering the putative gauche transition structures **E** and **Z** depicted in Scheme 3.[16] The 5-methyl group of the oxazoline anion shields the β-face, hence, the enoate will approach from the oxazoline α-face.[9] The organizational role ascribed to lithium is supported by the observation that in the presence of HMPA, diastereoselectivity is substantially eroded.

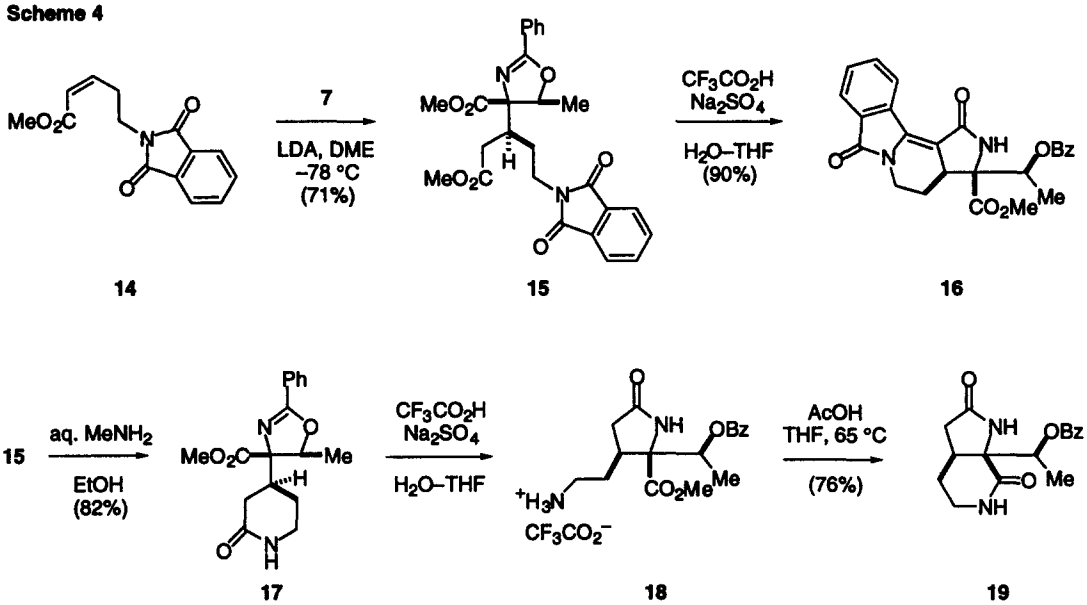
Similar high diastereoselectivity was seen in the reaction of the lithium salt of **7** with (*Z*)-enoate **14**[17] which provided **15** in 71% yield (Scheme 4).[13] Exposure of **15** to aqueous trifluoroacetic acid[14] triggered a reaction cascade involving oxazoline hydrolysis, γ-lactam formation, and lactam–imide condensation to deliver tetracycle **16** in 90% yield. In order to circumvent the lactam–imide condensation, we first removed the phthalimido group which provided oxazoline piperidone **17** in 82% yield.[18] Finally, exposure of this

intermediate to aqueous trifluoroacetic acid[14] generated 2-pyrrolidinone **18**, which upon heating in 5:1 THF-acetic acid cyclized to furnish diazabicyclononanedione **19** in 76% overall yield.

Scheme 3



Scheme 4



In summary, 1,4-addition of the lithium salt of threonine-derived oxazoline **7** to *E* and *Z* α,β-unsaturated esters proceeds with high enoate face selectivity to yield oxazoline derivatives of glutamic acids having side chains at carbons 2 and 3. Condensation with a *Z* enoate provides products containing the C4'–C3'–C7' stereotriad of the complex sarain alkaloids, and this strategy was recently employed to prepare the diazatricycloundecane core **4** of sarains A–C.[7] As exemplified by tetracycle **16** and diazabicyclononanedione **19**, it should be possible to access a variety of enantiopure nitrogen heterocycles from the highly functionalized glutamic acid derivatives reported here.

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References and Notes.

(1) Current address: Institute of Medicinal Chemistry, Preclinical Drug Research, Schering AG, D-13342 Berlin, Germany.

(2) Current address: Department of Synthetic Chemistry, SmithKline Beecham, 709 Swedeland Rd., Box 1539, King Of Prussia, PA 19406.

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(7) Downham, R.; Ng, F. W.; Overman, L. E. *J. Org. Chem.* **1998**, *63*, 8096.

(8) The study described in reference 7 was carried out in the *ent* series. For clarity it is depicted in the natural series in Scheme 1.

(9) (a) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311. (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592.

(10) Since C-5 of oxazoline **7** possesses the *S* configuration, these model studies were also in the series enantiomeric to the natural sarain alkaloids.

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(12) Oxazoline **7** was prepared by treatment of methyl *N*-benzoyl-(L)-threoninate with thionyl chloride: Elliot, D.F. *J. Chem. Soc.* **1950**, 62.

(13) Only one stereoisomer was detected by ^{1}H NMR analysis.

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(15) The stereochemical assignment for **11** is strengthened by single crystal X-ray analysis of the intermediate derived from a related oxazoline–*Z* enoate condensation *en route* to **4**.[7]

(16) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

(17) Enoate **14** was obtained by addition of phthalimide to acrolein (Taber, D. F.; Hoerrner, R. S.; Hagen, M. D. *J. Org. Chem.* **1991**, *56*, 1287) followed by reaction with methyl [bis(2,2,2-trifluoroethyl)phosphono]acetate (Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405).

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