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Total Synthesis of the Tetracyclic Antimalarial Alkaloid (±)-Myrioneurinol**

*Anthony J. Nocket and Steven M. Weinreb**

Abstract: *The first total synthesis of the tetracyclic antimalarial Myrioneuron alkaloid (±)-myrioneurinol has been accomplished using three highly diastereoselective reactions as pivotal steps: 1) an intramolecular Michael addition of a benzyloxycarbonyl-protected lactam titanium enolate to an α,β-unsaturated ester for construction of the spirocyclic C5 quaternary center and the a/d rings, 2) a malonate anion conjugate addition to a transient nitrosoalkene to install the requisite functionality and configuration at the C7 position, and 3) an intramolecular sulfonyliminium aza-Sakurai reaction to form the b ring and the attendant C9/C10 configuration of the natural product.*

The *Nitraria* and *Myrioneuron* alkaloids are two biogenetically related lysine-derived classes of plant metabolites.[1] In 2007, Pham, Bodo, and co-workers reported the isolation and structure determination of myrioneurinol (**1**), a new tetracyclic *Myrioneuron* alkaloid found in the leaves of the Southeast Asian plant *Myrioneuron nutans* (family Rubiaceae), a small tree indigenous to northern Vietnam.[2,3] The structure of this metabolite was established by detailed spectroscopic analysis, in particular 2D NMR spectroscopy. This interesting alkaloid contains a tightly fused, rigid array of chair six-membered rings, including a 1,3-oxazine moiety, along with five stereogenic centers (Figure 1). The absolute configuration of **1** was deduced to be as indicated using a modified Mosher ester analysis. Myrioneurinol was found to have weak cytotoxic activity against KB cells, but showed significant antimalarial activity against *Plasmodium falciparum*.

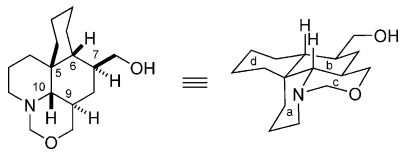

Figure 1. Structure and conformation of myrioneurinol (**1**).

[*] A. J. Nocket, Prof. Dr. S. M. Weinreb
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802 (USA)
E-mail: smw@chem.psu.edu

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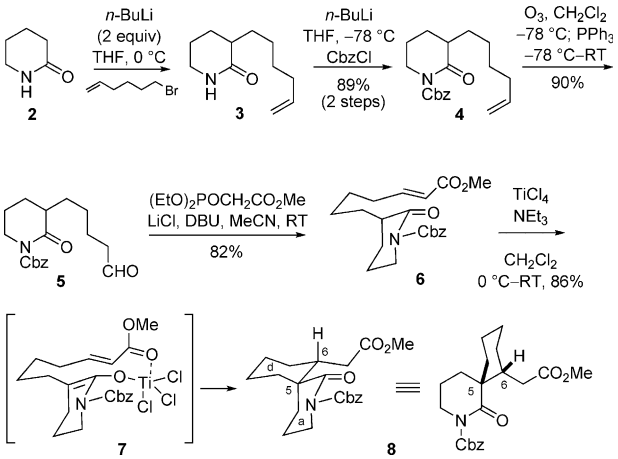
A substantial amount of synthetic work has appeared on various members of the *Nitraria* group of alkaloids.[4] However, relatively little has been done on the synthesis of the *Myrioneuron* alkaloids, and to date, these studies have involved the simpler members of the class.[3,5] In view of the fascinating structure and biological activity of myrioneurinol, we became interested in this metabolite. In this communication, we now describe the first total synthesis of racemic myrioneurinol (**1**).

Our synthetic strategy was predicated upon effecting the initial construction of the spirocyclic a/d ring unit with the attendant C5 (quaternary) and C6 configuration by a pivotal intramolecular Michael reaction.[6,7] To prepare the requisite substrate for this proposed transformation, valerolactam (**2**) was first converted into the dianion and C-monoalkylated with 6-bromohex-1-ene to produce lactam **3** (Scheme 1).[8] This compound was then N-acylated to form benzyloxycarbonyl-protected lactam **4**. Subsequent ozonolysis of alkene **4** led to aldehyde **5**, which was subjected to a Wadsworth–Emmons–Horner reaction to yield (*E*)-α,β-unsaturated ester **6**.

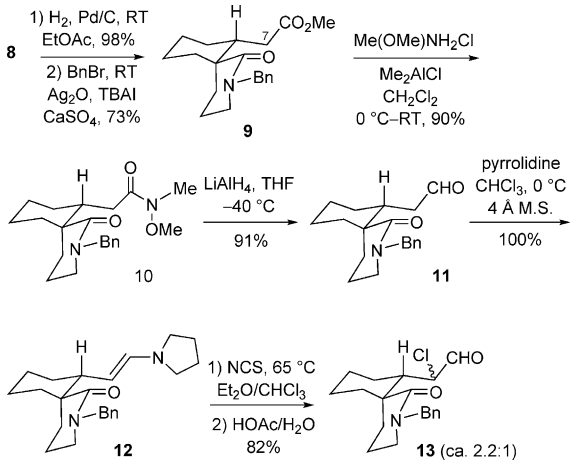


Scheme 1. Diastereoselective intramolecular Michael reaction to form the spirocyclic a/d ring system of myrioneurinol. Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

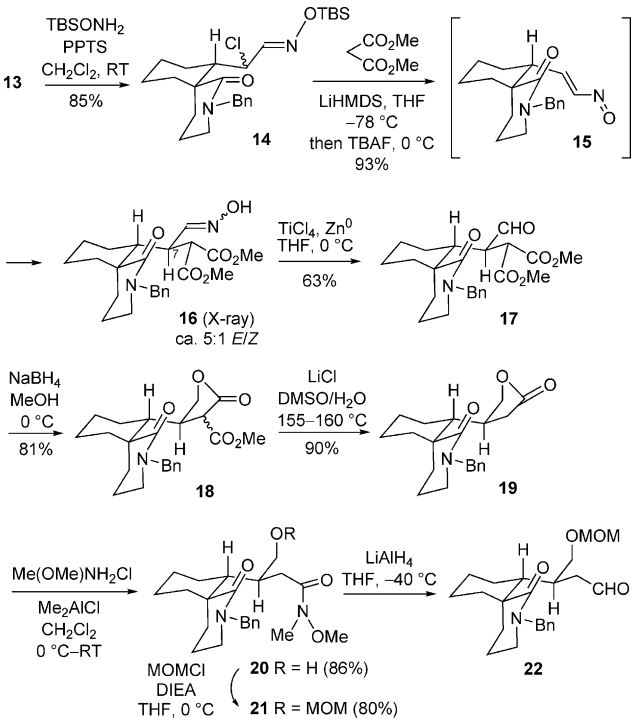
A number of experimental conditions were then screened in attempts to promote the key intramolecular Michael reaction.[9] It was ultimately found that soft enolization of substrate **6** with titanium tetrachloride/triethylamine led to the desired spirocycle **8** in high yield as a single stereoisomer.[10] We believe that this cyclization probably occurs via a chelated titanium enolate such as **7**, which undergoes

a conjugate addition to afford the spirocycle with the desired C5/C6 configuration for myrioneurinol.[11] The structure and configuration of **8** were eventually confirmed by X-ray analysis of a later intermediate (see below).

As the Cbz group on **8** proved to be labile, it was replaced by a more robust benzyl group, leading to lactam ester **9** (Scheme 2).[12] At this juncture, considerable effort was



Scheme 2. Conversion of spirocyclic ester **8** into α-chloroaldehyde **13**. Bn = benzyl, M.S. = molecular sieves, TBAI = tetrabutylammonium iodide.



Scheme 3. Synthesis of aldehyde **22** from α-chloroaldehyde **13** by a diastereoselective nitrosoalkene alkylation. DIEA = diisopropylethylamine, HMDS = hexamethyldisilazane, MOM = methoxymethyl, PPTS = pyridinium 4-toluenesulfonate, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

expended on attempting to alkylate ester **8** at the C7 position with the goal of eventually forming the b ring of the alkaloid. Inexplicably, however, we have been unable to form an enolate from this ester. Thus, it became necessary to develop an alternative strategy for homologation of the system at the C7 position.

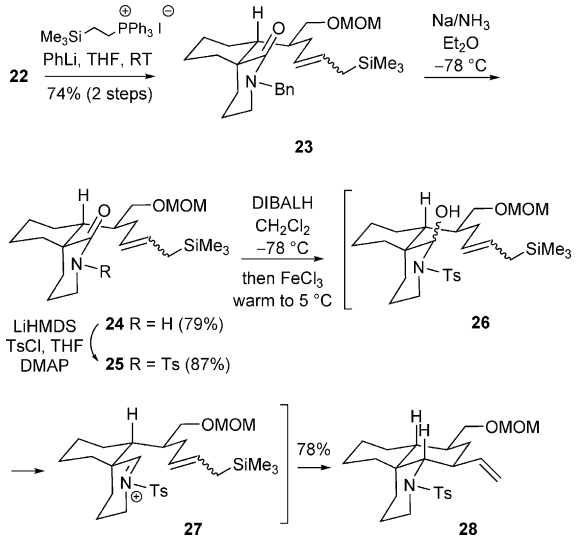
It was possible to convert ester **9** directly into *N*-methoxy-*N*-methylamide **10** using our aluminum-mediated procedure,[13] and subsequent reduction with lithium aluminum hydride led to aldehyde **11**.[14] Treatment of this aldehyde with pyrrolidine provided enamine **12** in high yield.[15] Despite many attempts, we have been unable to effect a Michael reaction of this enamine with acrylates or related electrophiles, and **12** could not be C-acylated with acid chlorides. In all of these cases, the enamine appeared to be unreactive. It was found, however, that enamine **12** did react with *N*-chlorosuccinimide and underwent subsequent acidic hydrolysis to afford α-chloroaldehyde **13** as a 2.2:1 mixture of diastereomers.[16]

With this chloroaldehyde in hand, we decided to explore the possibility of effecting a C7 "umpolung" alkylation through a conjugate addition of a carbon nucleophile to a nitrosoalkene derived from this intermediate.[17] Thus, using a method we recently described,[18] compound **13** was first transformed into the O-TBS-protected oxime **14** (Scheme 3). Treatment of this compound with the lithium enolate of dimethyl malonate at −78 °C, followed by the addition of tetra-*n*-butylammonium fluoride and warming to 0 °C led to the desired C7 alkylation product **16** in excellent yield as an approximately 5:1 mixture of isomers. Pure samples of each isomer could be isolated by partial crystallization, and the structures were individually determined by X-ray analysis.

We were pleased to find that both compounds have the desired C7 configuration needed for myrioneurinol and are simply aldoxime *E*/*Z* geometric isomers. It seems reasonable that this alkylation occurs by conjugate addition of the malonate anion to the least hindered face of the transient nitrosoalkene conformer depicted in **15**. However, at this point, we cannot rationalize why this should be the reactive conformation of the intermediate.

The next stage of the synthesis was to investigate the application of an intramolecular aza-Sakurai reaction to form the b ring and the remaining C9/C10 stereogenic centers of the alkaloid. Towards this end, the mixture of oximes **16** was cleaved, and the resulting aldehyde **17** was reduced, leading to α-carbomethoxylactone **18**. This product was then subjected to a Krapcho decarboxylation[19] to afford butyrolactone **19**. Opening of the lactone with *N*,*O*-dimethylhydroxylamine hydrochloride/dimethylaluminum chloride[13] yielded amide alcohol **20**, which was protected as methoxymethyl ether **21**, and subsequent reduction of the amide with lithium aluminum hydride then produced aldehyde **22**.[14]

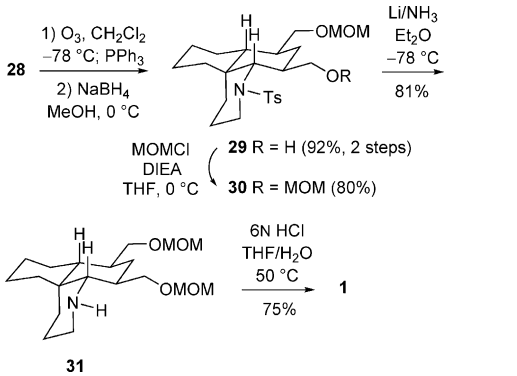
Wittig olefination of this aldehyde with the Seyferth silylethyl ylide[20] provided allylsilane **23** as an inconsequential *E*/*Z* mixture (Scheme 4). Removal of the *N*-benzyl group of lactam **23** with Na/NH_3 provided NH lactam **24**, and subsequent installation of a tosyl group afforded *N*-sulfonyl lactam **25**.



Scheme 4. Intramolecular aza-Sakurai reaction. DIBALH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, Ts = *para*-toluenesulfonyl.

The proposed aza-Sakurai reaction was then addressed, and it was found that conditions that we had previously applied to effect a related cyclization worked well here.[21] Thus, partial reduction of *N*-tosyl lactam **25** with diisobutylaluminum hydride at low temperature to afford intermediate **26**, followed by addition of ferric chloride and slow warming to approximately 5 °C gave tricycle **28** as a single stereoisomer in good yield. This compound has been assigned the configuration shown based upon its subsequent conversion into myrioneurinol (see below). This transformation probably proceeds via *N*-sulfonyliminium ion/allylsilane **27**, formed by $FeCl_3$-promoted elimination of **26**, which cyclizes through the chair-like conformation with the allylsilane moiety quasi-equatorial as shown, leading to the configuration observed in **28**.

To complete the total synthesis, the vinyl group of tricycle **28** was cleaved by ozonolysis, and the intermediate aldehyde was immediately reduced, giving alcohol **29** (Scheme 5). This alcohol was next converted into the bis(methoxymethyl)-protected ether **30**, and the sulfonamide was removed with Li/NH_3 to afford tricyclic amine **31**. Finally, exposure of compound **31** to aqueous HCl at 50 °C led to hydrolytic cleavage of one of the methoxymethyl groups and concomitant cyclization of the other to form the 1,3-oxazine ring, producing racemic myrioneurinol (**1**). This material had proton and carbon NMR spectra identical to those of the natural alkaloid.[22]



Scheme 5. Completion of the myrioneurinol total synthesis.

In conclusion, we have accomplished a total synthesis of the tetracyclic antimalarial *Myrioneuron* alkaloid (±)-myrioneurinol (**1**) using three highly diastereoselective reactions as the pivotal steps: an intramolecular Michael addition of a benzyloxycarbonyl-protected lactam titanium enolate to an α,β-unsaturated ester for construction of the spirocyclic a/d ring system and the C5/C6 relative configuration, a conjugate addition of a malonate enolate to a nitrosoalkene to install the requisite functionality and configuration at the C7 position, and an intramolecular sulfonyliminium-variant of the Sakurai reaction to form the b ring and the attendant C9/C10 configuration of the metabolite.

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[1] For a good review, see: E. Gravel, E. Poupon, *Nat. Prod. Rep.* **2010**, *27*, 32.
[2] V. C. Pham, A. Jossang, T. Sevenet, V. H. Nguyen, B. Bodo, *Tetrahedron* **2007**, *63*, 11244.
[3] Two related but much simpler tricyclic alkaloids, myrioxazines A and B, which also contain a 1,3-oxazine ring, have been isolated from the same plant; see: V. C. Pham, A. Jossang, A. Chiaroni, T. Sevenet, B. Bodo, *Tetrahedron Lett.* **2002**, *43*, 7565.
[4] For lead references to the existing synthetic studies on *Nitraria* alkaloids, see Ref. [1] and: a) M. J. Wanner, G.-J. Koomen, *J. Org. Chem.* **1994**, *59*, 7479; b) D. Francois, M.-C. Lallemand, M. Selki, A. Tomas, N. Kunesch, H.-P. Husson, *Angew. Chem. Int. Ed.* **1998**, *37*, 104; *Angew. Chem.* **1998**, *110*, 112; c) Y. Park, Y. J. Lee, S. Hong, M. Lee, H.-G. Park, *Org. Lett.* **2012**, *14*, 852, and references cited therein.
[5] a) V. C. Pham, A. Jossang, A. Chiaroni, T. Sevenet, V. H. Nguyen, B. Bodo, *Org. Lett.* **2007**, *9*, 3531; b) V. C. Pham, A. Jossang, P. Grellier, T. Sevenet, V. H. Nguyen, B. Bodo, *J. Org. Chem.* **2008**, *73*, 7565; c) A. J. M. Burrell, I. Coldham, N. Oram, *Org. Lett.* **2009**, *11*, 1515; d) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram, N. G. Martin, *J. Org. Chem.* **2009**, *74*, 2290.
[6] For a review on intramolecular Michael reactions, see: R. D. Little, M. R. Masjedizadeh, O. Wallquist, J. I. McLoughlin, *Org. React.* **1995**, *47*, 315.
[7] For a related spirocyclization through an aldol process in an approach to *Nitraria* alkaloids, see: a) M. J. Wanner, G. J. Koomen, *Tetrahedron* **1992**, *48*, 3935; b) M. J. Wanner, G. J. Koomen, *Pure Appl. Chem.* **1994**, *66*, 2239.
[8] K. T. Potts, T. Rochanapruk, *J. Org. Chem.* **1995**, *60*, 3795.
[9] We are grateful to Yiqing Feng for conducting some preliminary experiments on this reaction.
[10] D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, Y. Kato, *J. Org. Chem.* **1991**, *56*, 5750.
[11] An example of a chelation-controlled intramolecular Michael reaction has been reported; see: M. Ihara, M. Toyota, K.

Fukumoto, T. Kametani, *Tetrahedron Lett.* **1984**, *25*, 3235; for the formation of a related all-carbon spirocycle, see: J. d'Angelo, C. Ferroud, *Tetrahedron Lett.* **1989**, *30*, 6511.
[12] It should be noted that the *N*-benzyl lactam analogous to substrate **6** underwent a diastereoselective intramolecular Michael reaction but only in low yield. Furthermore, attempts to effect the spirocyclization with a substrate incorporating a C7 substituent were not fruitful.
[13] J. I. Levin, E. Turos, S. M. Weinreb, *Synth. Commun.* **1982**, *12*, 989.
[14] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
[15] G. Bélanger, M. Doré, F. Ménard, V. Darsigny, *J. Org. Chem.* **2006**, *71*, 7481.
[16] C. W. Seufert, F. Effenberger, *Chem. Ber.* **1979**, *112*, 1670.
[17] For reviews on nitrosoalkenes, see: a) T. L. Gilchrist, *Chem. Soc. Rev.* **1983**, *12*, 53; b) I. M. Lyapkalo, S. L. Ioffe, *Russ. Chem. Rev.* **1998**, *67*, 467.
[18] a) P. Li, M. M. Majireck, J. A. Witek, S. M. Weinreb, *Tetrahedron Lett.* **2010**, *51*, 2032; b) J. A. Witek, S. M. Weinreb, *Org. Lett.* **2011**, *13*, 1258.
[19] A. P. Krapcho, E. Ciganek, *Org. React.* **2013**, *81*, 1.
[20] D. Seyferth, K. R. Wursthorn, T. F. O. Lim, *J. Organomet. Chem.* **1979**, *181*, 293.
[21] S. Hong, J. Yang, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 2078, and references cited therein.
[22] We thank Professor B. Bodo and Dr. Van Cuong Pham for copies of the proton and carbon NMR spectra of natural myrioneurinol (**1**; see the Supporting Information).

