Symmetry-Driven Total Synthesis of Myrioneurinol

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ABSTRACT: We report a total synthesis of the *Myrioneuron* alkaloid myrioneurinol enabled by the recognition of hidden symmetry within its polycyclic structure. Our approach traces myrioneurinol's complex framework back to a symmetrical diketone precursor, a double reductive amination of which forges its central piperidine unit. By employing an inexpensive chiral amine in this key desymmetrizing event, four stereocenters of the natural product including the core quaternary stereocenter are set in an absolute sense, providing the first asymmetric entry to this target. Other noteworthy strategic maneuvers include utilizing a bicyclic alkene as a latent *cis*-1,3-bis(hydroxymethyl) synthon and a topologically controlled alkene hydrogenation. Overall, our synthesis proceeds in 18 steps and ~1% yield from commercial materials.

The *Myrioneuron* alkaloids are a relatively small class of polycyclic natural products isolated from various plants of the *Myrioneuron* genus (e.g., **1**–**6**, Figure 1A). Despite their limited number, these alkaloids display a range of bioactivities, including antimalarial, antiviral, and cytotoxic properties.[1] Biosynthetically, they are thought to originate from the combination of various lysine-derived units, resulting in a diverse array of structures containing a core decahydroquinoline framework fused to oxazine, diazine, or cyclohexane rings arranged in interlocked chair-like conformers.[1] Their challenging structures coupled with their biological properties have attracted the interest of synthetic chemists. Several simpler bi- and tricyclic members (e.g., **1**) were prepared by Bodo and coworkers[2] and others,[3] while efforts toward more complex members have proven rarer. Recent elegant syntheses of myrifabrals A and B (**5**–**6**) by She[4] and Stoltz,[5] and that of myrioneurinol (**2**) by Weinreb have begun to address this challenge.[6]

In continuation of our interest in alkaloid total synthesis,[7] we were drawn to myrioneurinol (**2**) as arguably one of the most structurally complex non-dimeric *Myrioneuron* alkaloids. This compound was isolated by Bodo and coworkers in 2007 and shown to display moderate antimalarial activity as well as weak inhibition of KB cell proliferation.[8] As noted above, this target was prepared in racemic form by the Weinreb group in 2014 utilizing a strategy built around two key Michael reactions – a spirocyclization and malonate nitrosoalkene addition – and a late-stage intramolecular Sakurai reaction to provide (±)-**2** in 27 steps (Figure 1B).[6] As we were finalizing our manuscript, Ma and coworkers reported a more step economical approach to (±)-**2** via an intramolecular [2+2] cycloaddition/retro-Mannich/Mannich approach in 14 steps from (6-iodohex-1-ynyl)trimethylsilane.[9,10] Herein, we report a distinct total synthesis of myrioneurinol enabled by the recognition of

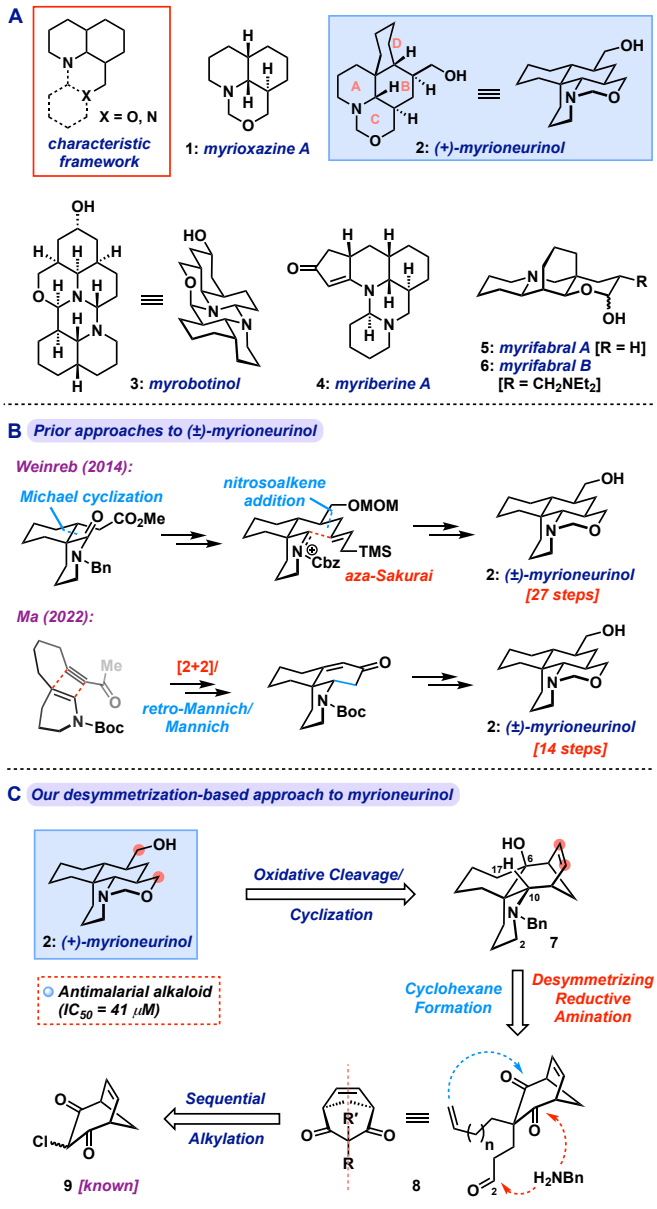


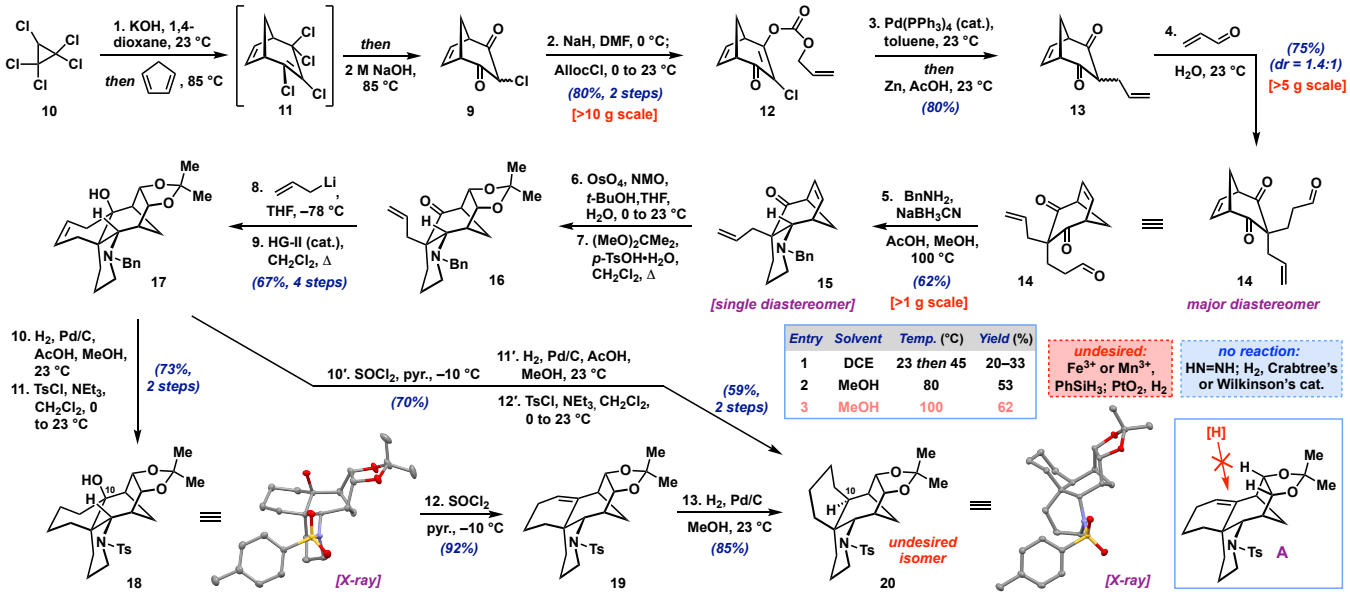
Figure 1. A. Representative *Myrioneuron* alkaloids. ***B.*** Prior racemic total syntheses of myrioneurinol (**2**). **C.** Our symmetry-driven approach to myrioneurinol.

hidden symmetry within its complex framework, leveraging this strategy to provide the first asymmetric entry to this target.

Key challenges in accessing **2** revolve around construction of its tetracyclic array of fused piperidine, oxazine, and cyclohexane rings with proper stereocontrol at its five stereogenic centers, including one core quaternary center. We planned to employ a desymmetrization approach to construct much of the complexity of **2** from a symmetrical precursor. Desymmetrization-based strategies can greatly expedite the synthesis of complex targets by simultaneously setting many stereocenters from prochiral or *meso*-substrates.[11] Such processes can either exploit local symmetry to allow for the use of simplified synthetic fragments or break symmetry within a fully symmetrical precursor, and have been utilized in alkaloid total synthesis.[12] These strategies become even more enabling when the synthetic target does not possess any inherent symmetrical elements and 'hidden symmetry' is unveiled by judicious retrosynthetic disconnection back to a symmetrical precursor.

Our approach to myrioneurinol (**2**), which does not possess an obvious plane of symmetry, is outlined retrosynthetically in Figure 1C. The oxazine ring of **2**, incorporating one of the two *cis*-hydroxymethyl units, might arise from oxidative cleavage and subsequent cyclization of a bicyclic alkene **7**. Disconnecting both the C_6–C_{17} bond of the D-ring and the C_2–N/C_{10}–N bonds of the piperidine A-ring of **7** leads back to a relatively simple symmetrical diketo aldehyde **8**. Bicycle **8** presents an opportunity for a key desymmetrizing double reductive amination onto the C-2 aldehyde and one of the two prochiral ketones to forge the piperidine A ring, leaving the remaining ketone available for a subsequent carbocyclic ring construction. It was unclear at the outset of our studies, however, whether such a process would occur with the desired diastereoselectivity in this complex bicyclic setting,[13] or how attainable an enantioselective version of the crucial desymmetrization might be.[14] Nonetheless, given that diketone **8** should arise via sequential alkylation of known chlorodiketone **9**,[15] we reasoned that these questions could be probed without significant initial investment.

Our synthesis began with the preparation of decagram quantities of **9** from commercial pentachlorocyclopropane **10** through a known[15] one-pot process involving initial HCl elimination to the cyclopropene, Diels–Alder reaction with cyclopentadiene and cyclopropane ring-opening to give **11**, and subsequent basic hydrolysis (Scheme 1). Although initial attempts at conversion of **9** to allyldiketone **13**, including dechlorination/monoallylation or Claisen rearrangement-based approaches, were plagued by poor selectivity and low yields, we ultimately found that a decarboxylative Tsuji–Trost allylation provided a scalable means to access **13**.[16] Thus, crude **9** was converted to *O*-Alloc derivative **12** in 80% yield (over 2 steps), followed by decarboxylative *C*-allylation with catalytic $Pd(PPh_3)_4$ to give an intermediate 2-chloro-2-allyldiketone that could be dechlorinated by addition of Zn and AcOH to the same reaction vessel. With robust access to multigram quantities of **13**, a mild Michael addition to acrolein delivered key tricarbonyl precursor **14** in 75% yield, albeit in moderate dr (1.4:1) favoring our desired diastereomer (despite significant attempts at improvement, see SI for full details).



Scheme 1. Synthesis of tetracyclic alkene **19** via desymmetrizing double reductive amination and its attempted stereoselective hydrogenation.

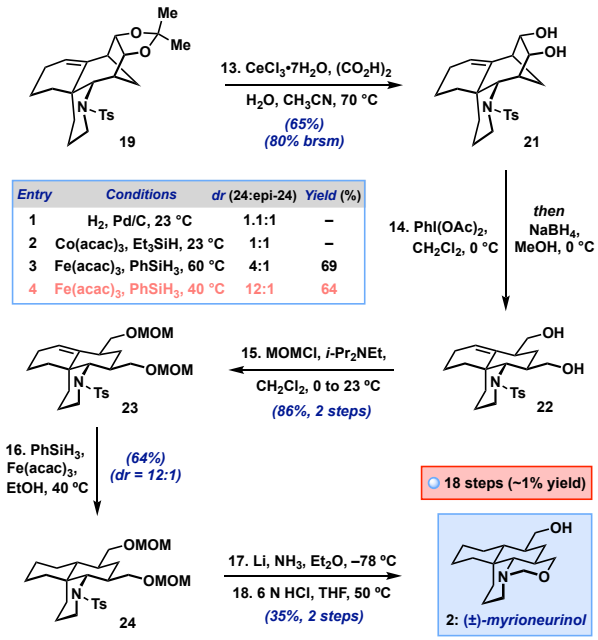
With an inseparable epimeric mixture of diketo aldehyde **14** in hand, we were poised to investigate the key desymmetrizing double reductive amination. Initially, we elected to pursue the transformation racemically using benzylamine, and preliminary screens identified $NaBH_3CN$ and AcOH as the optimal reductant and acid promoter, respectively. Through multiple screens (see selected results in the inset table in Scheme 1), we identified high temperature (100 °C) as the most impactful parameter for the success of this transformation; reaction monitoring by ^1H NMR showed the first reductive amination of the aldehyde to occur essentially instantaneously at room temperature, with the second reductive cyclization onto the hindered ketone requiring high temperature to proceed efficiently. Ultimately, we could access tricyclic amine **15** in 62% yield as a single diastereomer on gram-scale. This transformation constructs the piperidine A-ring with the correct relative configuration (initially confirmed by NOE studies) for myrioneurinol (**2**) and provides an opportunity to remove the minor aldehyde diastereomer, which likewise delivers a separable piperidine product as a single diastereomer (not shown).

Next, chemoselective dihydroxylation of the strained bicyclic alkene followed by acetonide protection produced a masked diol **16** as a single diastereomer, setting the stage for a later oxidative cleavage. Attempted allylation of ketone **16** proved surprisingly difficult with many common allylation protocols, including Grignard, organoboron, and organolanthanide nucleophiles, failing to engage this hindered carbonyl. Ultimately, this step was only successfully achieved through the use of excess (10 equiv) allyllithium, cleanly providing a single diastereomer of the allyl adduct (not shown). This crude diene was subjected to ring-closing metathesis (RCM) with Hoveyda–Grubbs Second Generation (HG-II) catalyst,[17] delivering pentacyclic alkene **17** in 67% yield over the 4 steps from **15** with only a single chromatographic purification being required. At this stage, the superfluous alkene could be hydrogenated (H_2, Pd/C, AcOH, MeOH) with concomitant hydrogenolysis of the *N*-Bn group. Reprotection of the crude secondary amine as a more tractable *N*-tosylamide gave a compound (**18**) whose relative configuration could be confirmed through X-ray crystallographic analysis.

At this stage, the final C-10 stereocenter of **2** could be addressed. Overall, this required a deoxygenation of the tertiary alcohol **18** with retention of configuration. While Barton–McCombie conditions failed due to our inability to derivatize this hindered hydroxyl, a simple workaround involved elimination to the alkene **19** with $SOCl_2$/pyridine (92%) followed by alkene hydrogenation (85%) to give a single diastereomer of saturated product **20**, at this stage of unknown configuration. Noting the prior hydrogenation in the sequence, we were able to execute a shorter sequence involving earlier elimination of **17** to its corresponding diene (not shown, 70%), which could similarly undergo hydrogenation/debenzylation and *N*-tosyl protection (59%, 2 steps) to deliver the same reduction product (**20**). Unfortunately, X-ray crystallography at this stage confirmed that the obtained diastereomer bore a C-10 configuration opposite to that of myrioneurinol. Further attempts to invert the stereoselectivity through a variety of hydrogen atom-transfer (HAT), homogeneous, and heterogeneous catalytic hydrogenations of **19** yielded solely this undesired diastereomer (**20**). We attribute this outcome to steric hindrance from the nearby bridged system (see inset **A**, Scheme 1).

Since this bicyclic substructure was ultimately not required for myrioneurinol (**2**), we sought to alleviate this steric issue by cleaving the bridging system prior to alkene hydrogenation (Scheme 2). The first step in such a plan, acetonide deprotection of **19**, proved to be unexpectedly challenging as standard acidic conditions led to decomposition or an undetermined rearranged product. After screening a variety of conditions, a mild cerium trichloride/oxalic acid system was discovered to provide a tractable solution delivering diol **21** in 65% yield along with some recovered **19** (18%).[18] Oxidative diol cleavage with $PhI(OAc)_2$[19] followed by reduction of the resulting dialdehyde in the same pot yielded a bridged-cleaved primary diol **22** that was advanced to bis-MOM ether **23** in 86% yield (two steps).

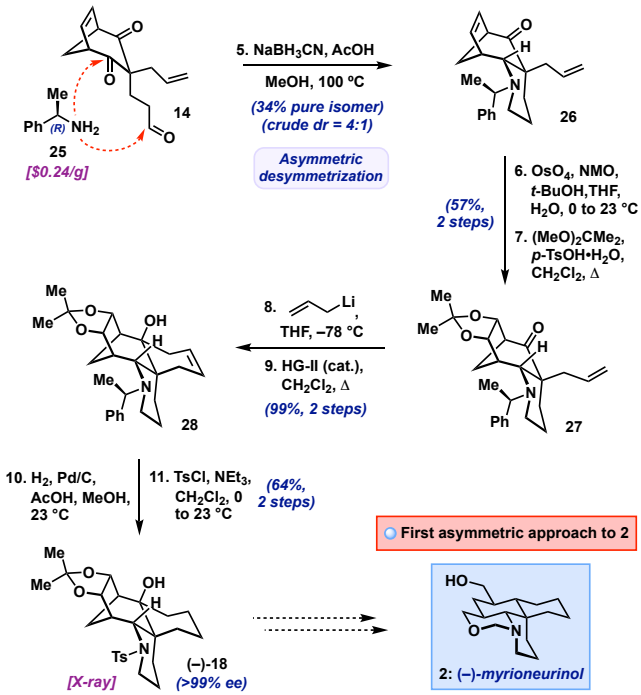
With the topology of the alkene altered in **23** and its precursor diol **22**, we attempted its hydrogenation. Unfortunately, preliminary screens again delivered unsatisfactory selectivity; the best result was obtained with bis-MOM ether **23** which yielded a 1.1:1 mixture of



Scheme 2. Completion of (±)-myrioneurinol (**2**) via a topologically controlled HAT hydrogenation.

diastereomers under standard hydrogenation conditions (H_2, Pd/C; entry 1, inset). Pleasingly, it was found that HAT reduction of **23** was able to favor the desired isomer, with optimized conditions using Baran's Fe-catalyzed system providing the desired saturated **24** as the major product (dr = 12:1) in 64% yield.[20] This major diastereomer (**24**) is a known intermediate in the prior Weinreb synthesis.[6] Subjection of **24** to a slightly modified version of their two-step sequence, involving tosyl deprotection with Li/NH_3 followed by local desymmetrization of the two primary MOM-ethers by acid-mediated oxazine formation and deprotection, respectively, gave racemic myrioneurinol [(±)-**2**] in 35% yield over the two steps. Overall, our total synthesis proceeds in 18 steps and ~1% yield from commercial materials.

A key advantage of our desymmetrization-based strategy is that it is readily adaptable to an asymmetric synthesis of myrioneurinol. Thus, simply substituting benzylamine for inexpensive (*R*)-α-methylbenzylamine (**25**) in the double reductive amination led to a diastereoselective desymmetrization proceeding with reasonable selectivity (dr = 4:1) for one of the two diastereotopic ketones (formally enantiotopic once the α-methylbenzyl unit is removed), allowing for the isolation of pure major isomer **26** in 34% yield by column chromatography (Scheme 3).[21,22] This transformation sets the absolute configuration of four of the five stereocenters of myrioneurinol (**2**), including the quaternary center, in a single step. **26** could be submitted to the same sequence of reactions (via intermediates **27**–**28**) as our racemic benzyl series to arrive at (–)-**18** (>99% ee by HPLC), whose absolute configuration was be determined by single-crystal X-ray analysis. The synthesis of (–)-**18** thus constitutes a formal asymmetric synthesis of (–)-*ent*-myrioneurinol [(–)-**2**]; given that (*S*)-α-methylbenzylamine is equally available, access to the natural (+)-enantiomer via such a process should be trivial.



Scheme 3. Formal synthesis of (–)-myrioneurinol [(–)-**2**] via asymmetric desymmetrization of **14**.

In summary, we have developed an 18-step total synthesis of myrioneurinol (**2**), including the first asymmetric approach via a formal synthesis of (–)-**2**. Our synthesis exploits hidden symmetry to construct its polycyclic framework, centering on a key desymmetrizing double reductive amination of a bicyclic diketo aldehyde to assemble its core tricyclic ring system in a stereocontrolled manner. Utilization of an inexpensive, enantiopure chiral amine in this process provides a convenient asymmetric entry to the myrioneurinol scaffold. Other noteworthy features of our synthesis include masking the *cis*-bis(hydroxymethyl) unit of **2** as a bicyclic olefin, and a diastereoselective alkene hydrogenation that relied on careful control of substrate topology. Future studies from our group will look to expand this symmetry-driven approach to other alkaloid targets both within the *Myrioneuron* class and beyond.

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22. Preliminary attempts to achieve a catalytic enantioselective double reductive amination through the use of a chiral Brønsted or Lewis acid catalyst gave only low enantioselectivity (≤10% ee).

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Graphical Abstract: