# Enantioselective Approach to the Hetisine Alkaloids. Synthesis of the 3-Methyl-1-aza-tricyclo[5.2.1.0<sup>3,8</sup>]decane Core via Intramolecular Dipolar Cycloaddition

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#### ABSTRACT



An efficient, enantioselective approach to the hetisine class of the  $C_{20}$ -diterpenoid alkaloids is described. The strategy involves an intramolecular oxidopyridinium dipolar cycloaddition as the key transformation, in which simultaneous formation of the C5–C6 and C10–C20 bonds in the 3-methyl-1-aza-tricyclo[5.2.1.0<sup>3,8</sup>]decane core of the hetisine alkaloids is effected.

The  $C_{20}$ -diterpenoid alkaloids isolated from the *Aconitum*, *Delphinium*, *Consolida*, and *Spiraea* species comprise a diverse family of compounds among which the atisane class of alkaloids (1, Figure 1) is a principal constituent.<sup>1</sup> This



Figure 1. Atisane and hetisine alkaloids.

class of compounds is in turn composed of several structural subclasses of alkaloids, exhibiting varied degrees of structural complexity and pharmacological activity. The hetisine class of alkaloids is among the most structurally complex subgroup of this family and is exemplified by kobusine (2),<sup>2</sup> incorporating additional C14–C20 and N–C6 linkages relative to the atisane skeleton.<sup>3</sup> Kobusine was among the earliest reported hetisine alkaloids, and it, together with several of its C15–*O*-acyl derivatives, has recently been shown to exhibit potent vasodilating activity in vivo.<sup>4</sup>

Although the structure of the hetisine alkaloids have been known for more than 40 years, synthetic investigations into these natural products have been rather sparse due to the formidable challenges in constructing the 3-methyl-1-aza-tricyclo[ $5.2.1.0^{3.8}$ ]decane substructure (**3**, Scheme 1) embed-

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ded within the diterpene-derived carbon scaffold. To this end, a few creative racemic approaches to the construction of bridged aza-*bi*cyclo substructures of the hetisine alkaloids have been reported.<sup>5</sup> Model structures of the aza-*tri*cyclo core have also been accessed via late-stage stepwise formation of the C–N bonds on a suitably derivatized polycyclic carbon skeleton,<sup>6</sup> with the latter efforts culminating in a recent synthesis of ( $\pm$ )-nominine in a 40-step sequence.<sup>7</sup> However, the notable paucity of efficient asymmetric strategies to the aza-*tri*cyclo core **3**, characteristic of all hetisine alkaloids, led us to consider the preparation of this substructure via simultaneous formation of the C5–C6 and C10–C20 bonds with the intramolecular combination of an appropriate azadipole and dipolarophile (**3**  $\rightarrow$  **4**).

Initial investigations into the feasibility of the strategy involved the use of an oxidopyridinium betaine as a relatively stable endocyclic aza-dipole<sup>8</sup> tethered to a 2-enenitrile dipolarophile in a dipole-HOMO-controlled cycloaddition (Scheme 2). Preparation of the cycloaddition precursor commenced with 1,4-addition of cyanide to 3-methylcyclohex-2-enone (5) with Et<sub>2</sub>AlCN. The putative aluminum enolate was then activated in situ with cesium fluoride and subsequently trapped with  $Tf_2O$  to give the vinyl triflate 6 in 69% yield. Reduction of the nitrile in 6 to the corresponding aldehyde with DIBAL-H (82%) followed by immediate reductive amination with furfurylamine provided furanylamine 7 (99%). Palladium-catalyzed cyanation<sup>9</sup> of the enol triflate in 7 proceeded in 75% yield and was followed by Br<sub>2</sub>-mediated oxidative rearrangement of the furan moiety<sup>10</sup> to afford oxidopyridinium ylide 9 in 65% yield. Heating the

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oxidopyridinium in a variety of solvents to effect dipolar cycloaddition on the C5–C10 dipolarophile (10) was, however, unsuccessful as direct intramolecular conjugate addition of the oxidopyridinium nucleophile to C5 (11) followed by re-aromatization was the dominant reaction manifold, affording the racemic tricyclic oxidopyridinium betaine 12 (73%).

While the formation of **12** in and of itself constitutes a novel approach to the preparation of highly substituted indolizinium heterocycles,<sup>11</sup> the suppression of direct 1,4-addition is critical to the construction of the hetisine aza-tricyclic core. This led to the consideration of a new cycloaddition substrate in which a removable electron-deficient auxiliary (*Z*) is introduced at C5 rather than at C10 of the dipolarophile to favor the cycloaddition manifold (**13**, Scheme 3). The undesired direct conjugate addition pathway



with this substrate would involve nucleophilic addition into the C10 position (i.e.,  $14 \rightarrow 15$ ). This process is likely to experience enhanced nonbonding interactions with the necessary positioning of both the C1 and C2 methylene groups directly over the oxidopyridinium ring in the formation of the unwanted bridged aza-bicyclo[3.3.1]nonane oxidopyridinium 15.

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To evaluate this hypothesis, preparation of the new cycloaddition precursor **22** proceeded in a sequence that is also readily amenable to asymmetric induction (Scheme 4).



Asymmetric  $\alpha$ -methylation of 2-oxo-cyclohexanecarboxylic acid ethyl ester (**16**) via its corresponding (*S*)-*t*-butylvaline enamine derivative<sup>12</sup> provided the  $\alpha,\alpha$ -disubstituted cyclohexanone **17** in 53% (98:2 er). Dehydrative condensation of **17** with thiophenol produced vinyl sulfide **18** in 93% yield to install the  $\pi$  system of the dipolarophile. Reduction of the ethyl ester within 18 to the alcohol with DIBAL-H (99%) followed by oxidation with IBX afforded the aldehyde 19 in 95% yield. Oxidation of the vinyl sulfide with mCPBA (94%) allowed for the introduction of the dipolarophileactivating group at C5 in the form of an aryl sulfone. Reductive amination of aldehyde 20 with furfurylamine afforded the furanylamine 21 (91%), which underwent facile oxidative rearrangement with bromine in aqueous acetic acid to produce oxidopyridinium betaine 22 in 77% yield. Heating of 22 in toluene (0.05 M) at reflux produced the cycloadduct 23 in 70% yield with no evidence of products arising from simple conjugate addition (i.e., 15). Initial structure determination of the cycloadduct 23 came from a battery of NMR data (<sup>1</sup>H, COSY, HMQC) including an observed nOe between the C4 methyl group and the C6 angular proton, data consistent with a regioselective dipole-HOMO-controlled cycloaddition. Structure verification of the cycloadduct ultimately came from single-crystal X-ray analysis. Conjugate reduction of 23 and subsequent triflation of the transient enolate with PhNTf2<sup>13</sup> yielded the corresponding vinyl triflate (70%), which was reduced to the alkene 24 with formic acid and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (84%).<sup>14</sup> Finally, desulfurization of the C5 sulfone to form 25 proceeded in 82% yield, demonstrating that this dipolarophile-activating auxiliary can be removed without rearrangement or  $\beta$ -elimination in the newly constructed aza-tricylcic skeleton.

In summary, the first asymmetric synthesis of the 3-methyl-1-aza-tricyclo[ $5.2.1.0^{3.8}$ ]decane core of the hetisine alkaloids is reported. The strategy involves an intramolecular oxidopyridinium dipolar cycloaddition as the key transformation in which simultaneous formation of the C5–C6 and C10–C20 bonds is effected. The facile preparation of (+)-**25** clearly demonstrates feasibility of this approach and holds promise for the efficient asymmetric synthesis of the hetisine class of alkaloids.

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**Supporting Information Available:** Experimental details and analytical data for synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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