

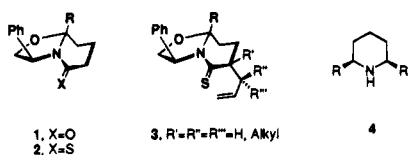
# A Novel Asymmetric Route to Chiral, Nonracemic *cis*-2,6-Disubstituted Piperidines. Synthesis of (+)-Pinidinone and (+)-Monomorine

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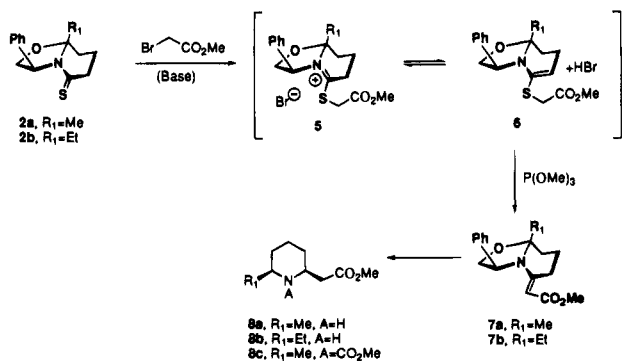
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The abundance of biologically active alkaloids containing the 2,6-disubstituted piperidine ring **4** has resulted in considerable synthetic efforts to reach these systems.<sup>1</sup> During our continuing studies on chiral bicyclic lactams **1**,<sup>2</sup> we recently studied the thiolactam version **2** and found that a number of highly stereoselective thio-Claisen rearrangements produced quaternary substituted systems **3**, which ultimately led to highly substituted cyclohexenones.<sup>3</sup>



We now describe, in preliminary form, our findings that the thiolactams **2** are readily transformed in three steps to chiral nonracemic 2,6-*cis* substituted piperidines **4** with very high stereoselectivity, and we are pleased to demonstrate this process by the asymmetric synthesis of two piperidine alkaloids, (+)-pinidinone (**9**) and (+)-monomorine (**14**).

The key to the disubstitution of thiolactam **2**<sup>3</sup> was to use the versatile Eschenmoser contraction,<sup>4</sup> a process which is well known to transform thioamides to vinylogous urethanes. We first attempted the contraction by addition of methyl  $\alpha$ -bromoacetate to thiolactam **2a**, prepared from **1** via Belleau's reagent,<sup>5</sup> and found that the only product formed was the ketene *N,S*-acetal **6**, similar to the products we observed during the Claisen rearrangements.<sup>3</sup> If the contraction was to proceed, it



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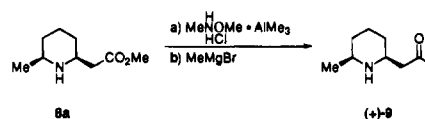
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was critical that some measurable quantity of the thioiminium salt **5** was present. Recently, this problem was encountered by Hart<sup>6</sup> in his synthesis of lythrancepine, and he showed that the equilibrium between a thioiminium salt (e.g., **5**) and a ketene *N,S*-acetal (e.g., **6**) could be initiated by heating the two in the presence of a base and a thiophile (Ph<sub>3</sub>P). In this fashion, Hart was able to perform the contraction in an analogous system in >92% yield. However, when these conditions were attempted with **2a**, only a trace of the contraction product (**7a**) was observed. After extensive study, optimum conditions were uncovered, and **7a** was formed according to the following procedure. The thiolactam **2a** was stirred overnight with 10 equiv of methyl (or ethyl)  $\alpha$ -bromoacetate in chloroform, and the volatiles were removed (*in vacuo*). The residue was taken up in chloroform and treated with trimethyl phosphite (4 equiv) and triethylamine (10 equiv), and the solution was heated at reflux for 2–3 days. After cooling and concentration of the solution, chromatography gave an 80% yield of the vinylogous urethane **7a**. Similarly, the lactam **2b** gave **7b** in 65–70% yield. Thus, stirring the *S*-alkyl products **5** and **6** in the presence of a base and a thiophilic reagent slowly allowed the episulfide to form, which then resulted in the extrusion of sulfur to **7a** or **7b**. This elaboration of the lactam **1** was not possible by use of organometallic reagents (e.g., lithio enolates, zinc enolates, etc.), and thus the Eschenmoser contraction sequence **2** → **5** → **7** was crucial to the success of the intended goal. The transformation of **7a** or **7b** to the 2,6-disubstituted piperidines **8a,b** was accomplished, after a number of unsuccessful attempts, in a single step. Thus, hydrogenation of **7a** or **7b** using Pd(OH)<sub>2</sub> on carbon at 3 atm after 12 h gave **8a** or **8b** in 60–80% as essentially one diastereomer (>97%).<sup>7</sup> The optical purity of **8a** was also assessed by comparing the methyl carbamate **8c** with the enantiomer prepared by Momose<sup>8</sup> via another route. The high level of stereoselectivity observed during the reduction of **7a,b**, wherein two centers of stereochemistry and three bonds are affected in a single step, may be assumed to occur from the *endo* face of **7**. Based on experiments using platinum as a hydrogenation catalyst, we observed that the C=C in **7** was initially reduced to give a single product. Also, monitoring the reduction showed that after the C=C was reduced, the C–O bond (via an iminium salt?) was reductively cleaved also from the *endo* face. We currently have no firm evidence as to the timing of the benzylic C–N cleavage step in the sequence.

To demonstrate that **7a** and **7b** are indeed important chiral precursors to piperidine alkaloids, we carried out two short sequences to known natural materials. Treatment of the piperidine ester **8a** with Weinreb's<sup>9</sup> reagent gave the *N*-methoxyamide, which was immediately treated with methylmagnesium bromide. The product, (+)-pinidinone (**9**), was



obtained in 56% yield and was identical by all spectral comparisons with the natural material.<sup>10</sup> Thus, starting with the lactam **1**, the enantiomerically pure piperidine alkaloid was obtained in five steps in 23% overall yield.

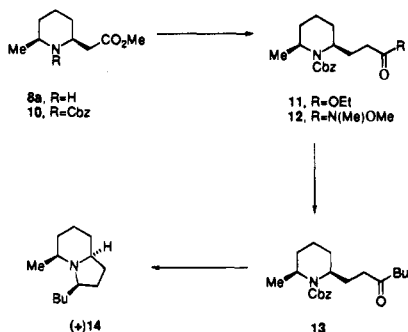
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(7) A single product was observed by 300 MHz <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

(8) The enantiomer of **8a** was previously reported by Momose et al. (ref 1e above) who reported [ $\alpha$ ]<sub>D</sub><sup>25</sup> = –40.0 for the pure enantiomer. The present work gave [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +41.3 (c 1.26, CHCl<sub>3</sub>).

(9) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

The indolizidine alkaloids have also attracted a great deal of attention owing to their potent biological activity.<sup>11</sup> Of these, the ant trail pheromone, monomorine, has received considerable attention<sup>12</sup> and has recently been synthesized<sup>13</sup> from the racemic piperidine ketone **13**. We felt the present route to chiral piperidines could readily access nonracemic **13** by homologation of the piperidine acetic ester **8a**. In the event, **8a** was initially



transformed to the carbobenzyloxy derivative **10** using benzyl chloroformate under Schotten–Bauman conditions.<sup>14</sup> The ester **10** was hydrolyzed to the corresponding carboxylic acid, transformed to the acid chloride (oxalyl chloride), and subjected to the Arndt–Eistert conditions<sup>15</sup> (ethereal diazomethane followed by silver oxide in ethanol), which produced the homolo-

(10) Tawara, J. N.; Blokhin, F. A.; Stermitz, F. R. *J. Org. Chem.* **1993**, *58*, 4813. A sample of natural material kindly provided by Professor Stermitz was compared with the synthetic material. The latter showed considerably higher specific rotation ( $[\alpha]_D +25.3$  (c 0.4, MeOH)) than the natural material ( $[\alpha]_D -4$ ), but this was clearly attributed to impurities present (<sup>13</sup>C and <sup>1</sup>H NMR) in the natural sample.

gated piperidine ester **11** in 75% yield. Again, utilizing the Weinreb amidation,<sup>9</sup> the *N*-methyl-*N*-methoxyamide **12** was treated with *n*-butylmagnesium bromide, affording the chiral piperidine ketone **13**. Comparison with the data reported by Kibayashi<sup>13</sup> confirmed the identity of the ketone, and utilization of his reduction conditions for ( $\pm$ )-**13** gave (+)-**14** in 70% yield. Thus (+)-monomorine was reached in seven steps in high enantiomeric purity,  $[\alpha]_D +35.0$  (lit.<sup>12</sup> +35.7).

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**Supplementary Material Available:** Complete experimental data and spectra for all compounds reported (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) Experimental details for these transformations are provided as supplementary material.

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