

## ALKALOID SYNTHESIS USING FUROPYRIDONE AS SYNTHON

—SYNTHESIS OF KEY INTERMEDIATES FOR THE SYNTHESSES OF

(±)-QUININE, (±)-AJMALICINE, AND (±)-7-DEMETHYLTECOMANINE—

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Abstract—Furopyridones (**4a**, **b**, and **c**) have been proved as the potential synthons for alkaloid synthesis from their facile conversion to the key intermediates (**9e**), (**10e**), and (**13**) for the synthesis of quinine, ajmalicine, and 7-demethyltecomanine.

Biogenetically loganin and secologanin stand as key intermediates in the biosynthetic pathway of monoterpenoid alkaloids.<sup>1</sup> Considering this, we have now explored a general and divergent synthetic route for a large number of monoterpenoid alkaloids employing unnatural heterocycle, furopyridones, as common synthons which were prepared via the route involving reductive photocyclization<sup>2</sup> of enamides substituted with  $\alpha$ -alkylthio group<sup>3</sup> which can be removed at a later step. N-Benzylthioacetamide (**1a**) and N-methylthiopropionamide (**1b**) were alkylated with dimethyl sulfate to give respective thioimidates (**2a**) and (**2b**) in quantitative yields which were then acylated with either 3-furoyl or 5-methyl-3-furoyl chloride to afford two enamides (**3a**)<sup>4</sup> or (**3b**)<sup>4</sup> both quantitatively. The latter enamide (**3b**) was found to be a 1:2 separable mixture of two geometrical isomers, though their stereochemistries remained unclarified. Reductive photocyclization<sup>2</sup> of the enamides (**3a**) and (**3b**) in the presence of sodium borohydride in acetonitrile-methanol proceeded smoothly to give the hydrogenated lactams (**4a**)<sup>5</sup> [55% from (**3a**)] and (**4b**)<sup>5</sup> and (**4c**)<sup>5</sup> [41% and 48% from (**3b**)].

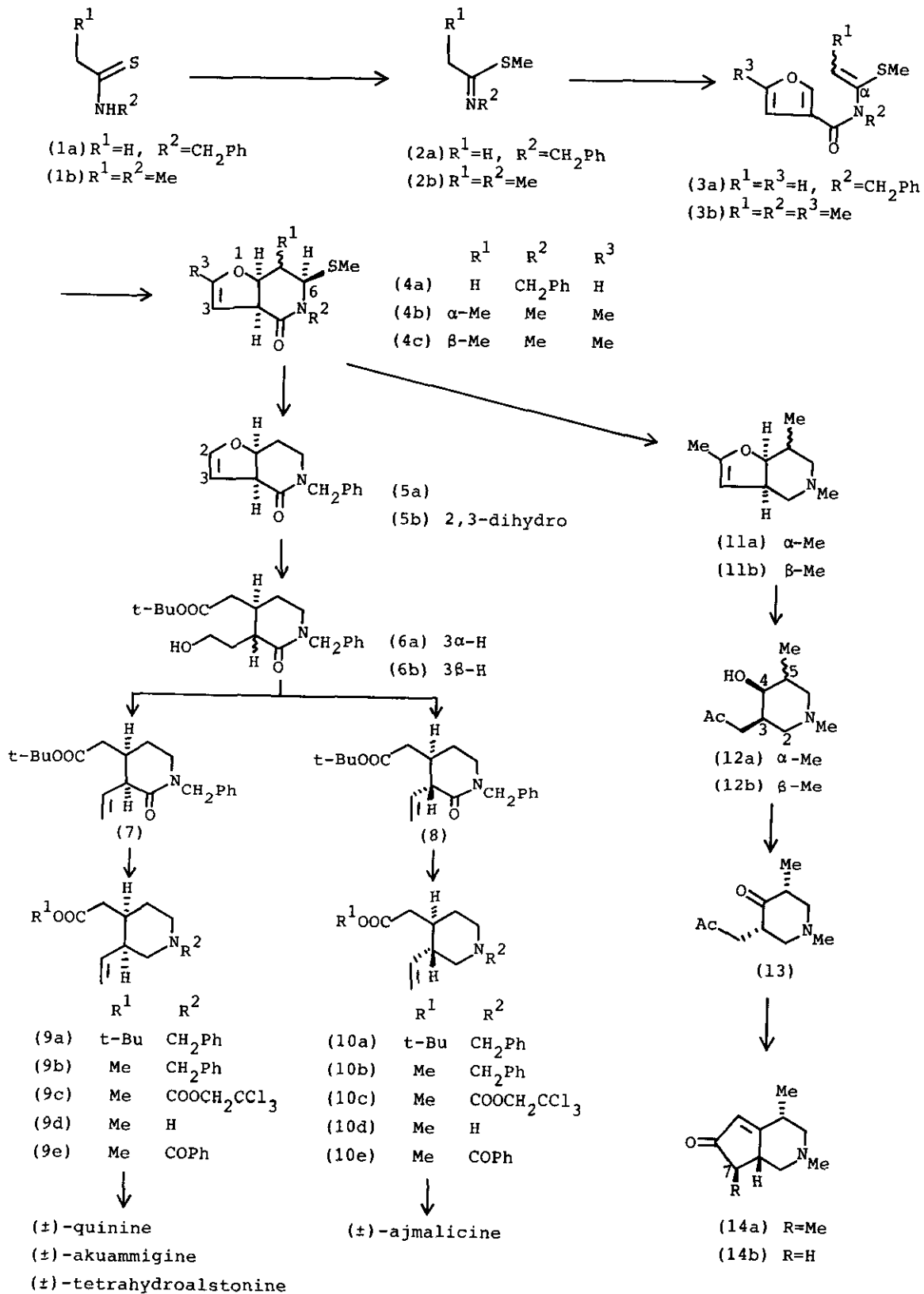
[Synthesis of the Key Intermediates (**9e**) and (**10e**) for (±)-Quinine, (±)-Akuammigine, and (±)-Ajmalicine]

Reduction of 6-methylthiofuropyridone (**4a**) with tributyltinhydride and 2,2'-azobisisobutyronitrile<sup>7</sup> followed by catalytic hydrogenation of the resulting 6-

unsubstituted furopyridone (5a) over platinum dioxide under hydrogen atmosphere afforded the tetrahydrofuran (5b)<sup>5</sup> in 71% yield which was also prepared by catalytic reduction of the 6-methylthiofuropyridone (4a) in the presence of Raney-Ni as catalyst in 51% yield. In order to introduce two carbon unit at the 4-position of the piperidone ring, the furopyridone (5b) was subjected to the elimination-addition reaction<sup>8</sup> which consists of opening reaction of the furan ring in (5b) by lithiation with lithium diisopropylamide followed by addition of the 2-lithioacetate to give the desired adduct (6a)<sup>5</sup> and (6b)<sup>5</sup> as a 1:1 diastereomeric mixture at the 3-position in 69% yield. Phenylselenylation of a mixture of the ethylols (6a) and (6b) with *o*-nitrophenylselenocyanate-tributylphosphine followed by oxidation with hydrogen peroxide gave a 1:1 mixture of the vinyl esters (7)<sup>5</sup> and (8)<sup>5</sup> in 64% yield which was separated by column chromatography. The *cis*-lactam (7) was converted into the known key intermediate (9e) for (±)-quinine,<sup>9</sup> (±)-akuammigine,<sup>10</sup> and (±)-tetrahydroalstonine<sup>10</sup> by the following reaction sequence. Chemoselective reduction of the lactam carbonyl group (AlH<sub>3</sub> at -50°C), transesterification (MeOH-H<sub>2</sub>SO<sub>4</sub>), carbamoylation (ClCOOCH<sub>2</sub>CCL<sub>3</sub>-NaHCO<sub>3</sub>), reductive decarbamoylation (Zn-AcOH), and finally benzylation (PhCOCl-Et<sub>3</sub>N) afforded the desired *cis*-N-benzoate (9e)<sup>6</sup> in almost quantitative yield. Similarly, the *trans*-lactam (8) was also converted into the known synthetic intermediate (10e)<sup>6</sup> of (±)-ajmalicine<sup>11</sup> quantitatively.

[Synthesis of the Key Intermediate (13) for (±)-7-Demethyltecomanine]

Tecomanine (14a) is a monoterpene alkaloid having hypoglycemic activity and has been recently synthesized by two groups.<sup>12,13</sup> The furopyridones (4b) and (4c) were converted into the known synthetic intermediate (13)<sup>14</sup> of 7-demethyltecomanine (14b). Reduction of the 6-methylthiolactams (4b) and (4c) with lithium aluminum hydride by refluxing in tetrahydrofuran gave the desulfurized amines (11a)<sup>5</sup> and (11b)<sup>5</sup> in 91 and 88% yields which were hydrolyzed with 10% hydrochloric acid to give the hydroxyketones (12a)<sup>5</sup> and (12b)<sup>5</sup> in 82 and 94% yields, respectively. Jones oxidation of the hydroxyketone (12b) gave the diketone (13)<sup>6</sup> in quantitative yield which was also prepared by the same reaction of the another hydroxyketone (12a) in 55% yield *via* presumable isomerization at the 3- or 5-position of the resulting thermodynamically unstable 3,5-*trans*-diketone. The *cis*-diketone (13) had been utilized as a key intermediate for the synthesis of (±)-7-demethyltecomanine.<sup>14</sup>



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