ALKALOID SYNTHESIS USING FUROPYRIDONE AS SYNTHON —SYNTHESIS OF KEY INTERMEDIATES FOR THE SYNTHESES 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.

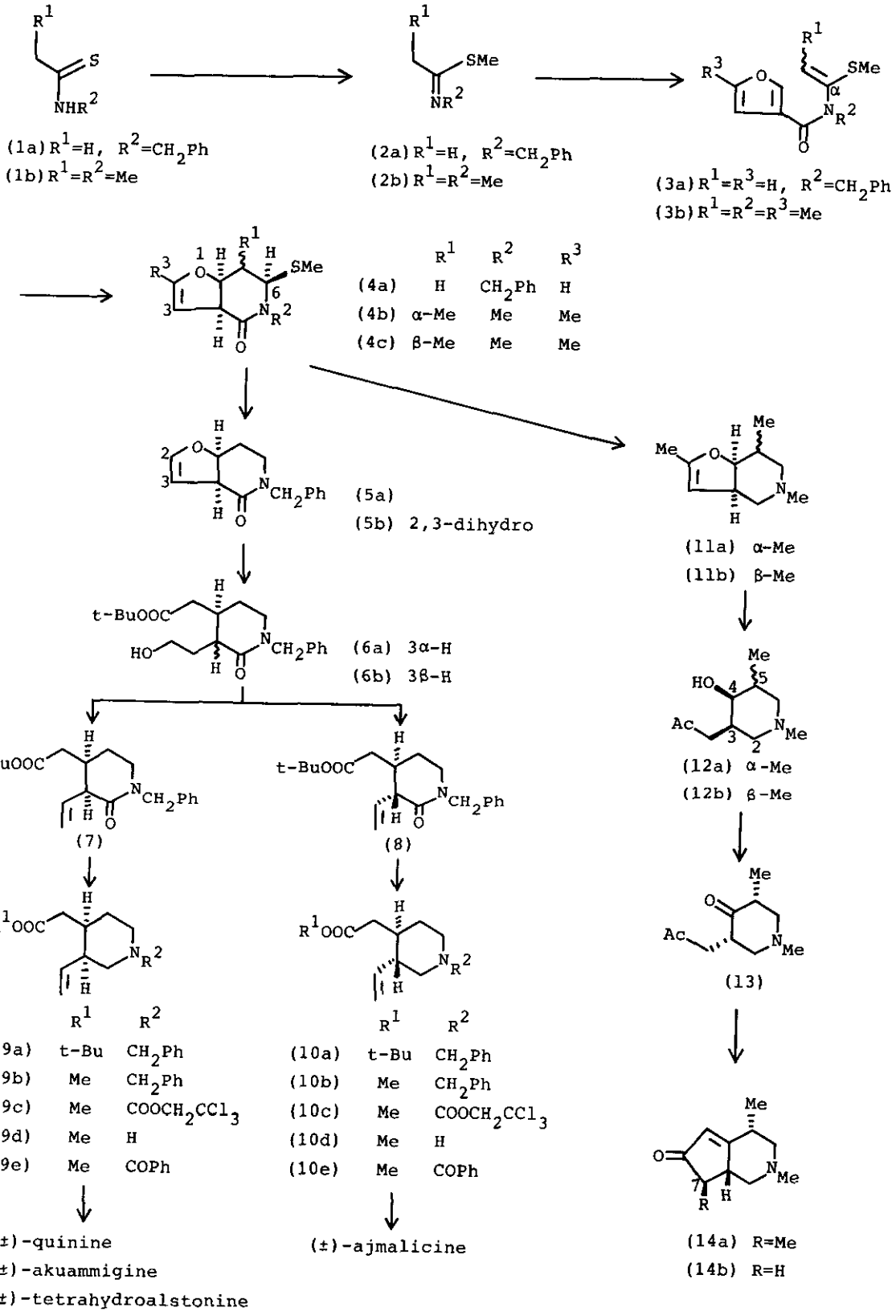
Biogenetically loganin and secologanin stand as key intermediates in the biosynthetic pathway of monoterpenoid alkaloids.[1] Considering this, we have now explored a general and divergent synthetic route for a large number of monoterpenoid alkaloids employing unnatural heterocycle, furopyridones, as common synthons which were prepared via the route involving reductive photocyclization[2] of enamides substituted with α-alkylthio group[3] 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**)[4] or (**3b**)[4] 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[2] of the enamides (**3a**) and (**3b**) in the presence of sodium borohydride in acetonitrile-methanol proceeded smoothly to give the hydrogenated lactams (**4a**)[5] [55% from (**3a**)] and (**4b**)[5] and (**4c**)[5][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[7] followed by catalytic hydrogenation of the resulting 6-

unsubstituted furopyridone (**5a**) over platinum dioxide under hydrogen atmosphere afforded the tetrahydrofuran (**5b**)[5] 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[8] 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**)[5] and (**6b**)[5] 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**)[5] and (**8**)[5] in 64% yield which was separated by column chromatography. The cis-lactam (**7**) was converted into the known key intermediate (**9e**) for (±)-quinine,[9] (±)-akuammigine,[10] and (±)-tetrahydroalstonine[10] by the following reaction sequence. Chemoselective reduction of the lactam carbonyl group (AlH_3 at -50°C), transesterification ($MeOH-H_2SO_4$), carbamoylation ($ClCOOCH_2CCl_3$-$NaHCO_3$), reductive decarbamoylation (Zn-AcOH), and finally benzoylation ($PhCOCl$-Et_3N) afforded the desired cis-N-benzoate (**9e**)[6] in almost quantitative yield. Similarly, the trans-lactam (**8**) was also converted into the known synthetic intermediate (**10e**)[6] of (±)-ajmalicine[11] quantitatively.

[Synthesis of the Key Intermediate (**13**) for (±)-7-Demethyltecomanine]
Tecomanine (**14a**) is a monoterpenoid alkaloid having hypoglycemic activity and has been recently synthesized by two groups.[12,13] The furopyridones (**4b**) and (**4c**) were converted into the known synthetic intermediate (**13**)[14] of 7-demethyltecomanine (**14b**). Reduction of the 6-methylthiolactams (**4b**) and (**4c**) with lithium aluminum hydride by refluxing in tetrahydrofuran gave the desulfurizated amines (**11a**)[5] and (**11b**)[5] in 91 and 88% yields which were hydrolyzed with 10% hydrochloric acid to give the hydroxyketones (**12a**)[5] and (**12b**)[5] in 82 and 94% yields, respectively. Jones oxidation of the hydroxyketone (**12b**) gave the diketone (**13**)[6] 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.[14]


(1a) R1=H, R2=CH2Ph
(1b) R1=R2=Me
(2a) R1=H, R2=CH2Ph
(2b) R1=R2=Me
(3a) R1=R3=H, R2=CH2Ph
(3b) R1=R2=R3=Me
(4a) H CH2Ph H
(4b) α-Me Me Me
(4c) β-Me Me Me
(5a)
(5b) 2,3-dihydro
(6a) 3α-H
(6b) 3β-H
(7)
(8)
(9a) t-Bu CH2Ph
(9b) Me CH2Ph
(9c) Me COOCH2CCl3
(9d) Me H
(9e) Me COPh
(10a) t-Bu CH2Ph
(10b) Me CH2Ph
(10c) Me COOCH2CCl3
(10d) Me H
(10e) Me COPh
(±)-quinine
(±)-akuammigine
(±)-tetrahydroalstonine
(±)-ajmalicine
(11a) α-Me
(11b) β-Me
(12a) α-Me
(12b) β-Me
(13)
(14a) R=Me
(14b) R=H

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