Communications to the Editor

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AN EFFICIENT SYNTHESIS OF (±)-EMETINE USING α,β-UNSATURATED LACTAM AS A MICHAEL ACCEPTOR

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A new and simple synthesis of (±)-emetine uses α,β-unsaturated lactams (4b), (4c), and (4e) as new Michael acceptors.

KEYWORDS——(±)-emetine; ipecac alkaloid; heteroyohimbine alkaloid; enamide; α,β-unsaturated lactam; furan; reductive photocyclization; Michael reaction

Because of the close biogenetic relationship in the ring systems common to the ipecac[1] and heteroyohimbine[2] alkaloids, considerable attention is being given to new and general methods for their synthesis.

Now we have established an efficient synthesis for both alkaloids incorporating a furan ring into a monoterpene unit of both of them. The method is demonstrated by the synthesis of (±)-emetine.

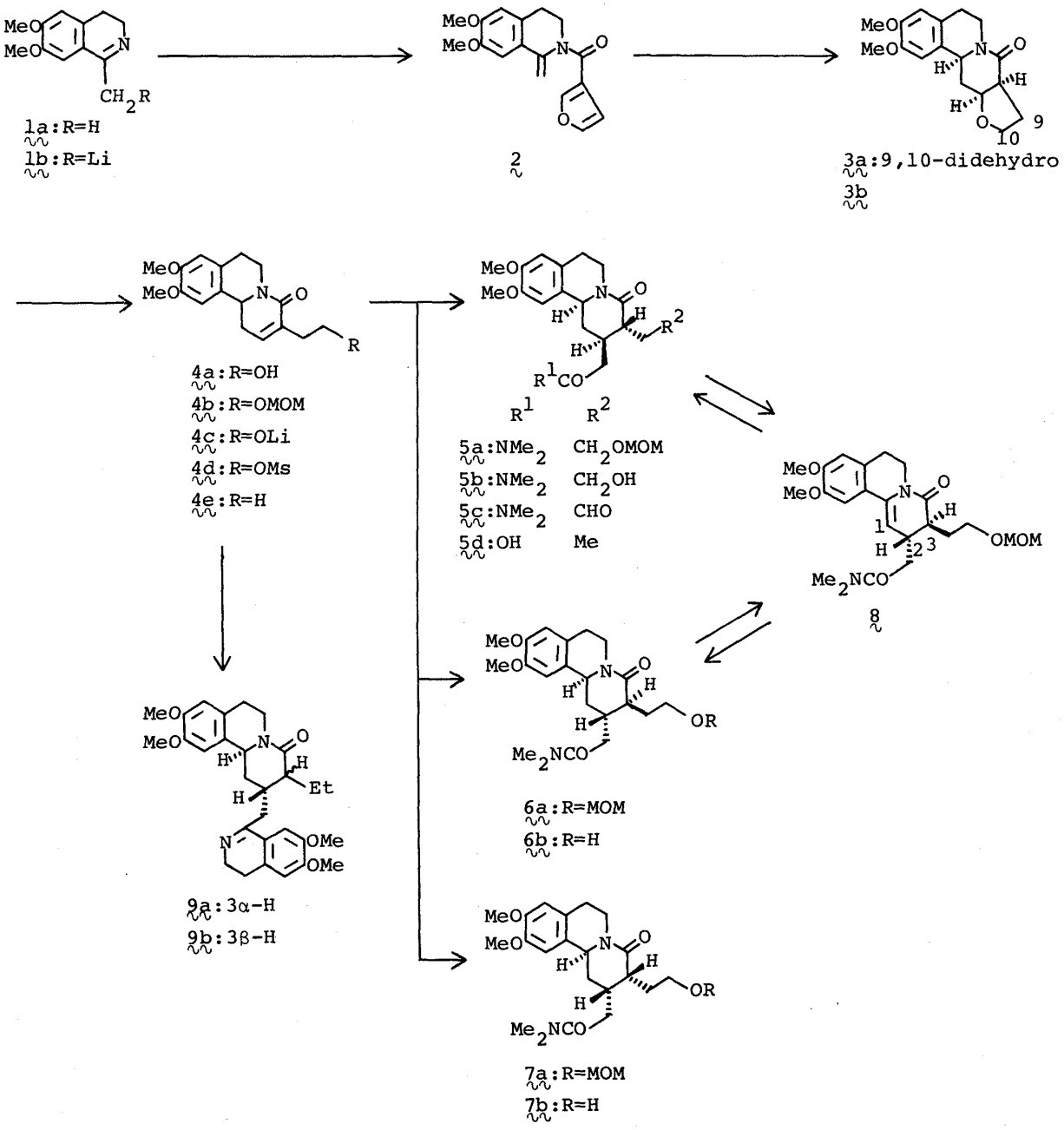
Acylation of the 1-methyl-3,4-dihydroisoquinoline (1a) with 3-furoyl chloride in the presence of triethylamine gave the enamide (2) in a quantitative yield. Reductive photocyclization[3] of the enamide (2) proceeded smoothly to give the furanoquinolizine (3a) in 96% yield. This is the basic skeletal structure of benzoquinolizine alkaloids substituted with a two-carbon substituent at the 3-position. Stereochemistry of the lactam (3a) was deduced by comparison of the NMR spectrum [($CDCl_3$)δ: 6.34 (1H, t, J=2.5 Hz), 5.28 (1H, t, J=2.5 Hz), 5.06 (1H, td, J=11, 6 Hz), 4.62 (1H, br dd, J=12, 2.5 Hz), 3.95 (1H, dt, J=11, 2.5 Hz), 1.85 (1H, br q, J=12 Hz)] with that of a reported analogous compound[4] which had been firmly characterized by spectral and X-ray analyses. The tetrahydrofuran (3b), obtained in a quantitative yield by catalytic hydrogenation of the dihydrofuran (3a) in the presence of platinum dioxide, is expected to undergo β-elimination to afford the α,β-unsaturated lactam (4a) as a result of ring opening reaction. As expected, treatment of the lactam (3b) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C gave the α,β-unsaturated lactam (4a) in 71% yield. 4a was characterized as its methoxymethyl ether (4b)[ν1665, 1615 cm^{-1}; ($CDCl_3$)δ: 6.70-6.33 (3H, m)]. Of the known examples of Michael reaction of α,β-unsaturated ketone, only a few[5,6] have been reported on Michael addition to α,β-unsaturated lactam, because of its low reactivity toward nucleophiles. We then investigated the Michael reaction of the lactam (4b) with the 2-lithioacetamide which was prepared *in situ* from N,N-dimethylacetamide and LDA, and obtained three adducts (5a), (6a), and (7a) in 67, 15, and 8% yields, respectively. These were separated by repeated preparative thin layer chromatography on silica gel [($CDCl_3$)δ:(5a) 1.37 (1H, br q, J=12 Hz); (6a)

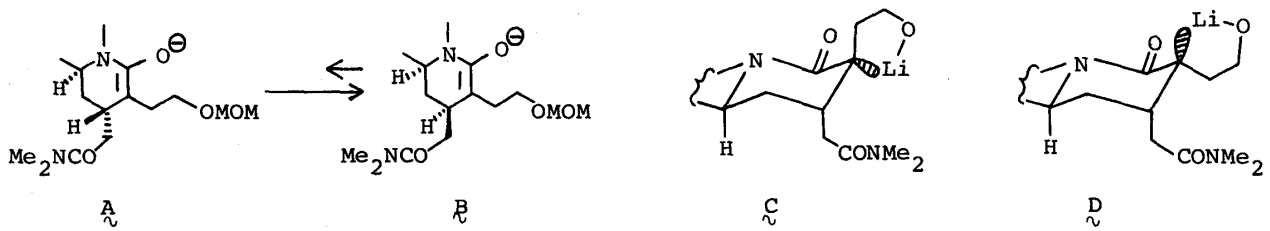
2.08 (1H, br t, J=11.5 Hz); (7a) 1.95 (1H, br t, J=12 Hz)].

On the other hand, when the starting tetrahydrofuran (3b) is treated with LDA, it can be expected that the lithium alcoholate (4c), formed in situ by β-elimination, will also have an α,β-unsaturated lactam structure and can react as a Michael acceptor in the presence of strong nucleophile. Therefore, we investigated a one-pot Michael reaction between the lithium alcoholate (4c), prepared by treatment of the tetrahydrofuran (3b) with LDA at -78°C, and the 2-lithioacetamide prepared as above. Three Michael adducts (5b), (6b), and (7b) were obtained in 5, 48, and 25% yields, respectively. The structures of all six of the Michael adducts (5a), (6a), and (7a), prepared from the methoxymethyl ether (4b), and (5b), (6b), and (7b), prepared directly from the tetrahydrofuran (3b), were deduced as follows. Acid treatment of the respective methoxymethyl ethers (5a), (6a), and (7a) with 10% hydrochloric acid afforded the corresponding deprotected alcohols (5b), (6b), and (7b) in quantitative yields. These were identical with the respective Michael adducts prepared as above by the one-pot Michael reaction of 3b. One of the three adducts (5b) was readily converted into the known[4,7] key intermediate (5d) for the synthesis of (±)-emetine as follows. Oxidation of the hydroxyl group in 5b with pyridinium chlorochromate followed by Huang-Minlon reduction of the resulting aldehyde (5c) and alkaline hydrolysis of the amide group in 5c afforded the acid (5d)[4,7] [mp 180-183°C; ν 3200-2500, 1720 cm^{-1}] in 10% yield from 5b. Two adducts (6a) and (7a) were interconverted to each other by treatment with sodium hydride in refluxing THF leading to a 1:1 equilibrium mixture of 6a and 7a, proving their epimeric relationship with respect to the 3-position. Catalytic hydrogenation of the 1,11b-dehydrolactam (8)[($CDCl_3$)δ: 5.84 (1H, dd, J=7, 1 Hz)], which was obtained by standing either 5a or 6a in organic solvent at room temperature in the presence of platinum dioxide gave a mixture of two saturated lactams (5a) and (6a). This suggests that the lactam (5a) has the trans-syn[8] configuration while the other (6a) has the trans-anti[8] one.

The different stereochemistry of the major products (5a) and (6b) prepared by the two Michael reactions using two different Michael acceptors (4b) and (4c) can be explained as follows. When the methoxymethyl ether (4b) is used as an acceptor, the kinetically formed adduct (A) is converted into the thermodynamically stable adduct (B) which affords the most stable lactam (5a) as the final product. On the other hand, when the lithium alcoholate (4c) is used as an acceptor, the kinetically formed adducts (C) and (D) are stabilized by chelation of the carbanion at the 3-position with lithium alcoholate as shown. The resulting lack of equilibrium leads to the formation of trans- and cis-anti adducts (6b) and (7b).

An alternative and short approach to (±)-emetine was investigated by using the 1-(lithiomethyl)isoquinoline (1b)[9] as a versatile donor and the ethyllactam (4e) as a simple acceptor. The latter was readily prepared by reduction of the corresponding mesylate (4d) of the alcohol (4a) with tri-n-butyltin hydride-2,2'-azobis-iso-butyronitrile in 74% overall yield. Michael reaction of the α,β-unsaturated lactam (4e) with the 1-(lithiomethyl)isoquinoline (1b), prepared from the isoquinoline (1a), proceeded smoothly at temperatures, ranging from -78°C to 25°C to give two adducts (9a) and (9b) in 43 and 11% yields, respec-





MOM=CH_2OMe

Ms=SO_2Me

tively [(9a) mp 154-155.5°C; ($CDCl_3$)δ: 1.92 (1H, br td, J=11, 4 Hz); (9b) mp 150.5-152°C; ($CDCl_3$)δ: 1.73 (1H, ddd, J=13, 11, 3 Hz)]. These adducts (9a) and (9b) were also interconverted to each other by treatment with sodium hydride in refluxing THF leading to ca. a 1:1 mixture of (9a) and (9b), as in the case of 6a and 7a. The main adduct (9a) is known to be a key intermediate[6] for the stereoselective synthesis of (±)-emetine. Thus, we have succeeded in the formal total synthesis of (±)-emetine by preparing the known[6] key intermediate (9a) in seven steps and in 22% overall yield from the isoquinoline (1a).

In conclusion, we have established an efficient synthesis of two key intermediates (5d) and (9a) for the synthesis of (±)-emetine. This has provided a new and general synthesis for other monoterpenoid alkaloids as well, such as corynantheine-heteroyohimbine group of alkaloids.[2]

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