AN ALTERNATIVE SYNTHESIS OF THE EMETINE ALKALOIDS FROM (±)-NORCAMPHOR INTENDING FOR A CHIRAL SYNTHESIS. A SYNTHESIS OF (±)-PROTOEMETINOL AND (±)-PROTOEMETINE AND A FORMAL SYNTHESIS OF (±)-EMETINE

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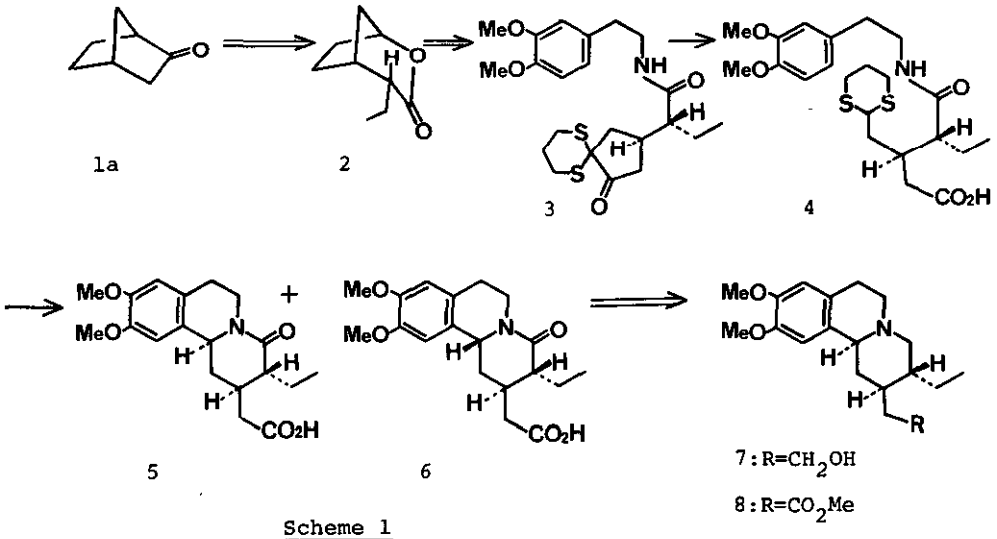
Intending for using (-)-norcamphor as a chiral precursor, (±)-norcamphor(1) has been converted into (±)-protoemetinol(7), (±)-protoemetine (20) and the emetine precursor(5) stereoselectively through a novel epimerization reaction.

Recently we have developed a new route to (±)-protoemetinol(7) and (±)-methyl protoemetinate(8) from (±)-norcamphor(1) by a stereoselective sequence and the method is expected to lead to a formation of these alkaloids in the natural configuration starting from (+)-norcamphor(1a) with bright promise.[1] However it would have a limited value from the practical point of view since the more accessible

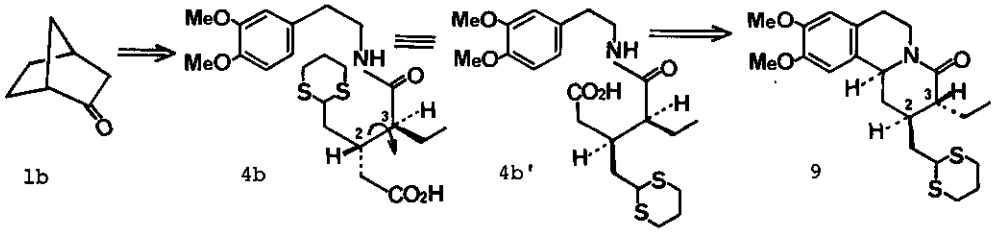


Scheme 1

alternative (-)-enantiomer(1b)[2] could not be utilizable (Scheme 1). In connection with our recent chiral synthesis of (-)-norcamphor(1b)[3], we report here a stereoselective synthesis of the emetine alkaloids in racemic forms which would make a construction of the natural configuration from (-)-norcamphor(1b) possible.

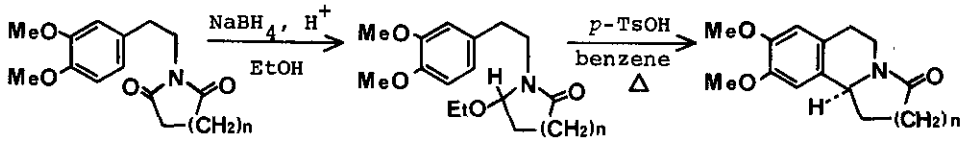
Following to the method described in Scheme 1, (-)-norcamphor(1b) would afford the amido carboxylic acid(4b) possessing useless unnatural configuration which, however, can be transformed into the desirable natural configuration provided two conversions, i) the cyclization at the carboxy carbon and ii) the epimerization at the C-3 carbon, are possible.

One can expect the lactam(9) with the natural configuration from 4b', an alternative description of 4b, through the specific cyclization at the carboxy carbonyl and the epimerization at C-3 carbon (Scheme 2). Based on these considerations we hoped to achieve a synthesis of (±)-protoemetine(20) according to the two ample precedents developed by Speckamp[4] and Kametani[5], respectively(Scheme 3).



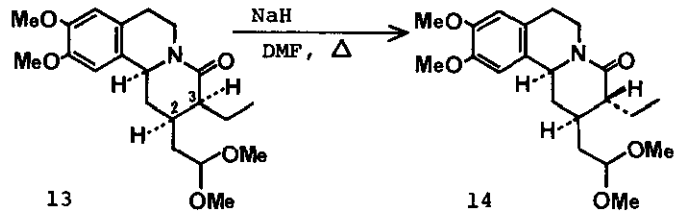
Scheme 2

Speckamp:



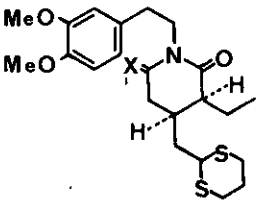
10:n=1∿2 11:n=1∿2 12:n=1∿2

Kametani:



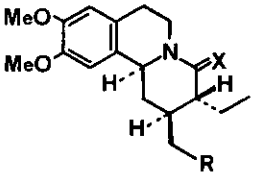
Scheme 3

By following Speckamp[4], the imide(15), prepared quantitatively from 4 by heating at 180°, was treated with sodium borohydride in aqueous ethanol keeping pH 8∿10 with dropwise addition of 2N hydrochloric acid to give the ω-ethoxy lactam(16), which, without purification, was then refluxed in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid giving three lactams, (17), (21) and (24), in yields of 24, 24 and 20 % from 15. Stereoselective cyclization could not be resulted, however it is noteworthy that the rest of the four possible stereoisomers and any of possible regioisomers were never detected from the reaction mixture. Since an application of the Kametani's condition[5] as well as the acidic condition[4] did not effect the stereochemistry of 24, the epimerization of the C-3 carbon was presumably taken place through a conjugated iminium ion(27) prior to the cyclization. However another possibility could not be excluded as high temperature was applied in the formation of the imide(15) which was nevertheless pure chromatographically.



15: X=O

16: X=H, OEt

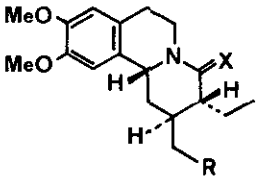


17: R=  , X=O

18: R=CHO, X=O

19: R=  , $X=H_2$

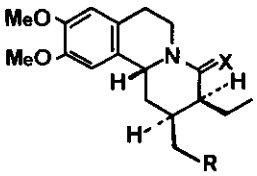
20: R=CHO, $X=H_2$



21: R=  , X=O

22: R=CHO, X=O

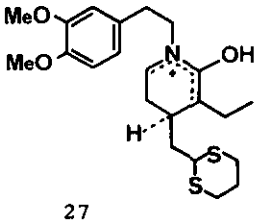
23: $R=CH_2OH$, $X=H_2$



24: R=  , X=O

25: R=CHO, X=O

26: $R=CH_2OH$, $X=H_2$



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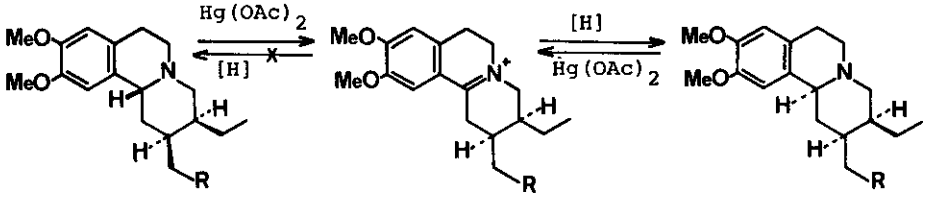
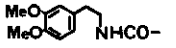
Scheme 4

Structures of three lactams were determined by converting them into the known compounds, respectively. Thus the first lactam(17) was hydrolyzed with methyl iodide in aqueous acetonitrile to give the corresponding aldehyde(18) which was oxidized with silver oxide in a diluted sodium hydroxide solution to give the known lactam acid(5)[1,6,7] in 75 % overall yield. Similarly the second lactam(21) was converted to the known lactam acid(6)[1,6,7] in 62 % overall yield *via* 22. Since both of the lactam acids have been converted into (±)-protoemetinol(26)[1] and (±)-emetine[1,6,7], these formation consisted a formal synthesis of these alkaloids. While the third lactam(24) on the same condition afforded the aldehyde(25) which on reduction with lithium aluminum hydride furnished three epimeric compounds, two known and one unknown. The former two compounds, (±)-protoemetinol(7) and (±)-11*b*-epiprotoemetinol(23), were determined by a comparison with the authentic materials. The third compound(26) which should have the same relative configuration of the parent lactam(24) was dehydrogenated by mercuric acetate in acetic acid[1,8] after acetylation to give the iminium salt(29c) which on reduction with sodium borohydride, followed by removal of the acetyl group yielded known C-3 epiprotoemetinol(30:R= CH_2OH)[5] exclusively. Exclusive formation of 30 from 26 was completely compatible with the results observed in the related compounds with the same configuration by Openshaw and Whittaker[8] who showed the exclusive conversion of 28a,b into 30a,b through the dehydrogenation-hydrogenation sequence (Scheme 5).

Openshaw and Whittaker:



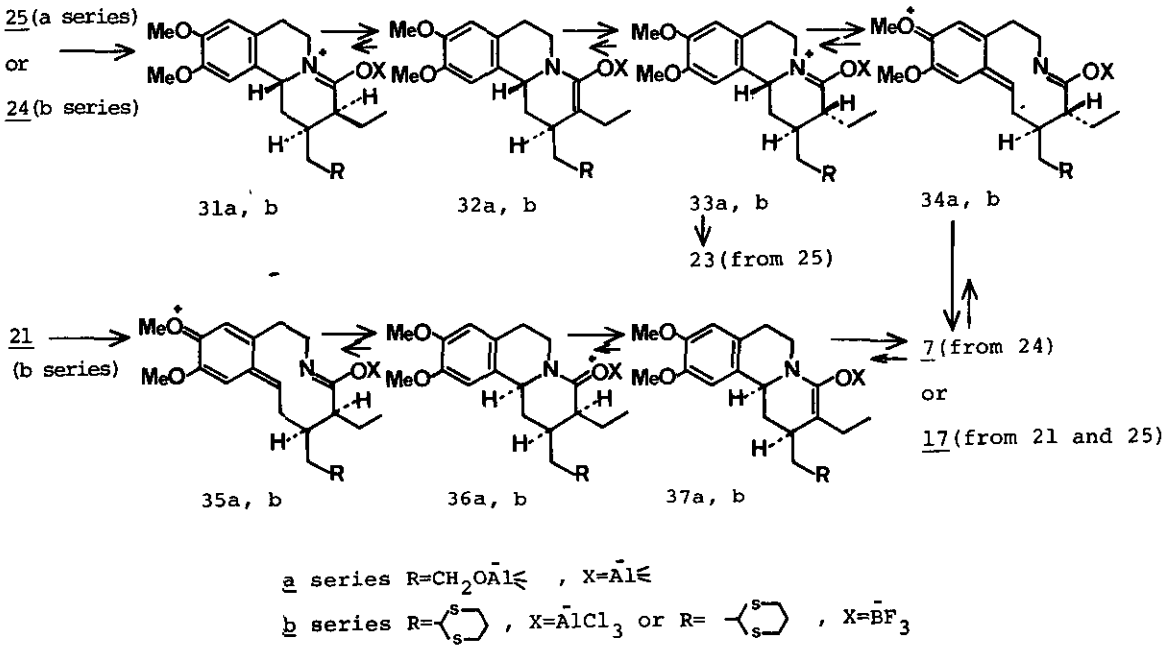
28a, b, c 29a, b, c 30

a series R=CO_2Me b series R=  c series R=CH_2OAc

Scheme 5

As we assumed that the concomitant epimerization during the reduction occurred through a transient formation of the B/C-seco intermediates[1], such as 34a and 35a, the lactam(24) was exposed to an excess of aluminum chloride in benzene expecting

to isomerize to the thermodynamically more stable lactam 17 with the natural configuration through the B/C seco-intermediates, 34b and 35b. Expected reaction really did take place giving 17 after stirring at room temperature for 20 hr and the reaction found to occur more readily using boron trifluoride etherate which could bring a complete epimerization of 24 within 2 hr at room temperature. In the conversion initial formation of the second lactam(21) was clearly recognized by thin layer chromatography. At this point our initial intention using (-)-norcamphor (1b) as a chiral synthon for the emetine alkaloids possessing the natural configuration would have achieved, since no epimerization at the C-2 carbon should be expected in the conversion. (Scheme 6)



Scheme 6

The lactam(17) which could be now obtained quantitatively from the epimeric lactams was transformed into (±)-protoemetine(20) in 56 % overall yield through a two step sequence. Thus 17 was reduced with lithium aluminum hydride in boiling tetrahydrofuran to give the amino dithiane(19) whose hydrochloride on treatment with methyl iodide in aqueous acetonitrile[9] and workup furnished (±)-protoemetine (20)[10]

Acknowledgment We wish to thank Professor Tetsuji Kametani, Pharmaceutical Institute, Tohoku University, for providing (±)- C-3 epiprotoemetinol(30:R=CH_2OH) and the spectra of (±)-protoemetine(20).

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Received, 9th March, 1979