Tetrahedron Letters,Vol.24,No.42,pp 4577-4580,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF (±)-CONHYDRINE, (±)-EPHEDRINE, AND (±)-*N*-METHYLEPHEDRINE[1]

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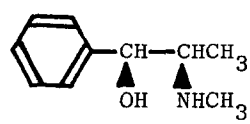
(±)-Conhydrine, (±)-ephedrine, and (±)-*N*-methylephedrine have been synthesized with a complete stereochemical control by utilizig carbanions in which the negative charge is located at the position α to the nitrogen atom of *N*-acylamines.

Some naturally occurring physiologically active compounds possess a vicinal *erythro*-aminoalcoholic moiety as exemplified by ephedrine **1**.[2] Carbanions **3**[3] where the negative charge is located at the position α to the nitrogen atom of *N*-acyl-,[4] *N*-thioacyl-,[5] or *N*-nitroso-amines[6] or amidines[7] **2** have recently been shown to be promising intermediates for the formation of a vicinal aminoalcoholic structure, though the stereochemistry is generally not controlled (eq. 1).



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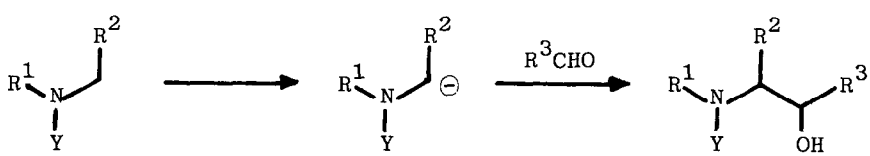


2 **3** **4**

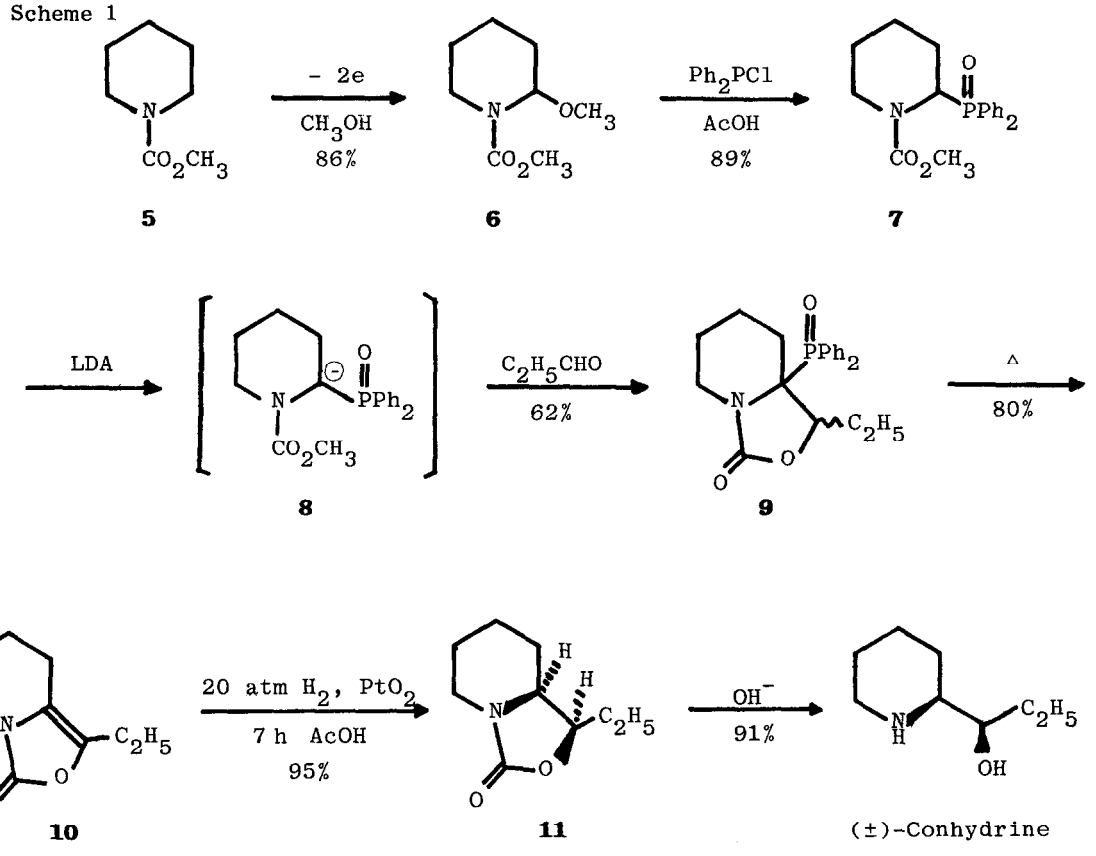
Y : -COR, -CSR, -NO, -CH=N-R (1)

We wish to report herein efficient methods for the synthesis of compounds having a vicinal *erythro*-aminoalcoholic moiety from **2** (Y = CO_2CH_3) with a complete stereochemical control.

The synthesis of (±)-conhydrine from *N*-carbomethoxypiperidine **5** is shown in Scheme 1 as a typical example of our new method, in which the following points are the noteworthy characteristics of the new method.

Developing a cationic center at the position α to the nitrogen atom of an *N*-acylamine followed by carbon-carbon bond formation at the α-position has been shown to be achievable by anodic α-methoxylation of the *N*-acylamine and subsequent treatment of the α-methoxyl compound with a nucleophile in the presence of an acidic catalyst.[8]

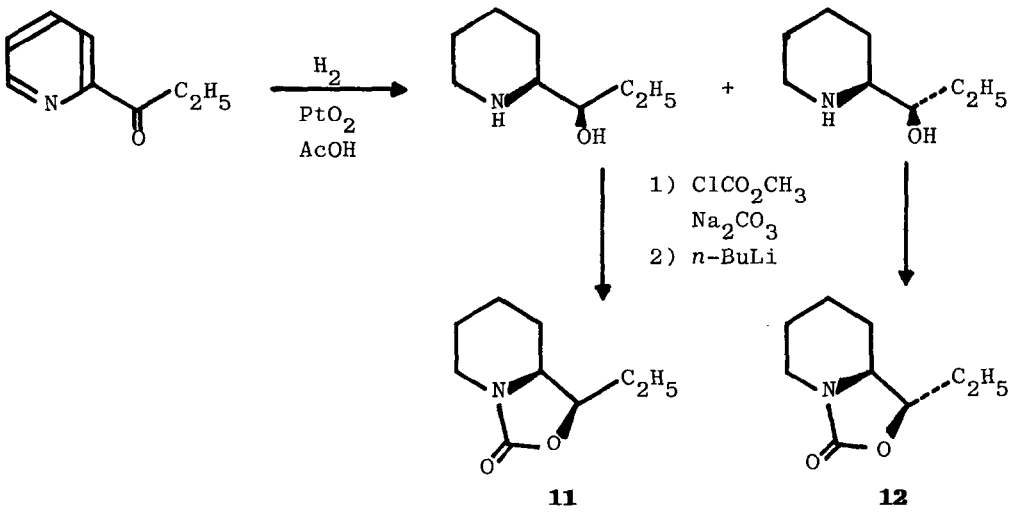
Scheme 1



On the other hand, developing an anionic center at the α-position of the *N*-acylamine requires a highly strong base[5a-d, 7] which may bring about undesirable side reactions. One of the characteristics of our method shown in Scheme 1 is that the α-anion **8** of the *N*-acylamine was easily formed by the reaction[9] of chlorodiphenylphosphine with α-methoxylated carbamate **6** followed by the deprotonation at the α-position. The product yielded by the reaction of **8** with propionaldehyde easily formed 2-oxazolidone ring **9**, which was one of the key points to make this synthesis stereoselective. The easy thermal removability of the diphenylphosphinyl group gave the corresponding 2-oxazolone derivative **10** in high yield.[10] The hydrogenation of **10** in acetic acid in the presence of PtO_2 proceeded with perfect stereoselectivity to yield the *erythro*-isomer **11** (the selectivity, > 98.5%). The identification of **11** was carried out gas chromatographically by comparison with authentic samples **11** and **12** independently prepared from 2-propionylpyridine as described in Scheme 2.[11] Alkaline hydrolysis of **11** gave (±)-conhydrine[2] as expected.

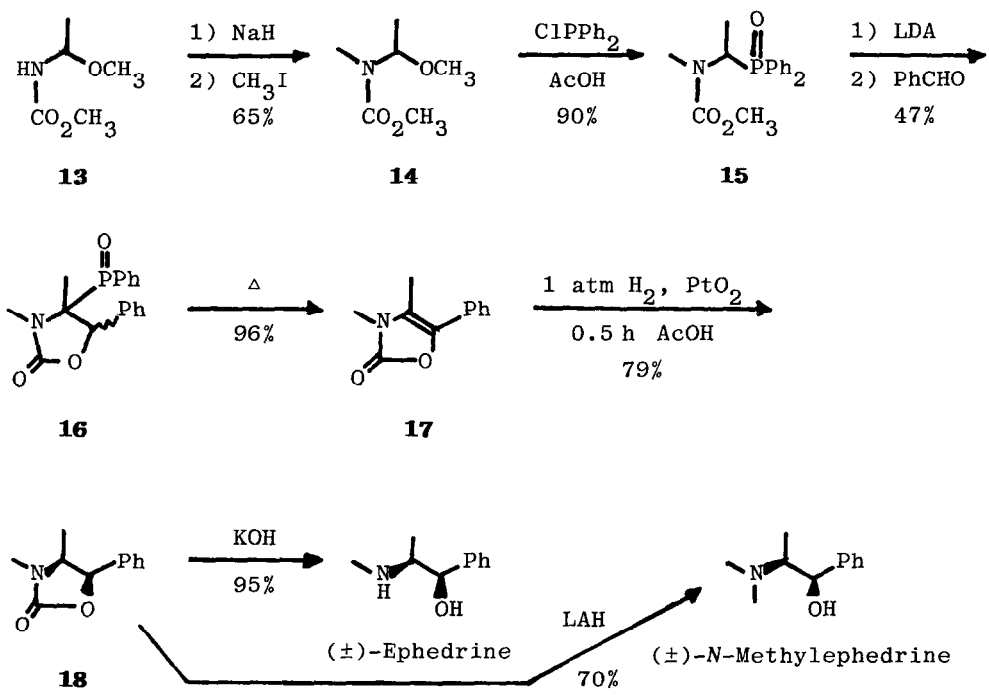
Our method was also successfully applied to the synthesis of (±)-ephedrine and (±)-*N*-methylephedrine (Scheme 3). The starting α-methoxycarbamate **13** was prepared by the anodic

Scheme 2



11 **12**

Scheme 3



13 **14** **15** **16** **17** **18**

oxidation of *N*-carbomethoxyethylamine in methanol (83%).[12] The *N*-methylation of **13** followed by the treatment of the *N*-methylated product **14** with chlorodiphenylphosphine gave **15**, which was subsequently allowed to react with benzaldehyde to yield 2-oxazolidone **16**. The formation of 2-oxazolone **17** from **16** was achieved in a similar way to the transformation of **9** to **10**,[13] while the hydrogenation of **17** to **18** required careful reaction conditions. Namely, in the presence of PtO_2, **17** was satisfactorily hydrogenated in acetic acid by the treatment with an atmospheric pressure of hydrogen for a rather short period (0.5-0.7 h), whereas prolonged reaction decreased the yield of **18**. Alkaline hydrolysis of **18** afforded (±)-ephedrine selectively, while the reduction of **18** with LAH yielded (±)-*N*-methylephedrine.[2]

Acknowledgment. One of the authors (Y.M.) wishes to thank the Ministry of Education, Science, and Culture, Japan, for a Grant-in-Aid for Scientific Research (B) (No. 57470066).

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(10) A small amount of a by-product **10'** was formed in 7% yield.
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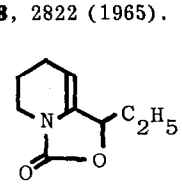
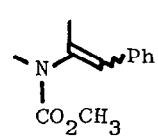
(13) The uncyclized product **16'** was also obtained as a by-product in 46% yield.



10'



16'

(Received in Japan 30 June 1983)