Tetrahedron Letters No. 52, pp 4595 - 4598, 1977. Pergamon Press. Printed in Great Britain.

ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED DIHYDROISOCARBOSTYRIL DERIVATIVES

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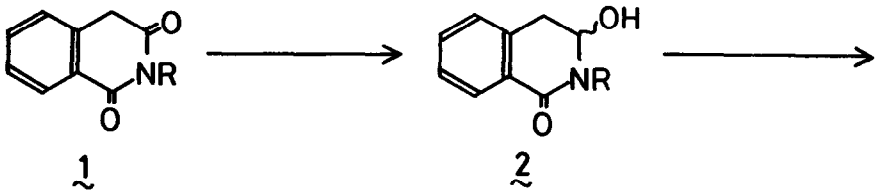
(Received in Japan 29 September 1977; received in UK for publication 27 October 1977)

Despite well-developed methodology for the carbon-carbon bond formation at C-1 position in isoquinoline skeleton (e.g., Reissert reaction[1]), there is no comparable procedure for the introduction of an alkyl group at C-3 position in dihydroisocarbostyril derivatives. We have recently developed a novel asymmetric syntheses of 2-oxo-5-pyrrolidineacetic acid and 2-oxo-6-piperidineacetic acid by Wittig-Horner reaction of 5-hydroxy pyrrolidone and 6-hydroxy piperidone derivatives respectively.[2,3] In this report we describe a facile method for the introduction of an alkyl group at C-3 position in heterocyclic nuclei of isocarbostyril derivatives, which is both general and asymmetric.

Reaction of homophthalic acid with (S)-(-)-α-phenethylamine at 200°C for 4 hr afforded the optically active imide 1 [oil, $[\alpha]_D^{22}$-155° (C=1.2, EtOH)[4]]. The imide 1 was reduced with $NaBH_4$ at 19°C to give 2-(S)-α-phenethyl-3-hydroxy-3,4-dihydroisocarbostyril (2) as a diastereomeric mixture in 94% yield. The ratio of the diastereomers was ca. 2.8 : 1, although they were used without separation for the next step. At this stage we applied Wittig-Horner reaction. Treatment of 2 with methyl diethylphosphonoacetate (1.8 mol. equiv.) and sodium hydride in tetrahydrofuran (THF) at 4°C for 15 hr gave a mixture of diastereomeric esters (3a and 4a) in 65% yield. The ratio of the two diastereomers (3a : 4a) could be determined as 70 : 30 from the nmr assay of the methyl signals (in $CDCl_3$, δ 3.61 and 3.46 ppm) of the ester groups in these diastereomers. Hydrolysis of the above mixture of esters (3a and 4a) with aqueous methanolic potassium hydroxide



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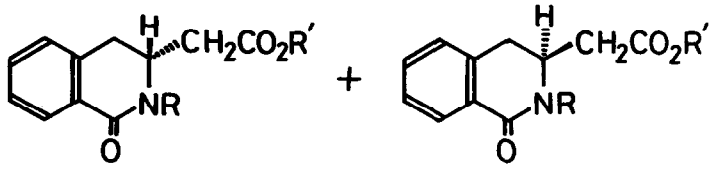
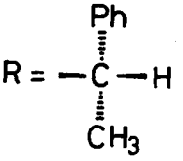
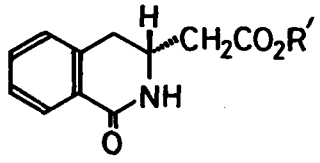


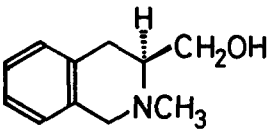
3 a: R′=CH3
b: R′=H

4 a: R′=CH3
b: R′=H





5 a: R′=CH3
b: R′=H



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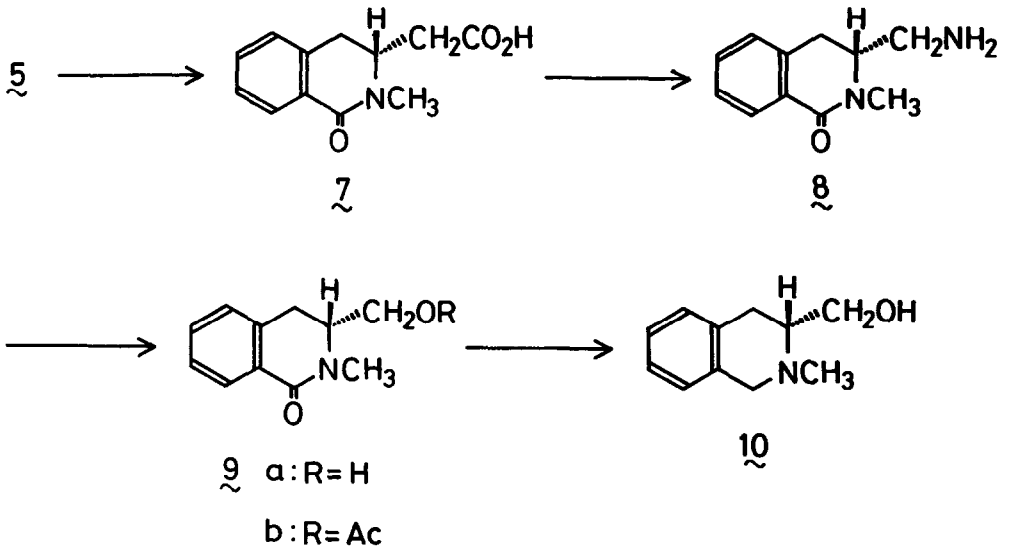
to a mixture of the acids (3b and 4b) and subsequent recrystallization from a mixture of ethanol and methanol afforded optically pure 3b in 31% yield [m.p. 232-233°C, $[\alpha]_D^{26}$-161° (C=1.0), nmr (in DMSO-d_6, δ); 1.60 (3H, d, J=7 Hz), 3.72-3.98 (1H, m), 5.98 (1H, q, J=7 Hz), and 12.32 (1H, s)]. In order to remove the chiral controlling (S)-α-phenethyl group the optically pure acid 3b was treated with 6N-HCl under reflux to give enantiomerically pure (R)-(-)-3-carboxymethyl-3,4-dihydroisocarbostyril (5b) in 85% yield [m.p. 178-180°C, $[\alpha]_D^{25}$-23.8° (C=0.7)]. Esterification of 5b with CH_2N_2 gave the ester 5a [m.p. 134-135°C,

$[\alpha]_D$-41.3° (C=1.0), δ ($CDCl_3$) 2.56-2.70 (2H, m, $C\underline{H}_2CO_2CH_3$), 3.68 (3H, s, $CO_2C\underline{H}_3$), and 3.99-4.31 (1H, m, $C\underline{H}CH_2CO_2CH_3$)]. We have also found that the same reaction of 2 in dimethylformamide instead of THF afforded a 66.5 : 33.5 mixture of diastereomeric esters (3a : 4a) in 62% yield.

The absolute configuration of 5b was determined by the chemical correlation as follows. Kato et al[5] recently reported the formation of (S)-(-)-2-methyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (6) [lit. $[\alpha]_D^{15}$-92.3°] from L-phenylalanine. In order to relate 5b to Kato's compound 6, 5b was methylated with methyl iodide and NaH and was followed by alkaline hydrolysis to yield (R)-(-)-2-methyl-3-carboxymethyl-3,4-dihydroisocarbostyril (7) [m.p. 208-210°C, $[\alpha]_D^{24}$-189° (C=0.75)] in 77% yield. The compound 7 was converted to the amine 8 [$[\alpha]_D^{24}$-224° (C=0.6)] in 76% yield by treatment with diphenyl phosphorazidate[6]-benzylalcohol and then by catalytic reduction (5% Pd-C) successively. Nitrous



acid deamination of the amine 8 in aqueous acetic acid afforded the alcohol 9a $[\alpha]_D^{24}$-201° (C=0.8)] in 24% yield and the acetate 9b [$[\alpha]_D^{24}$-194° (C=0.7)] in 31% yield. Reduction of 9a with lithium aluminum hydride in THF gave R-(+)-2-methyl-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (10) [m.p. 108-109°C,

$[\alpha]_D^{24}$+85.1° (C=0.6, MeOH)] in 86% yield which showed identical spectra (IR, NMR) and TLC mobilities with the compound 6 prepared according to the literature[5], but the sign of optical rotation of 10 was opposite. Therefore, the absolute configuration at C-3 in 5b was rigorously determined as R.

Thus, this newly developed methodology for the asymmetric C-C bond formation at C-3 in 3,4-dihydroisocarbostyril skeleton will open new synthetic routes for a broad category of optically active 1,2,3,4-tetrahydroisoquinoline derivatives.

Acknowledgement.

We thank Drs. S. Ishimoto and Y. Kato for their encouragement and advice.

References and Notes

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3. T. Wakabayashi, K. Watanabe, Y. Kato, and M. Saito, Chemistry Letters, 223 (1977).
4. All the optical rotation measurement was carried out in EtOH unless otherwise specified.
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