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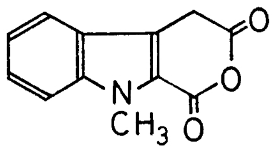
ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED 3,4-DIHYDRO-β-CARBOLINONES

Toshio WAKABAYASHI* and Kenzo WATANABE
Teijin Institute for Biomedical Research
4-3-2 Asahigaoka, Hino, Tokyo 191

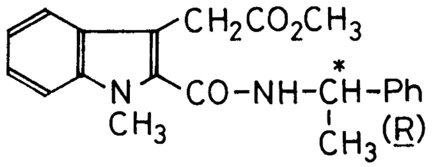
A novel method of phase-transfer catalysed alkylation at C-3 position of 3,4-dihydro-β-carbolinones and an asymmetric synthesis of (*S*)-3-carbomethoxymethyl-9-methyl-3,4-dihydro-β-carbolinone (**7**) are reported.

There is no general methodology for direct introduction of an alkyl group at the C-3 position of β-carboline derivatives. Here we describe a novel method for the direct introduction of an alkyl group at the C-3 position of 3,4-dihydro-β-carbolinones, which offers an access to optically active 3-substituted β-carboline derivatives.

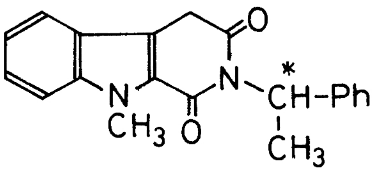
The anhydride (**1**)[1], after methanolysis (NaOMe, MeOH), was treated with (*R*)-(+)-α-phenethylamine and diethyl phosphorocyanidate[2] in DMF to give the amide (*R*)-(**2**) {$[\alpha]_D^{22}$ - 41.6° (EtOH), m.p. 124-125°C, 78% from (**1**)}. Reaction of (*R*)-(**2**) with NaOMe (1.1 equiv.) in MeOH afforded the imide (*R*)-(**3**) {$[\alpha]_D^{22}$ + 167.4° ($CHCl_3$), m.p. 139-140°C, 36%}. Reduction of (*R*)-(**3**) with $NaBH_4$ by Iida's procedure[3] afforded the alcohol (*R*)-(**4**), which without purification was subjected to phase-transfer catalysed Wittig-Horner reaction {diethyl cyanomethylphosphonate, 50% NaOH, nBu_4NBr (0.1 mole equiv.), CH_2Cl_2} to afford a diastereomeric mixture of {(*RS*)-(**5a**) and, (*RR*)-(**6a**)}. Hydrolysis (KOH-aq. EtOH) of the above mixture was followed by esterification with CH_2N_2 to give a mixture of diastereomeric esters {(*RS*)-(**5b**) and (*RR*)-(**6b**), 42% from (*R*)-(**4**)}. The ratio of the two diastereomers {(*RS*)-(**5b**) : (*RR*)-(**6b**)} could be determined as 70 : 30 by the ^1H NMR assay of the methyl signals of the methyl ester groups {in $CDCl_3$: (*RS*)-(**5b**), δ 3.62 ; (*RR*)-(**6b**), δ 3.45}.



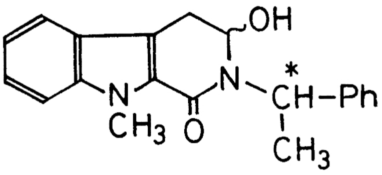
(1)



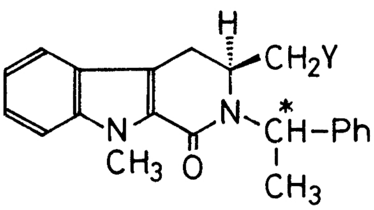
(R)-(2)



(R)-(3)

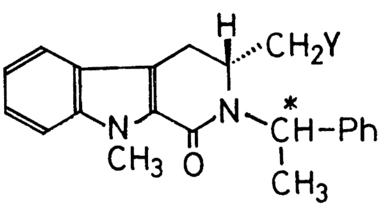


(R)-(4)



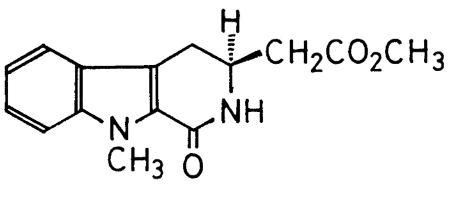
(5a) ,Y=CN

(5b) ,Y=CO_2CH_3

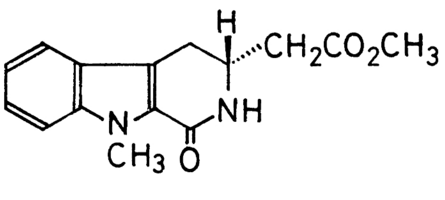


(6a) , Y=CN

(6b) ,Y=CO_2CH_3



(7)

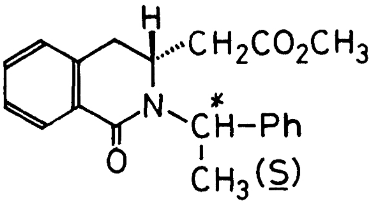


(8)

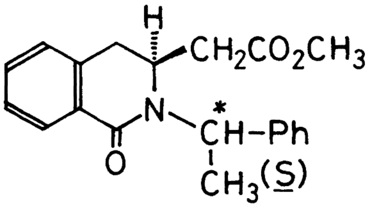
In our previous work, the absolute configurations of (SR)-(9)[4], (SS)-(10)[4], (RS)-(11)[5] and (RR)-(12)[5] were determined by chemical correlations. The ^{1}H NMR chemical shift values of the ester methyl groups of these pairs of diastereomers were as follows: (SR)-(9), δ 3.61 ; (SS)-(10), δ 3.46 ; (RS)-(11), δ 3.63 ; (RR)-(12), δ 3.53. In these compounds the ester methyl group of (SR) or (RS) diastereomer resonates in lower field than that of (SS) or (RR) diastereomer.

Also, Wittig-Horner reaction of (S)-(13) afforded a mixture of diastereomers {(SR)-(9) and (SS)-(10)} in the ratio of 69 to 31 favoring (SR)-(9)[6]. Therefore it is reasonable to assign the S absolute configuration at the C-3 position of the present (5b), which showed the lower chemical shift of its ester methyl group and was the major diastereomer.

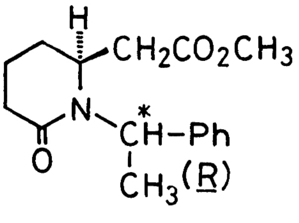
The above mixture of diastereomeric esters (5b) and (6b) was separable by column chromatography on silica gel. In order to remove the R-α-phenethyl group by an acid catalyst the major diastereomer (RS)-(5b) {$[\alpha]_D^{21}$ + 40.6° (EtOH), m.p. 107-109°C} was exposed to methanolic HCl under reflux to furnish enantiomerically pure (S)-3-carbomethoxymethyl-9-methyl-3,4-dihydro-β-carbolinone (7) {IR ($CHCl_3$) 3410 cm^{-1} (NH), $[\alpha]_D^{23}$ + 47.2° (EtOH), m.p. 135-127°, 76%}. The minor one (RR)-(6b) {$[\alpha]_D^{21}$ - 21.7° (EtOH)} resulted in (R)-(8) {$[\alpha]_D^{21}$ - 44.8° (EtOH)} in the same way.[7]



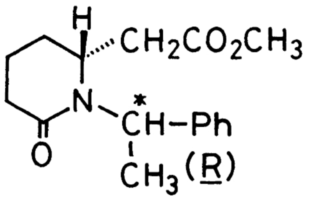
(SR)-(9)



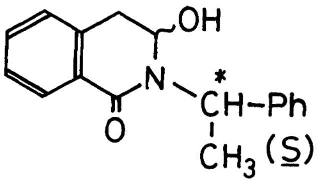
(SS)-(10)



(RS)-(11)



(RR)-(12)



(S)-(13)

Table

Entry	PTC (mole equiv.)	Temp. (°C)	Time (min)	%Diastereomer Excess*
1	nBu_4NBr (0.2)	20	15	42
2	benzylquininium bromide (0.2)	20	15	45
3	methylquininium bromide (0.2)	20	15	45

* The major diastereomer is (*RS*)-(**5a**).

Further, we used chiral phase-transfer catalysts (benzylquininium bromide, methylquininium bromide) in stead of tetrabutylammonium bromide for the above mentioned phase-transfer catalysed Wittig-Horner reaction of (*R*)-(**4**) in order to know the effect of these chiral catalysts on the diastereoselectivity of the reaction. But the results (in Table) did not show any appreciable change in the products ratio between (*RS*)-(**5a**) and (*RR*)-(**6a**).

Acknowledgement.

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References and Notes

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7. The smaller absolute value of optical rotation of (*R*)-(**8**) is due to slight contamination with (**7**).

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