SYNTHESIS OF 1,3-LINKED 1,4-DIHYDROPYRIDINES CONTAINING THE L-TYROSINE RESIDUE AND THE INFLUENCE OF THEIR STRUCTURES UPON THE ENANTIOSELECTIVE REDUCTION

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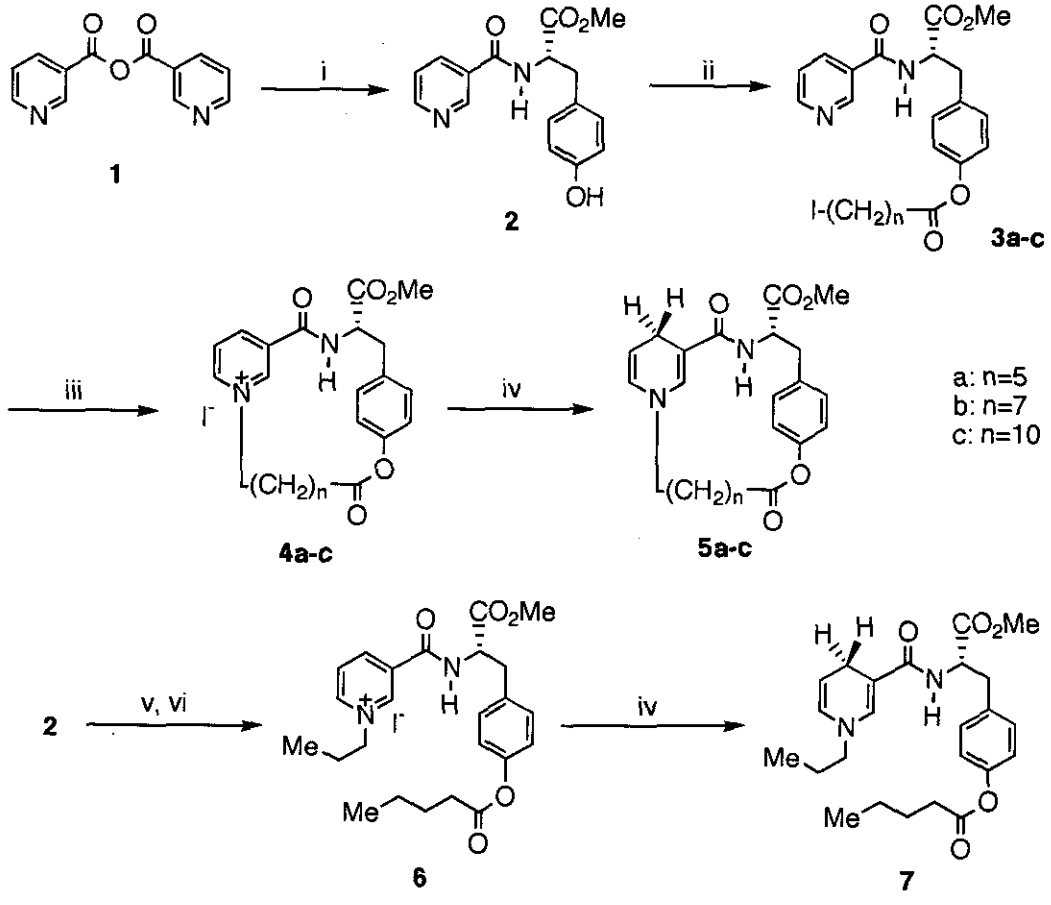
Abstract — Novel 1,3-linked chiral 1,4-dihydropyridines (**5a-c**) bearing the L-tyrosine residue and the long alkyl chains have been synthesized. The ring size gave a large influence upon the enantioselective reduction of methyl benzoylformate, where 1,12-oxo-2,20-diaza-3-methoxycarbonyl-11-oxa-20,23-dihydro[4.9]metaparacyclophane (**5b**) showed the highest enantiomer excess (ee, 70%). Further, the 1,3-cyclic structure (**5**) was demonstrated to be effective on the enantioselective reduction compared to the corresponding acyclic one (**7**), *N*-(1-propyl-1,4-dihydro-3-pyridylcarbonyl)-L-(*O*-pentanoyl)tyrosine methyl ester.

Ohno and co-workers have reported the first example of the stereoselective reduction of an achiral substrate with a NAD(P)H model.[1] Since then, numerous 1,4-dihydronicotinamide analogues[2-17] containing various chiral auxiliaries and functional groups have been synthesized in order to investigate the feature of the stereospecific reduction and to apply them to synthetic organic chemistry. Surprisingly, no paper has been reported on 1,4-dihydropyridine bearing the cyclic structure at 1- and 3-positions, to the best of our knowledge. It is known that only one of two prochiral hydrogens on the C-4 position in the dihydropyridine ring of NAD(P)H is transferred to a prochiral substrate, and this stereospecificity is attributed to the shielding of one side of the dihydropyridine plane by the protein structure. Therefore, we describe herein the synthesis of novel 1,3-linked chiral 1,4-dihydropyridines bearing the L-tyrosine residue and the long alkyl chain as components of the cyclic structure, which

would be expected to show the shielding effect of one of two sides by the benzene ring by virtue of the restricted conformation, and their enantioselectivity upon reduction of methyl benzoylformate.

The synthetic procedure for 1,3-linked 1,4-dihydropyridines (**5a-c**) was depicted in Scheme 1. Nicotinic anhydride (**1**) was allowed to react with L-tyrosine methyl ester (H-Tyr-OMe) in the presence of Et_3N to give nicotinamide (**2**) in a 72% yield. Treatment of compound (**2**) with ω-iodoalkanoyl chlorides and subsequent cyclization of compounds (**3a-c**) in MeCN under the high dilution condition afforded the 1,3-



Reagents and conditions: i) HCl.H-Tyr-OMe, Et_3N, in dry THF 5 h at rt.; ii) I-$(CH_2)_n$COCl/ Et_3N in $CHCl_3$ 2 h at 0 °C; iii) reflux in MeCN (20 days for **4a**, 7 days for **4b** and **4c**); iv) $Na_2S_2O_4$/aq. $NaHCO_3$ in MeCN/CH_2Cl_2, 5 h in the dark at rt under N_2; v) $Me(CH_2)_3COCl$/ Et_3N in $CHCl_3$ 2 h at 0 °C; vi) $Me(CH_2)_2I$ reflux for 2 days in $CHCl_3$.

Scheme 1

linked pyridinium salts (**4a-c**) in 30 to 86% yields. On ^{1}H NMR spectra in DMSO-d_6 solutions, the H-2 proton chemical shift (9.35 ppm) of the pyridinium ring of compound (**4c**) was very close to that (9.42 ppm) of acyclic compound (**6**), while H-2 protons of compounds (**4a**, 8.51 ppm) and (**4b**, 8.71 ppm) were shifted to the upper-magnetic field, indicating the existence of the anisotropic effect of the benzene ring of the tyrosine residue by virtue of the restricted conformation. Finally compounds (**4a-c**) were subjected to the reduction with sodium dithionite in the presence of $NaHCO_3$ to give the desired 1,3-linked 1,4-dihydropyridines (**5a-c**)[18] in 33 to 89% yields.

The acyclic model compound (**7**)[19] was also prepared from compound (**2**) in a similar manner to compound (**5**) as shown in Scheme 1.

A typical procedure for the reduction of methyl benzoylformate with synthetic NAD(P)H models is as follows. A mixture of compound (**5a**) (80 mg, 0.2 mmol), methyl benzoylformate (33 mg, 0.2 mmol), and $Mg(ClO_4)_2$ (45 mg, 0.2 mmol) in dry MeCN (4 mL) was stirred for 72 h at 20 °C under N_2 atmosphere in the dark. H_2O (5 mL) and Et_2O (50 mL) was added to the reaction mixture and then the organic phase separated was dried over anhydrous Na_2SO_4. The chemical yield and the enantiomer excess (ee) of the resulting methyl mandelate were determined by means of GC[20] and HPLC[21], respectively, and the results are summarized in Table 1.

Table 1. Chemical yield, ee, and configuration of methyl mandelate

model	chemical yield (%)	ee (%)	configuration
5a	29	67	*S*
5b	46	70	*S*
5c	31	40	*S*
7	74	10	*R*

1,3-Linked 1,4-dihydropyridine models (**5a-c**) showed higher ee values than the acyclic one (**7**), and ee values were also affected by the methylene chain length. Further, the influence of temperature and of the amount of $Mg(ClO_4)_2$ upon chemical yield and ee value was examined using compound (**5b**). (Figure 1) It was ascertained that the chemical yield was remarkably increased with a rise in temperature and with an increase of $Mg(ClO_4)_2$, while the ee value was little affected by both factors.

In conclusion, the ring size and structure (cyclic vs acyclic) give a great influence upon the enantioselective reduction of methyl benzoylformate to methyl mandelate.

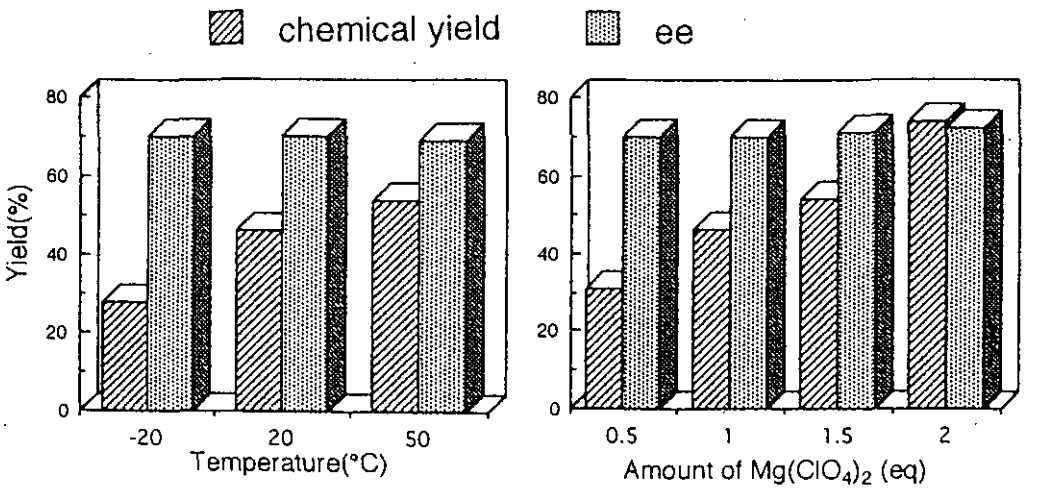


Figure 1 Influence of temperature and the amount of $Mg(ClO_4)_2$ upon reduction of methyl benzoylformate with compound (**5b**)

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18. Compound (**5a**): yield: 33 %; IR(KBr): 1737, 1683, and 1630 cm^{-1}; ^1H NMR(δ, 270 MHz, $CDCl_3$): 1.45-1.82 (m, 6H, $NCH_2(CH_2)_3$), 2.46 (m, 2H, CH_2CO_2), 2.57-3.44 (m, 6H, $CHCH_2Ph$, NCH_2 and 4-CH_2), 3.81 (s, 3H, CO_2CH_3), 4.66 (dt, 1H, J=3 and 8 Hz, 5-*H*), 5.03-5.20 (m, 2H, *NH* and *CH*), 5.60 (d, J=8 Hz, 6-*H*), 6.35 (s, 1H, 2-*H*) and 7.13 ppm(m, 4H, *Ph*); $[\alpha]_D$: -123° (c=0.8, in $CHCl_3$); λ_{max} ($CHCl_3$): 245 and 356 nm. Compound (**5b**): yield: 40 %; ^1H NMR(δ, 270 MHz, $CDCl_3$): 1.13-1.84 (m, 10H, $NCH_2(CH_2)_5$), 2.51-2.59 (m, 2H, CH_2CO_2), 2.82-3.39 (m, 6H, $CHCH_2$, NCH_2Ph and 4-CH_2), 3.81 (s, 3H, CO_2CH_3), 4.66 (dt, 1H, J=3 and 8 Hz, 5-*H*), 5.00 (m, 1H, *CH*), 5.47 (d, 1H, J=9 Hz, *NH*), 5.64 (d, J=8 Hz, 6-*H*), 6.26 (s, 1H, 2-*H*) and 7.04 ppm(m, 4H, *Ph*); $[\alpha]_D$: -49°(c=0.3, in$CHCl_3$); λ_{max} ($CHCl_3$): 243 and 355 nm. Compound (**5c**): yield: 89 %; ^1H NMR(δ, 270 MHz, $CDCl_3$): 1.22-1.82 (m, 16H, $NCH_2(CH_2)_8$), 2.55 (m, 2H, CH_2CO_2), 2.88-3.20 (m, 6H, $CHCH_2$, NCH_2Ph and 4-CH_2), 3.79 (s, 3H, CO_2CH_3), 4.68 (dt, 1H, J=3 and 8 Hz, 5-*H*), 5.01 (m, 1H, *CH*), 5.54 (d, 1H, J=9 Hz, *NH*), 5.65 (d, 1H, J=8 Hz, 6-*H*), 6.67 (s, 1H, 2-*H*), 6.98(d, 2H, J=9 Hz, *Ph*), and 7.09 ppm (d, 2H, J=9 Hz, *Ph*); $[\alpha]_D$: +3.5° (c=0.5, in $CHCl_3$). λ_{max} ($CHCl_3$): 241 and 347 nm.

19. Compound (**7**): yield: 91 %. IR(KBr): 1751 and 1684 cm^{-1}; ^1H NMR: (δ, 270 MHz, $CDCl_3$) 0.87 (d, 3H, J=7 Hz, CH_3), 0.92 (d, 3H, J=7 Hz, CH_3), 1.38-1.63 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.68-1.79 (m, 2H, NCH_2CH_2), 2.54 (t, 2H, J=7 Hz, CH_2CO_2), 3.00-3.18 (m, 6H, NCH_2, $CHCH_2Ph$ and 4-CH_2), 3.70 (s, 3H, CO_2CH_3), 4.69 (m, 1H, 5-*H*), 4.97 (m, 1H, NHC*H*), 5.57 (d, 1H, J=8 Hz, *NH*), 5.72 (d, 1H, J=8 Hz, 6-*H*), and 6.98-7.13 ppm (m, 5H, *Ph* and 2-*H*); $[\alpha]_D$: +28.5° (c=0.5, in $CHCl_3$). λ_{max} ($CHCl_3$): 244 and 358 nm.

20. The chemical yield was determined by means of GC in the following conditions: apparatus: Shimadzu GC-8A equipped with a flame ionization detector using a capillary column containing DB-5MS (30 m x 0.319 mm x 0.5 mm); carrier gas: N_2 (50 mL/min); injector temperature: 250 °C; column temperature: 110 °C; retention time: 19 min (methyl mandelate) and 20 min (methyl

benzoylformate).

21. The ee value of methyl mandelate was determined by means of HPLC in the following conditions: apparatus: Jasco 980-PU and 970-UV equipped with a Jasco 807 IT integrator using an optically active column (Daicel CHIRALCEL OJ); solvent: hexane:2-propanol (9:1) mixture; flow rate: 0.5 mL/min; retention time: 27 min ((*R*)-methyl mandelate) and 31 min ((*S*)-methyl mandelate).

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