A Stereoselective Route to Enantiomeric 2-Alkyl-1,2,3,6-tetrahydropyridines

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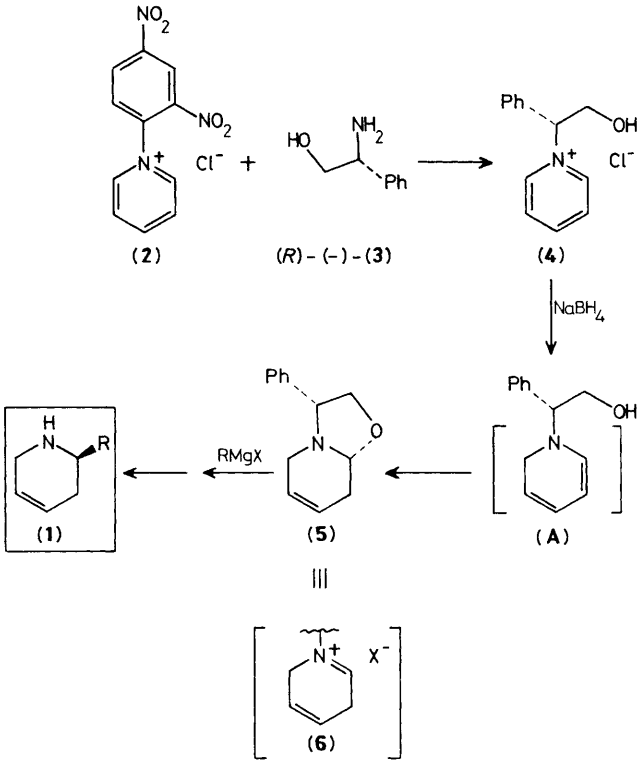
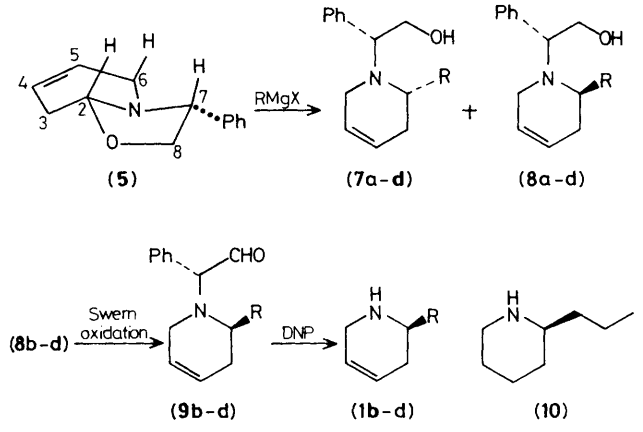
A synthesis of (*R*)- or (*S*)-2-alkyl-1,2,3,6-tetrahydropyridines (**1**), starting from (*R*)- or (*S*)-phenylglycinol and Zincke's salt (**2**), and proceeding *via* the new oxazolidine derivative (**5**) as a key intermediate, is described.

Stereoselective alkylation of the carbon atoms adjacent to the nitrogen of the piperidine ring is an important goal in alkaloid synthesis, but stereoselective methods reported so far are relatively limited. A general strategy, known as the CN(*R*,*S*) approach, allowing substitution at positions 2 and 6, makes use of cyano-oxazolidines obtained from phenylglycinol *via* '1,4-dihydropyridine' intermediates.[1] Other syntheses of chiral 2-alkyl-1,2,5,6-tetrahydropyridines[2] and 2-alkyl-piperidines[3] have also been reported. We describe a new route which, based upon the sequence of reactions depicted in Scheme 1,† provides easy access to chiral 2-alkyl-1,2,3,6-tetrahydropyridines (**1**).

† The sequence is depicted starting from (*R*)-(−)-(**3**) but could be applied to readily available (*S*)-(+)-(**3**) as well.



Scheme 1



Scheme 2

a; R = Pr^n
b; R = $PhCH_2$
c; R = Ph
d; R = 3-pyridyl

Coupling of Zincke's salt (**2**) with chiral amines and reduction of the resulting pyridinium salts with $NaBH_4$ in an alkaline medium offers a practical, non-racemizing route to 1,2-dihydropyridines *N*-substituted with various chiral auxiliaries.[4] This two-step procedure has now been applied to amino alcohols derived from amino acids such as (*R*)- or (*S*)-phenylglycinol (**3**) affording, after reduction of the salt (**4**), the new oxazolidine derivative (**5**) in good yield. This intermediate (**5**) could be considered as an equivalent of 2,5-dihydropyridinium salts (**6**).

Thus, refluxing the readily accessible Zincke's salt (**2**) with one equiv. of (*R*)-(−)-phenylglycinol (**3**) in propan-1-ol overnight led to the pyridinium salt (**4**), isolated as a viscous oil in 70% yield after chromatography over silica gel using CH_2Cl_2–MeOH as eluant. Reduction with sodium borohydride in a two-phase system (Et_2O–5 M NaOH, 0 °C, 30 min) afforded oxazolidine (**5**) in 70% yield, presumably *via* the 1,2-dihydropyridine intermediate (**A**). Compound (**5**) was rather unstable but could be stored at −20 °C under nitrogen. In chloroform solution one diastereoisomer predominated (>95%), as shown by 400 MHz n.m.r. spectroscopy. The observed nuclear Overhauser enhancements (n.O.e.s) between H-2 and H-6 and between H-6 and H-7 strongly suggested a *cis* relationship between the C-2–O and the C-7–Ph bonds [see (**5**) in Scheme 2].

Nucleophilic addition of several Grignard reagents to oxazolidine (**5**) in ether solution, at room temperature overnight, was then investigated (Scheme 2). In each case, a mixture of diastereoisomeric alcohols, (**7**) and (**8**), was obtained.‡ The selectivity was in favour of adducts (**8**) in all experiments. In addition, alcohols (**7**) and (**8**) were easily separable by chromatography over silica gel. Total yields for these adducts, (**7a—c**) and (**8a—c**), fell in the range 60—70% [(**7a**) 11% yield, (**8a**) 49%; (**7b**) 12%, (**8b**) 62%; (**7c**) 10%, (**8c**) 56%; diastereoisomeric excess (d.e.) 62—70%]. This yield decreased to 30% for (**7d**) and (**8d**) [(**7d**) 4%, (**8d**) 26%; d.e. 75%], the magnesium salt obtained from 3-bromopyridine[5] being less reactive.

Conditions for removal of the chiral auxiliary to give 1,2,3,6-tetrahydropyridines (**1b—d**) were then explored. We found that the aldehydes (**9b—d**), easily obtained by Swern oxidation[6] of alcohols (**8b—d**), afforded the desired products (**1b—d**) when treated with 3 equivalents of 2,4-dinitrophenylhydrazine (DNP) in a mixture of propan-1-ol and acetic acid, refluxing for 24 h, presumably *via* ozazone intermediates.[7] Bulb-to-bulb distillation of the crude mixture, after alkaline extraction, afforded pure bases (**1b—d**). The overall yields of this two-step procedure (not optimized) were of the order of 50%.

Absolute configurations of bases (**1b—d**), and consequently of the major adducts (**8a—d**), have been assigned as follows. Hydrogenolysis (10% Pd–C, HCO_2NH_4, MeOH, reflux)[8] of alcohol (**8a**) afforded (*S*)-(+)-coniine (**10**) {(**10**)·HCl, m.p. 216–217 °C, $[\alpha]_D$ +5° (*c* 0.5, EtOH); lit.[1a] $[\alpha]_D$ +5.2° (EtOH)}. Base (*R*)-(+)-(**1d**) {colourless oil, $[\alpha]_D$ +156° (*c* 1, $CHCl_3$)} was the enantiomer of the natural tobacco alkaloid (*S*)-(−)-anatabine {$[\alpha]_D$ −177.8°[9]}. Since the reaction scheme can be applied starting from (*S*)-(+)-phenylglycinol, this constituted the first enantiospecific synthesis of this alkaloid.[10] Relevant to our synthesis was the involvement of a 2,5-dihydropyridinium salt (**6**), considered as an intermediate in the biosynthesis of (*S*)-(−)-anatabine.[10a] From the aforementioned correlations with (*S*)-(+)-coniine (**10**) and (*R*)-(+)-anatabine (**1d**), we can reasonably attribute the same absolute configuration to (**1b**) and (**1c**), which also have positive optical rotations {(**1b**), $[\alpha]_D$ +47° (*c* 0.55, $CHCl_3$); (**1c**), $[\alpha]_D$ +95° (*c* 2, $CHCl_3$)}. Benzyl tetrahydropyridine (**1b**), obtained in 15—20% overall yield from phenylglycinol, could be a useful intermediate in the synthesis of chiral benzomorphans.[11]

Finally, the optical purities of (+)-(**1b**) and (+)-(**10**) were checked by comparing the 400 MHz ^{1}H n.m.r. data of their Mosher amides[12] with those of the Mosher amides of racemic (**1b**) and (**10**). An enantiomeric excess (e.e.) of 90% was

‡ (**7a**) $[\alpha]_D$ −48° (*c* 1, $CHCl_3$); (**7b**) $[\alpha]_D$ +41° (*c* 1.5, $CHCl_3$); (**7d**) $[\alpha]_D$ −103° (*c* 0.75, $CHCl_3$); (**8a**) $[\alpha]_D$ −45° (*c* 2, $CHCl_3$); (**8b**) $[\alpha]_D$ −145° (*c* 1.9, $CHCl_3$); (**8c**) $[\alpha]_D$ −37° (*c* 1, $CHCl_3$); (**8d**) $[\alpha]_D$ −21° (*c* 1.55, $CHCl_3$).

found in each case; the optical rotation of synthetic (+)-anatabine (*vide supra*) was in agreement with this e.e. when compared with the absolute rotation value[9] reported for the natural alkaloid. Thus, the extent of racemization during the synthetic process reported here did not exceed 10%, thereby confirming our initial observations[4] on Zincke's reaction with chiral amines.

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