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Novel 2-(Hydroxyalkyl)pyridines Derived from the Chiral Pool

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Abstract: Two diastereomeric 2-(1-hydroxyalkyl)pyridines were conveniently prepared starting from (-)-menthol. The pyridylalcohols were subsequently allowed to react with phosphorus oxychloride to yield, in one step, C_3-symmetric tripodal tripyridine ligands.

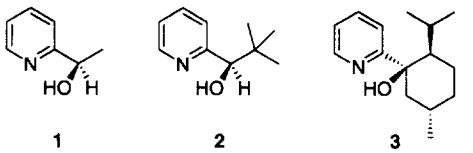
Introduction

Transition metal catalysis is a highly attractive method to obtain chiral enantiopure compounds since the chirality may be transferred from a small amount of a chiral compound to a large amount of product.[1] To achieve this, efficient chiral ligands are required, and extensive current interest is therefore devoted to the preparation of new ligands.[2]

Chiral pyridine alcohols have proven to be versatile ligands in a variety of catalytic applications, in many cases inducing high stereoselectivity.[3] For example, 2-(hydroxyalkyl)pyridines catalyze the enantioselective addition of diethylzinc to aldehydes,[4] the nickel-catalyzed conjugate additions to enones,[5] and asymmetric epoxidations.[6] These compounds also serve as useful starting materials for the preparation of pyridineoxazolinealcohols,[7] which catalyze other types of processes.[8]

Chiral 2-(1-hydroxyalkyl)pyridine derivatives can be prepared according to at least five different procedures. Asymmetric reduction of 2-ketopyridines has been demonstrated in some cases to afford the desired alcohols in high chemical yields and optical purity. Thus, reduction of 2-acetylpyridine using magnesium perchlorate and (*S*)-*N*-benzyl-3-methoxy-4-methyl-1,4-dihydropyridine afforded the alcohol (*R*)-**1** in about 87% ee.[9] The reduction of 2-(1-oxo-2,2-dimethylpropyl)pyridine using (-)-chloro-diisopinocampheylborane [(-)-Ipc_2BCl] proceeded with approximately the same enantioselectivity, affording the alcohol (*R*)-**2** in 91% ee.[10] The second method employs chromatographic separation of diastereomeric derivatives of a racemic mixture of alcohols. By this manner, the pure enantiomers of **2** were obtained,[11] although large quantities were difficult to obtain. Certain derivatives are possible to obtain via enzymatic resolution of a racemate, although this method is not quite general.[12] In this way, enantiopure 2-(1-hydroxyethyl)pyridine **1**, in both optical forms, was obtained, whereas only low stereoselectivity was observed upon resolution of the *t*-butyl derivative.[12a] In the fourth method, the 2-(1-hydroxyalkyl)pyridine derivatives are obtained by cobalt(I) catalyzed cyclotrimerization of acetylenes with optically active nitriles.[13] Finally, one method employing the chiral pool has also been reported.[10] Menthone, for example, was shown to react

with 2-pyridyllithium to yield an alcohol **3** with high stereoselectivity. This alcohol showed poor performance in catalytic applications,[10,14] however, probably due to the resemblance of the two alkyl substituents.

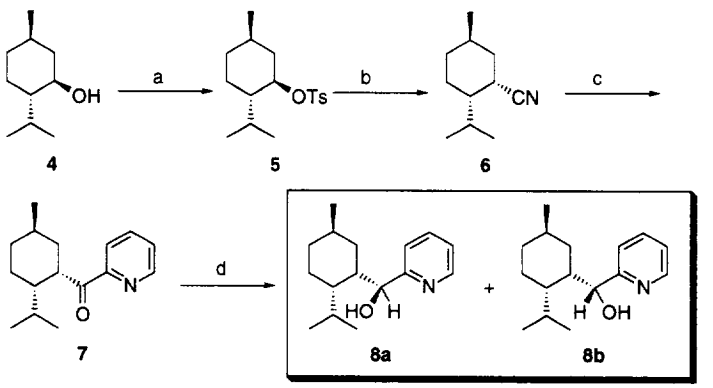


1 **2** **3**

We have now devised a new method, starting from (-)-menthol **4**, which is presented in this paper together with its application to the synthesis of a C_3-symmetric tripodal ligand.

Results and Discussion

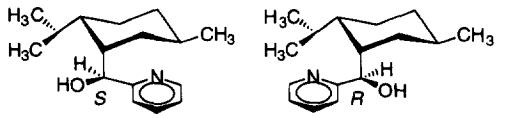
Preparation of chiral enantiopure 2-(1-hydroxyalkyl)pyridines. (1*R*,2*S*,5*R*)-(-)-Menthol was transformed into its tosylate **5**,[15] which was reacted with sodium cyanide in DMSO to yield nitrile **6** (99%). This nitrile gave ketone **7** upon reaction with 2-pyridyllithium (41%, Scheme 1). Reduction using sodium borohydride afforded a mixture of two diastereomeric alcohols in a ratio of 83:17. The alcohols were easily separated by chromatography to yield pure **8a** and **8b** (90% total yield).



Scheme 1. a) TsCl, pyridine b) NaCN, DMSO c) 2-lithiopyridine, diethyl ether d) $NaBH_4$, MeOH

The coupling constants in the ^1H NMR spectra of compounds **8a** and **8b** indicated that the two compounds assume chair conformations with the hydroxypyridyl substituents in axial position. As a consequence of a stereoelectronic effect present in these types of compounds, it was also assumed that the hydroxymethylpyridine part of the molecule adopts a conformation in which the carbon-oxygen bond is parallel to the pyridine ring, with the heteroatoms *anti* to one another.[16] However, intramolecular hydrogen bonding resulting in a *syn* conformation can not be excluded. In either of these conformations, one of the isopropyl methyl groups in the *R* isomer **8b** is shielded by the pyridine ring, which should result in an upfield shift for that proton, whereas in the epimer **8a**, the methyl groups are not influenced by the pyridine ring

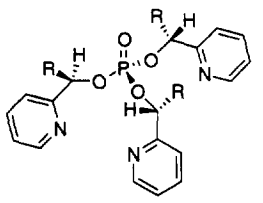
(Figure 1). Therefore, **8b** was thought to be the major isomer. In order to verify this assumption, the Mosher esters of the two alcohols were prepared.[17] According to the generally accepted rule, it was concluded that **8b** was, indeed, the major diastereomer.



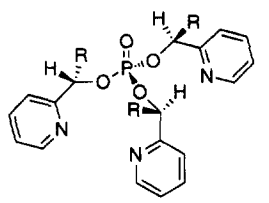
8a **8b**

Figure 1. Assumed conformations of the pyridylalcohols **8a** (minor diastereomer) and **8b** (major diastereomer).

Preparation of C_3-symmetric phosphorus triesters. With these chiral alcohols in hand, we turned to the synthesis of tripodal pyridine ligands. First, the reactions of racemic alcohols (±)-**1** and (±)-**2** with phosphorus oxychloride were studied. From (±)-**1**, the expected statistical 1:3 mixture of homochiral : heterochiral diastereomers **9** was observed by ^{1}H NMR spectroscopy. In contrast, we were pleased to note that reaction with (±)-**2** resulted in an apparent 1:1 mixture of diastereomers (**10** and stereoisomers), showing that homochiral (*R,R,R*)* isomers were preferred over the heterochiral (*R,R,S*)* isomers, probably due to the high steric demand of the ligand. The phenomenon of nonstatistical distribution of isomers was further demonstrated employing an 85:15 scalemic mixture of alcohol **2**, obtained by asymmetric reduction of 1-(2-pyridyl)-2,2-dimethylpropanone with (-)-Ipc_2BCl, in the reaction. In this case, a 5:1 ratio of homochiral : heterochiral isomers was obtained. This observation implies that care should be taken when analysis of the diastereomeric ratio of phosphoric esters is used for the determination of the ee:s of scalemic mixtures, even if this topic has been carefully examined in several examples.[18]



9. R = Me
10. R = *t*-Bu
11b. R = neomenthyl



11a. R = neomenthyl

As expected, the pure *R,R,R*-isomer **9** was obtained when enantiopure **1** was used in the reaction with phosphorus oxychloride. This was also the case for the tri-ester obtained from enantiopure alcohols **8a** and **8b** (**11a** and **11b**, respectively).

The practical and simple method for the preparation of the chiral pyridylalcohols **8a** and **8b** is yet another example which demonstrates the utility of the chiral pool. The chiral alcohols obtained proved to be useful in the preparation of a new class of C_3-symmetric pyridine ligands. In future work, we will focus on the preparation of transition metal complexes of the C_3-symmetric ligands and to investigate their potential as catalysts in asymmetric synthesis.

Experimental section

General. The synthesis of (*R*)-1-(2-pyridyl)ethanol **1** was performed using an enzymatic method.[12a] (*R*)-1-(2-Pyridyl)-2,2-dimethylpropanol **2** was produced by reduction of the corresponding ketone with (-)-Ipc_2BCl.[19] (1*R*,2*S*,5*R*)-Menthyltosylate **5** was prepared according to a literature procedure from (1*R*,2*S*,5*R*)-(-)-menthol.[15] ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, unless otherwise stated.

(1*S*,2*S*,5*R*)-1-Cyano-2-isopropyl-5-methylcyclohexane 6. (1*R*,2*S*,5*R*)-Menthyltosylate (2.60 g, 8.44 mmol) and sodium cyanide (830 mg, 16.9 mmol) were stirred in DMSO (50 mL) at 90 °C for 5 h. The product was extracted using EtOAc/H_2O, the combined organic phases were dried ($MgSO_4$) and the solvent evaporated. Kugelruhr distillation afforded the desired nitrile (1.39 g, 99%). ^1H NMR: 0.80-1.04 (2H, m), 0.91 (3H, d, J = 6.5 Hz), 0.95 (6H, d, J = 6.5 Hz), 1.14 (1H, ddd, J = 13, 12 and 4 Hz), 1.21-1.34 (1H, m), 1.52-1.64 (1H, m), 1.66-1.84 (2H, m), 1.85-1.92 (1H, m), 1.98 (1H, dq, J = 13 and 3 Hz), 3.03-3.08 (1H, m). ^{13}C NMR: 20.61, 20. 73, 21.81, 26.97, 28.50, 31.14, 31.27, 34.55, 37.38, 45.65, 121.05.

[(1*S*,2*S*,5*R*)-1-(2-Isopropyl-5-methyl)cyclohexyl](2-pyridyl)ketone 7. Nitrile **6** (600 mg, 3.64 mmol) in diethyl ether (4 mL) was added to 2-pyridyllithium, prepared in situ from 2-bromopyridine (380 µL, 4 mmol) and butyllithium (1.6 mL, 2.5 M, 4 mmol) in diethyl ether (16 mL, stirring at -78 °C under N_2 for 30 min). After stirring at -78 °C for 2 h, the reaction mixture was allowed to reach room temperature and then stirred at this temperature for a further 1 h. 1M H_2SO_4 (16 mL) was added and the product extracted with diethyl ether. The combined organic phases were washed with aqueous Na_2CO_3 and dried ($MgSO_4$). Liquid chromatography (column 2.5 x 15 cm, eluent: 300 mL of hexane:EtOAc 92:8) yielded 363 mg (41%) of **7**. R_f 0.6 (hexane:EtOAc 92:8) ^1H NMR: δ 0.78 (6H, d, J = 7 Hz, CH_3), 0.8-2.0 (8H, m), 0.91 (3H, d, J = 7 Hz, CH_3), 1.99 (1H, dq, J = 13 and 4 Hz), 4.56-4.64 (1H, m), 7.43 (1H, ddd, J = 8, 5 and 1 Hz, 5-pyridyl), 7.82 (1H, dt, J = 8 and 1.5 Hz, 4-pyridyl), 8.01 (1H, d, J = 8 Hz, 2-pyridyl), 8.66 (1H, bd, J = 5 Hz, 6-pyridyl). ^{13}C NMR: 21.58, 22.30, 26.36, 27.15, 30.09, 35.48, 37.39, 40.54, 45.59, 46.90, 122.07, 126.64, 136.92, 148.78, 153.74, 204.48.

(*S*)-[(1*S*,2*S*,5*R*)-1-(2-Isopropyl-5-methyl)cyclohexyl](2-pyridyl)methanol 8a and (*R*)-[(1*S*,2*S*,5*R*)-1-(2-isopropyl-5-methyl)cyclohexyl](2-pyridyl)methanol 8b. Sodium borohydride (92 mg, 2.4 mmol) was added to **7** (113 mg, 0.46 mmol) in methanol (5 mL). The reaction mixture was stirred for 94 h, quenched with water (5 mL), extracted with CH_2Cl_2 (3 x 15 mL) and dried ($MgSO_4$). Liquid chromatography (column 2 x 12 cm, eluent: hexane:EtOAc 95:5; 90:10; 80:20; 70:30; 50:50 100 mL of each) gave 18 and 85 mg, respectively, of the two diastereomers (total yield 90%, de 65%). **8a** (minor diastereomer): $[\alpha]_D^{20}$ +10 (c 0.80, EtOH).^1H NMR: δ 0.66-1.90 (2H, m), 0.69 (3H, d, J = 6.5 Hz, CH_3), 1.01 (3H, d, J = 5.5 Hz, CH_3), 1.03 (3H, d, J = 5.5 Hz, CH_3), 1.10-1.20 (1H, m), 1.20-1.27 (1H, m), 1.69-1.90 (4H, m), 1.90-2.04 (1H, m), 2.18 (1H, app. hept., J = 2.5 Hz, 1-neomenthyl), 4.50 (1H, bd, J = 4 Hz, C*H*OH), 5.10 (1H, bs, OH), 7.17-7.21 (1H, m, 5-pyridyl), 7.22 (1H, dd, J = 8 and 1 Hz, 3-pyridyl), 7.67 (1H, dt, J = 8 and 1.5 Hz, 4-pyridyl), 8.55 (1H, dt, J = 5 and 1 Hz, 6-pyridyl). ^{13}C NMR: δ 21.67, 21.82, 23.46, 26.36, 28.22, 29.47, 35.87, 36.04, 40.99, 47.92, 72.95, 120.30, 121.81, 136.54, 147.64, 162.73. **8b** (major diastereomer): $[\alpha]_D^{20}$ +5.3 (c 0.79, EtOH). ^1H NMR: δ 0.67 (3H, d, J = 6.5 Hz, CH_3), 0.81-0.97 (2H, m), 0.92 (3H, d, J = 6.5 Hz, CH_3), 1.03 (3H, d, J = 6.5 Hz, CH_3), 1.08-1.18 (2H, m), 1.43-1.65 (2H, m), 1.76-1.88 (2H, m), 2.08 (1H, dquint, J = 10 and 6.5 Hz,

C*H*(CH_3)$_2$), 2.36 (1H, app. dq, *J* = 8 and 4 Hz, 1-neomenthyl) 3.11 (1H, d, *J* = 8 Hz, OH), 4.95 (1H, app. t, *J* = 8 Hz, C*H*OH), 7.19 (1H, ddd, *J* = 7.5, 5 and 1 Hz, 5-pyridyl), 7.24-7.25 (1H, m, 4-pyridyl), 7.65 (1H, dt, *J* = 7.5 and 2 Hz, 3-pyridyl), 8.58 (1H, ddd, *J* = 5, 1.5 and 1 Hz. 6-pyridyl). ^{13}C NMR: δ 22.31, 22.55, 22.78, 25.04, 27.15, 30.08, 36.08, 39.14, 42.39, 49.96, 74.64, 121.77, 122.40, 136.22, 149.05, 163.31. Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.51; H, 10.02; N, 5.63.

(*R*,*R*,*R*)-Tris[1-(2-pyridyl)ethyl] phosphate 9. $POCl_3$ (12 μL, 0.13 mmol) was added to **1** (48 mg, 0.39 mmol, 99% ee) and Et_3N (54 μL, 0.39 mmol) in dichloromethane (5 mL) at 0 °C. The mixture was allowed to reach room temperature, stirred for five days and the reaction was quenched by the addition of aqueous NH_4Cl (5 mL). The phases were separated and the organic phase was washed with an additional 5 mL of NH_4Cl and dried ($MgSO_4$). The solvent was evaporated giving an oil (37 mg, 69%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.59 (9H, d, *J* = 6.6 Hz, CH_3), 5.52 (3H, app. quintet, *J* (C-H) = ^3J(P-H) ≈ 7 Hz), 7.12 (3H, ddd, *J* = 7.5, 5 and 1 Hz, 5-pyridyl), 7.29 (3H, d, *J* = 7.5 Hz, 3-pyridyl), 7.58 (3H, dt, *J* = 7.5 and 1.5 Hz, 4-pyridyl), 8.44 (3H, bd, *J* = 5 Hz, 6-pyridyl).

(*R*,*R*,*R*)-Tris[1-(2-pyridyl)-2,2-dimethylpropyl] phosphate 10. $POCl_3$ (26 μL, 0.17 mmol) was added to **2** (83 mg, 0.50 mmol, 71% ee) and Et_3N (70 μL, 0.50 mmol) in diethyl ether (10 mL) at 0 °C. The mixture was allowed to reach room temperature overnight and the reaction was then quenched by addition of aqueous NH_4Cl (2 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL) and the organic phase was dried ($MgSO_4$). The solvent was evaporated to give an oil which was purified by liquid chromatography [column: 0.5 x 6 cm, eluent: hexane (5 mL), EtOAc (10 mL), acetone: EtOAc (1:9, 10 mL) and acetone (3 mL)] to give white crystals of **10** [4.2 mg, 4.6%, (*R*,*R*,*R* + *S*,*S*,*S*):(*R*,*R*,*S* + *R*,*S*,*S*) > 95:5]. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.57 (27H, s, C(CH_3)$_3$), 5.11 (3H, d, ^3J (P-H) = 8.9 Hz, CH), 7.12-7.20 (3H, m, 5-pyridyl), 7.31 (3H, d, *J* = 8 Hz, 3-pyridyl), 7.67 (3H, bt, *J* = 8 Hz, 4-pyridyl), 8.50-8.54 (3H, m, 6-pyridyl).

(*S*,*S*,*S*)-Tris-{[(1*S*,2*S*,5*R*)-1-(2-isopropyl-5-methyl)cyclohexyl](2-pyridyl)methyl} phosphate 11a. $POCl_3$ (43 μL, 0.46 mmol) was added to **8a** (368 mg, 1.49 mmol) and Et_3N (207 μL, 1.49 mmol) in diethyl ether (5 mL) at 0 °C. The mixture was allowed to reach room temperature and then stirred for 7 days, after which time reaction was quenched by addition of aqueous NH_4Cl (5 mL). The reaction mixture was extracted with CH_2Cl_2 and the organic phase was dried ($MgSO_4$). The solvent was removed in vacuo and the product was purified by column chromatography to give 212 mg (58 %) of **11a:** $[\alpha]_D^{20}$ -22 (c 0.9, $CHCl_3$). ^{1}H NMR: δ 0.43-0.98 (9H, m), 0.58 (9H, d, *J* = 6 Hz, CH_3), 0.85 (9H, d, *J* = 6.5 Hz, CH_3), 0.86 (9H, d, *J* = 6.5 Hz, CH_3), 1.15-1.29 (6H, m), 1.34-1.59 (12H, m), 2.31-2.39 (3H, m), 5.70 (3H, dd, *J* (C-H) = 5 Hz *J* (P-H) = 8.5 Hz), 7.18 (3H, ddd, *J* = 8, 5 and 1 Hz, 5-pyridyl), 7.21 (3H, bd, *J* = 8 Hz, 3-pyridyl), 7.62 (3H, dt, *J* = 8 and 2 Hz, 4-pyridyl), 8.52 (3H, ddd, *J* = 5, 2 and 1 Hz, 6-pyridyl). ^{13}C NMR. δ 21.55, 22.11, 23.27, 25.41, 26.82, 28.05, 35.55, 35.78, 39.76, 48.34, 37.53 (*J* = 7.5 Hz), 121.66, 122.13, 135.51, 148.76, 160.88.

(*R*,*R*,*R*)-Tris-{[(1*S*,2*S*,5*R*)-1-(2-isopropyl-5-methyl)cyclohexyl](2-pyridyl)methyl} phosphate 11b. Compound **11b** was prepared from $POCl_3$ (86 μL, 0.92 mmol) and **8b** (720 mg, 2.91 mmol) according to the procedure described for the preparation of **11a**. The crude product was purified with column chromatography to give 350 mg (48%) of **11b:** $[\alpha]_D^{20}$ -45 (c 1.35, $CHCl_3$). ^{1}H NMR: δ 0.49 (9H, d, *J* = 6.5 Hz, CH_3), 0.57-0.72 (6H, m), 0.80-0.98 (6H, m), 0.82 (9H, d, *J* = 6.5 Hz, CH_3), 0.96 (9H, d, *J* = 6.5 Hz, CH_3), 1.00-1.13 (3H, m), 1.44-1.58 (9H, m), 1.89-2.02 (3H, m), 2.47-2.53 (3H, m), 5.44 (3H, app. t, *J* (C-H) = ^3J(P-H) =7.5 Hz), 7.04 (3H, bd, *J* = 8 Hz, 3-pyridyl), 7.07 (3H, ddd, *J* = 8, 5 and 1 Hz, 5-pyridyl), 7.48 (3H, dt, *J* = 8 and 2 Hz,

4-pyridyl), 8.54 (3H, dd, J = 5 and 1 Hz, 6-pyridyl). ^{13}C NMR: δ 22.07, 22.51, 22.70, 24.60, 26.68, 29.03, 35.75, 36.55, 40.49, 49.08, 80.58 (J = 5 Hz), 122.50, 122.72, 135.74, 148.49, 160.31.

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