Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Asymmetric Synthesis XXIII.[1] A 100% cis Diastereoselectivity in the SYnthesis of Enantiomerically Pure 2,6-Dialkylpiperidines

Emmanuel Theodorakis [a], Jacques Royer [a] & Henri-Philippe Husson [a]

[a] Institut de Chimie des Substances Naturelles CNRS , 91198, Gif-sur-Yvette, Cedex, France

Published online: 23 Sep 2006.

To cite this article: Emmanuel Theodorakis , Jacques Royer & Henri-Philippe Husson (1991) Asymmetric Synthesis XXIII.[1] A 100% cis Diastereoselectivity in the SYnthesis of Enantiomerically Pure 2,6-Dialkylpiperidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:4, 521-529, DOI: 10.1080/00397919108016778

To link to this article: http://dx.doi.org/10.1080/00397919108016778

SYNTHETIC COMMUNICATIONS, 21(4), 521-529 (1991)

ASYMMETRIC SYNTHESIS XXIII.[1] A 100% CIS DIASTEREOSELECTIVITY IN THE SYNTHESIS OF ENANTIOMERICALLY PURE 2,6-DIALKYLPIPERIDINES .

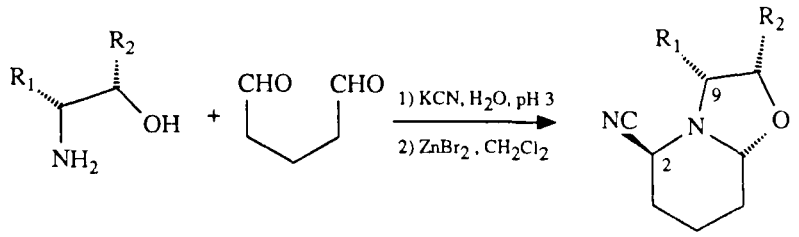
Emmanuel Theodorakis, Jacques Royer,*
and Henri-Philippe Husson

Institut de Chimie des Substances Naturelles
CNRS, 91198 Gif-sur-Yvette Cedex, France.

Abstract: Enantiomerically pure (+)-(2S,6R)-2-propyl-6-methyl-piperidine 6 has been obtained in 4 steps, 66% overall yield and without separation of diastereomers from the chiral 2-cyano-6-oxazolopiperidine synthon 1c derived from (+)-1,2-diphenyl-2-aminoethanol

During the past few years we have developed a strategy for the asymmetric synthesis of piperidine alkaloids using synthon 1a which can be considered as a chiral 1,4-dihydropyridine equivalent.[2] This new strategy, which we call the CN(*R,S*) method,[3] permits the enantioselective preparation of a variety of piperidine alkaloids, including 2-alkylpiperidines, 2,6-dialkylpiperidines, substituted indolizidines, etc...[4]

Although the synthesis of 2-alkylpiperidines from 1a could be carried out in an entirely stereospecific fashion, the second alkylation leading to 2,6-dialkylpiperidines was achieved with "only" a good stereoselectivity (*cis/trans*= 83:17).[2] In our previous work, use of synthon 1b -derived from (+)-norephedrine- gave better results with a stereoselectivity of cis/trans= 95:5. Nevertheless, this latter synthon was not developed for the asymmetric



a) R_1 = Ph , R_2 = H
b) R_1 = CH_3 , R_2 = Ph
c) R_1 = R_2 = Ph

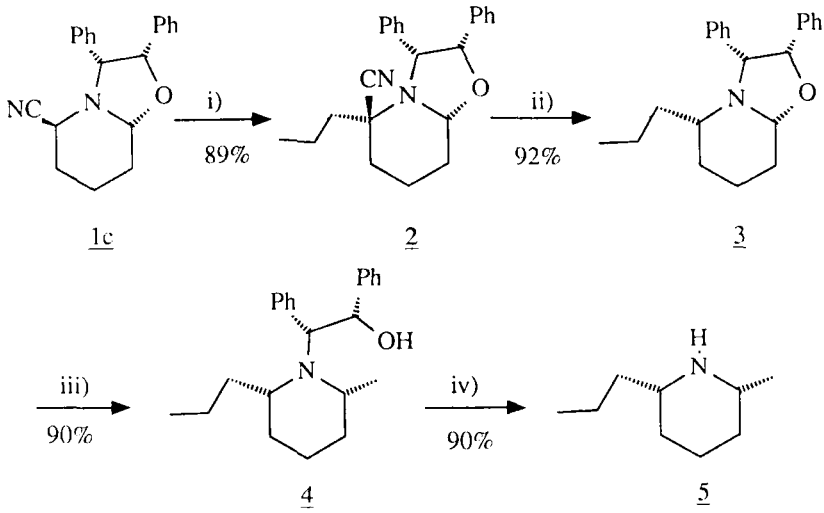
1

scheme 1

synthesis of piperidine alkaloids because of the difficulty of cleavage of the chiral auxiliary which necessitates drastic conditions incompatible with a large variety of funtional groups. With the intention of improving the *cis* stereoselectivity in the synthesis of 2,6-dialkylpiperidines, we investigated the chiral cyano oxazolidine synthon 1c derived from 1,2-diphenyl-2-aminoethanol.

The chiral synthon (-)-1c was prepared easily in 80% yield by condensing (1S,2R)-(+)-1,2-diphenyl-2-aminoethanol[5] and glutaraldehyde in the presence of potassium cyanide, followed by equilibration with a catalytic amount of zinc bromide in CH_2Cl_2 (scheme 1).

This procedure parallels the preparation of 1a from R-(-)-phenylglycinol.[7] The relative stereochemistry of 1c was easily deduced on the basis of ^1H NMR data, except for the relationship between H-9 and H-2 which was presumed to be *trans* by analogy with compound 1a. The synthesis of (+)-dihydropiperidine 5, is outlined in scheme 2. This scheme is analogous to that which we used for the preparation of the same compound starting from 1a or 1b..



reagents: i) LDA, THF, -78°C; $CH_3CH_2CH_2Br$ ii)$AgBF_4$, THF, rt; then $Zn(BH_4)_2$ -78°C
iii) MeMgI, Et_2O, 0°C iv) H_2, Pd/C, MeOH

scheme 2

Alkylation of 1c with propyl bromide after deprotonation by LDA in THF at -78°C afforded compound 2 (89% yield) which was reduced regio- and stereospecifically to 3 in 92% yield. Only one isomer could be found by analysis of the 200 MHz ^1H NMR of the crude reaction mixture. Treatment of 3 with methylmagnesium iodide gave exclusively the pure *cis*-dialkylated piperidine derivative 4 (90% yield after purification). Not even trace quantities of the other diastereomer could be detected in the crude reaction mixture.[8] Finally the N-debenzylation of 4 by hydrogenolysis on Pd/C afforded the desired (+)-dihydropinidine 5 in 90% yield [5-HCl $[\alpha]_D^{20}$ +12.5° (c 1.0, EtOH)]. Then, from the chiral synthon 1c, (+)-dihydropinidine 5 was obtained in 4 steps and 66% overall yield without requiring any diastereomeric

separation. This synthesis represents a significant improvement in the stereoselectivity of the addition of a Grignard reagent to the oxazolidine system. The reason for this improvement is not yet clearly established and we are currently investigating this issue.

Either enantiomer of 1,2-diphenyl-2-aminoethanol can be easily obtained[5] and the enantiomeric synthon (+)-1c $[\alpha]_D^{20}$ +314° (c .095, $CHCl_3$) has been prepared. Using (+)-1c as starting material the synthesis of enantiomeric (-)-dihydropinidine 6 [6-HCl $[\alpha]_D^{20}$ -12.7° (c .09, $CHCl_3$)] has been also performed by the same route. (This later enantiomer could also been accessed from synthon (-)-1c in a route where the order of introduction of each substituent is inverted)

Experimental:

preparation of synthon 1c: To a cooled (0°) solution of 5.02 g (0.023 mol) of (1S,2R)-(+)-diphenyl-2-aminoethanol[6] and 20 g of citric acid in 200 mL of water was added dropwise 18 mL of a 25% glutaraldehyde solution in water (0.044 mol). The mixture was stirred at 0°C for 30 min and 3 g (0.046 mol) of potassium cyanide in 100 mL of water was added rapidly. The mixture was allowed to warm to room temperature and stirred for 3 h. The solution was made alkaline by addition of diluted Na_2CO_3 and extracted (3 X 100 mL) with methylene chloride. The organic solution was dried (Na_2SO_4), filtered and $ZnBr_2$ (0.9 g) was added with vigourous stirring. Agitation was continued for 3h then the solution was concentrated to a volume of approximately 50 mL. This solution was applied directly to a flash-chromatography column which was then eluted with hexane-ether 80:20. The major compound was isolated as white crystals (5.6 g, 80% yield).

mp 182°C (hexane); $[\alpha]_D^{20}$ -313° (c 0.95, $CHCl_3$); IR: 2200 cm^{-1}; MS (CI, isobutane) mz: 305 (MH^+,100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.6-2.3 (m, 6H, CH_3), 3.82 (broad s, 1H, C<u>H</u>-CN), 4.3 (d, J=9Hz, 1H,N-C<u>H</u>-Ph), 4.38 (dd, J=8, 2Hz, 1H, N-C<u>H</u>-O), 5.38 (d, J=9Hz, 1H, O-C<u>H</u>-Ph), 6.85-7.1 (m, 10H, ar.); ^{13}C NMR (50MHz, $CDCl_3$) δ (ppm): 19.5, 28.1, 29.9 (CH_2), 47.9 (<u>C</u>H-CN), 68.8 (N-<u>C</u>H-Ph), 82.1 (O-<u>C</u>H-Ph), 89.5 (N-<u>C</u>H-O), 115.6 (CN), 127.1-128.6 (CH ar.), 134.8, 138.7 (Cq ar.); Analysis calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C,78.72; H, 6.64; N, 9.06.

<u>aminonitrile 2</u>: To a solution of LDA [from 7.5 mL (0.054 mol) of diisopropylamine and 34 mL of 1.6 M solution of butyllithium in hexane (0.054mol)] in 100 mL of dry THF ,cooled to -78°C, under argon atmospher was added slowly 1.458 g (0.048 mol) of synthon <u>1c</u> dissolved in 20 mL of dry THF. The mixture was stirred 15 min before the addition of propyl bromide (4.8 mL, 0.051 mol) and then allowed to stir for 3 h at -78°C. The reaction was quenched by addition of a saturated NH_4Cl solution and then extracted with methylene chloride (3 X 50 mL). After drying (Na_2SO_4) and distillation of the solvent, the residual oil was purified by flash chromatography on silica gel (hexane-ether 7:3 as eluant) to give 1.48 g (89%) of pure <u>2</u> as white crystals.
mp 74°C (hexane); $[\alpha]_D^{20}$ -86° (c 0.6, $CHCl_3$); IR 2200cm^{-1}; MS (CI, isobutane) m/z: 347 (MH^+, 8), 320 (MH^+-HCN, 100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.53 (t, J=8Hz, 3H, CH_3), 0.8-2.3 (m, 10H, CH_2), 4.3 (d, J=8Hz, 1H, N-C<u>H</u>-Ph), 4.4 (dd, J=9, 2Hz, 1H, N-C<u>H</u>-O), 5.23 (d, J=8Hz, 1H, O-C<u>H</u>-Ph), 6.8-7.1 (m, 10H, ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.3 (CH_3), 17.0, 19.9, 29.2, 34.4, 41.2 (CH_2), 61.8 (<u>C</u>-CN), 65.9 (N-<u>C</u>H-Ph), 83.2 (O-<u>C</u>H-Ph), 118.9 (CN), 126.3-&27.9 (CH ar), 136.8, 140.5 (Cq ar); Analysis

calcd. for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.43; H, 7.50; N, 7.98.

oxazolidine 3: To a cooled (0°C) solution of aminonitrile 2 (0.33 g, 0.95 mmol) in 10 mL of dry THF, under a nitrogen atmospher was added a solution of $AgBF_4$ (0.64 g, 3.6 mmol) in 1 mL of THF. A white precipitate appeared during the addition and the mixture was stirred for 15 min at 0°C. The temperature was lowered to -78°C and 5 mL of a 0.15 M solution of $Zn(BH_4)_2$ in ether was added slowly to the mixture. Stirring was continuted for 2 h at low temperature and the reaction was quenched with a saturated NH_4Cl solution. The mixture was allowed to reach room temperature, filtered and extracted with CH_2Cl_2 . The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. Rapid purification on silica gel using hexane-ether 9:1 as eluant gave 0.28 g of white crystals of 3 (92% yield).

mp 76°C (hexane); $[\alpha]_D^{20}$ -16.5° (c 1, $CHCl_3$); MS (EI) m/z: 321 (M^+, 0.5), 320 (10), 278 (45), 215 (100), 173 (75), 172 (50); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.5 (t, J=7Hz, 3H, CH_3), 0.7-2.2 (m, 10H, CH_2), 2.4 (t, J=7 Hz, 1H, N-C<u>H</u>-Pr), 3.97 (dd, J=10, 2Hz, 1H, N-C<u>H</u>-O), 4.08 (d, J=9Hz, 1H, N-C<u>H</u>-Ph), 5.2 (d, J=9Hz, 1H, O-C-Ph), 6.8-7.1 (m, 10H, ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.9 (CH_3), 19.0, 22.6, 30.3, 31.4, 36.9 (CH_2), 62.0 (N-<u>C</u>H-Pr), 69.7 (N-<u>C</u>H-Ph), 83.3 (O-<u>C</u>H-Ph), 95.1 (N-<u>C</u>H-O), 126.1-128.4 (<u>C</u>-H ar), 138.7, 141.6 (<u>C</u> q ar); Analysis calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.46; N, 4.36. Found: C, 82.09; H, 8.43; N, 4.56.

alcohol 4: A 1M solution of methylmagnesium iodide (1.2 mL , 1.2 mmol) in ether was slowly added to a cooled solution (0°C) of 145 mg (0.45 mmol) of 3 in 10 mL of ether. Stirring was continued during 2 h and the reaction was

quenched by addition of a saturated NH_4Cl solution. After separation of the two phases, the aqueous solution was extracted with CH_2Cl_2 (4 X 20 mL) and the organic phases were combined, dried (Na_2SO_4) and the solvent removed *in vacuo*. Rapid purification on silica gel using CH_2Cl_2-MeOH 95-5 as eluant gave analytically pure 4 as white crystals (136 mg, 90% yield).

mp 96°C (CH_2Cl_2); $[\alpha]_D^{20}$ +82° (c 1, $CHCl_3$); MS (CI, isobutane) m/z: 338 (MH^+, 100), 320 (50), 230 (15), 142 (8), 107 (20); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.86 (d, J=7Hz, 3H, CH_3), 1.06 (t, J=7Hz, 3H, CH_3), 1.26-2.0 (m, 10H, CH_2), 3.1 (m, 1H, N-CH-CH_3), 3.36 (dd, J=9, 2Hz, 1H, N-CH-CH_2), 3.76 (s, 1H, O-H), 4.1 (d, J=4Hz, 1H, N-CH-Ph), 5.4 (d, J=4Hz, O-CH-Ph), 6.8-7.1 (m, 10H,ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm):14.5 (CH_3), 14.7 (CH_2), 16.4 (CH_3), 22.2, 28.3, 31.4 ,31.9, (CH_2), 48.5, 53.2 (N-CH), 70.0 (N-CHPh), 71.4 (O-CHPh), 126.0-129.8 (CH ar), 136.7, 141.5 (Cq ar); Analysis calcd. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.93; H, 9.10; N, 4.16.

(+)-dihydropinidine 5: Aminoalcool 4 (120 mg, 0.35 mmol) was dissolved in 20 mL of methanol and hydrogenated over 5% Pd/C (20 mg) at atmospheric pressure during 15 h. The catalyst was filtered off and a few drops of dry HCl methanol solution were added to the solution before evaporation of the solvent. The residue was triturated with ether and the resultant crystals were filtered and washed thoroughly with ether to remove diphenylethanol. White crystals of pure (+)-dihydropinidine chlorydrate 5-HCl (56 mg, 90%) were then obtained. $[\alpha]_D^{20}$ +12.5° (c 1.0, EtOH); mp 215°C (dec.) (lit.[9] $[\alpha]_D^{20}$ +12.8° (c 1.07, EtOH), mp 215°C).

Acknowledgments: The authors wish to thank P. Duret for valuable technical assistance in this work, and M.-T. Adeline and J. Hamon for HPLC analysis.

references and notes:

1- Part XXII: Zhu, J.; Royer, J.; Quirion, J.-C.; Husson, H.-P., submitted.

2- Guerrier, L.; Royer, J.; Grierson, D. S.: Husson, H.-P., J. Am. Chem.Soc. 1983, 105, 7754.

3- Yue, C.; Royer, J.; Husson, H.-P., J. Org. Chem. 1990, 55, 1140.

4- Husson, H.-P., J. Nat. Prod. 1985, 48, 894.

5- This compound can be prepared on large scale using the method described by Tishler[6] using the stereoselective reduction of the benzoin oxime followed by resolution with L-glutamic acid.

6- Weijlard, J.; Pfister, K.; Swanesy, E. F.; Robinson, C. A.; Tishler, M., J. Am. Chem. Soc. 1951, 73, 1216.

7- Bonin, M.; Grierson D. S.; Royer, J.; Husson, H.-P., Organic Syntheses, vol. 69, in press.

8- The crude reaction mixture was found to be homogeneous by TLC (silica) using two different eluting systems (CH_2Cl_2/MeOH 95:5 or heptane/AcOEt 70:30). The HPLC analysis (Waters Ultra-base C-18 packed column, eluted with MeOH/H_2O 9:1 +0.1% Et_3N at 1mL/min.) showed the presence of a small

impurity which exhibits an UV spectrum different from that for 3. Finally, from the careful examination of the 400 MHz ^{1}H and 50 MHz ^{13}C NMR spectra of the crude mixture no trace of *trans* diastereomer could be detected.

9- Hill, R. K.; Yuri, T., Tetrahedron, 1977, 33, 1569.

(Received in The Netherlands 13 December, 1990)