Acta Chemica Scandinavica, 1999: 53: 521–527
Printed in UK. All rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Synthesis of Hydroxypiperidinecarboxylic Acids from Pyridinedicarboxylates

Anders Damsgaard, Rita Hazell and Mikael Bols*

Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

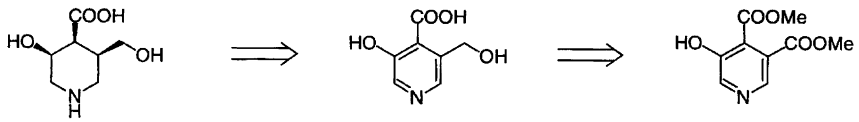
Damsgaard, A., Hazell, R. and Bols, M., 1999. Synthesis of Hydroxypiperidinecarboxylic Acids from Pyridinedicarboxylates. – Acta Chem. Scand. 53: 521–527. © Acta Chemica Scandinavica 1999.

(3*RS*,4*SR*,5*SR*)-5-Hydroxy-3-hydroxymethyl-4-piperidinecarboxylic acid 4,3′-lactone was synthesised in eight steps from ethyl glycinate via selective hydrolysis and reduction of 4,5-di-(methoxycarbonyl)-3-hydroxypyridine. The regioisomer (3*RS*,4*RS*,5*SR*)-5-hydroxy-4-hydroxymethyl-3-piperidinecarboxylic acid 3,4′-lactone was also synthesised. The regio- and stereo-chemistry of the reactions were confirmed by five X-ray crystallographic structure determinations.

In a project where the goal was to construct an oligosaccharide mimetic based on hydroxypiperidine carboxylic acids (for more information about this strategy see Refs. 1 and 2) we were interested in synthesising hydroxypiperidinecarboxylic acid **1**. Compound **1** and similar compounds were not known. Since we needed the compound in gram quantities the problem was to find a short and efficient synthesis. The idea was conceived that pyridine **2**, which could be expected to be hydrogenated stereoselectively to (±)-**1** would be a good starting material (Scheme 1). We expected to be able to prepare compound **2**, also unknown, by selective reductive transformation of the known pyridine **3**. The plan was based on the premise that pyridinedicarboxylic ester **4** reacts selectively with nucleophiles in the 4-position; **4** is, for example, hydrolysed by NaOH to monoester **5** in good yield (Scheme 2).[3] If a similar hydrolysis could be carried out on **3** then selective reduction of the ester in presence of the carboxylic acid would give **2**. The report that anhydride **6** was also attacked selectively by organolithium reagents in the 4-position[4] further indicated that this route might be feasible. Here we report our findings regarding the realisation of the above synthetic plan, and the synthesis of the corresponding lactone of **1**.

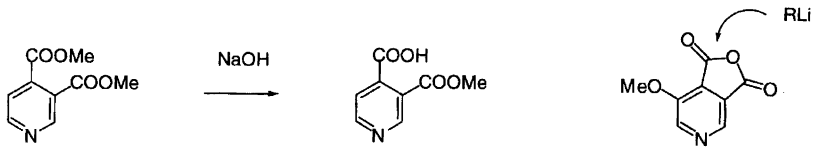
Results and discussion

A number of synthetic routes to the starting material **3** were investigated,[4–7] and the synthesis via oxazole **7** was found to be the best (Scheme 3).[4] This method starts from ethyl glycinate, which is reacted with diethyl oxalate to form an amide, dehydration of which, with phos-



1 **2** **3**

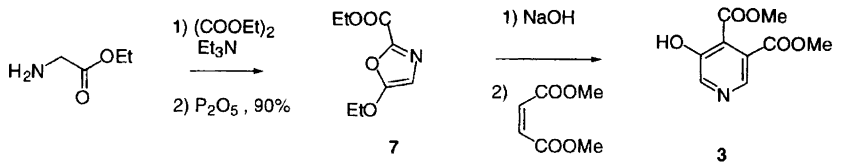
Scheme 1. Plan for the synthesis of **1** from pyridine **3**.



4 **5** **6**

Scheme 2. Previously known selectivity in reactions of pyridinedicarboxylate derivatives.

* To whom correspondence should be addressed.



Scheme 3. Synthesis of the starting material **3**.

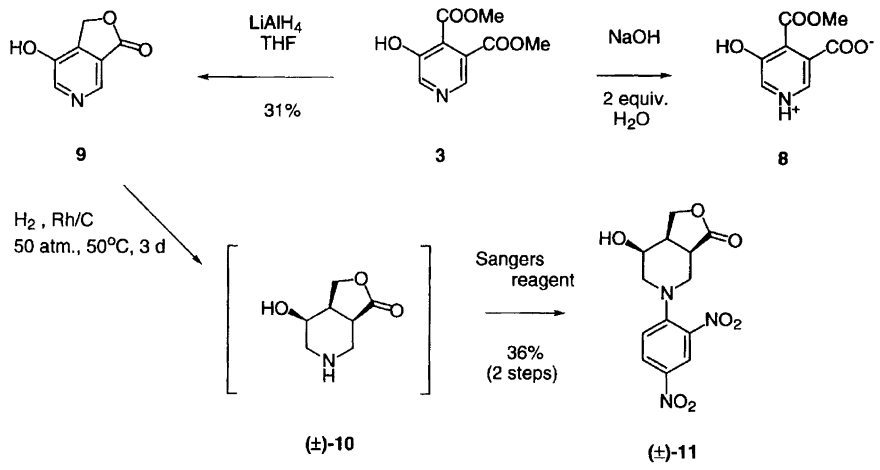
phorus pentoxide, gives oxazole **7**. Saponification of the ethyl ester and subsequent Diels–Alder reaction of the corresponding acid with the dienophile dimethyl maleate gives simultaneous decarboxylation to form the product **3**. This method[4] allows for the production of **3** in large amounts.

Selective saponification of the diester **3** was then attempted by treatment with 2 equivalents of NaOH for 2 h (Scheme 4). This gave only one monoester **8** as the product, which was isolated crystalline in 96% yield. We expected this compound to have the carboxylic acid group at C-4 in analogy with the transformation **4** to **5**, and the findings regarding reactions to **6** (Scheme 2) described above. However X-ray crystallographic analysis of **8** revealed that the carboxylic acid group was in the 3-position (Fig. 1, Table 1). This difference in the regioselectivity of hydrolysis of **3** and **4** must be caused by the phenoxide by an inductive effect, either by electron donation through bonds making the C-2, C-4 and C-6 positions more electronegative which would make the 4-ester less reactive, or by a through-space deterring effect by the phenoxide negative charge on negative nucleophiles. The X-ray structure also revealed that **8** in the crystal is found in the zwitterionic form (there are equal C–O bonds in the carboxylate group), and that the structure is stabilized by intermolecular hydrogen bonds from the pyridinium and hydroxy groups to carboxylate. The carboxy group is twisted ca. 33° from the plane of the pyridine ring, while the ester group is twisted ca. 70°.

Though the original plan of ester reduction of **8** was unsuccessful, this result suggested that selective reduction of **3** would lead to the desired product, because the electronic effect controlling saponification should similarly control reduction. Reaction of **3** with 1.5 mol equivalents of $LiAlH_4$ gave mainly a monoester that on evaporation lactonised so that the lactone **9** was isolated in 49% yield. The structure of **9** was elucidated with the aid of an X-ray structure determination (Fig. 1, Table 1), which revealed, to our surprise, that reduction had occurred at C-4. Thus a switch in regioselectivity had occurred compared with saponification. An explanation for this result could be that $LiAlH_4$ reacts with the phenol to form an aluminium phenoxide, which then reduces the neighbouring ester by an intramolecular reaction. The X-ray structure of **9** showed intermolecular hydrogen bonds from the OH group to nitrogen (Fig. 1).

Synthesis of lactone **9** has previously been claimed[8] with the only characterisation being elemental analysis and an IR spectrum. The IR spectrum of our compound appeared identical with the previously published one.

Though **9** had an undesired substituent pattern, it was nevertheless hydrogenated as a model reaction. Reaction of **9** with 50 atm of H_2 at 50 °C in the presence of rhodium-on-carbon[9] gave the piperidine (±)-**10**, which was not completely characterised but reacted with 2,4-dinitrofluorobenzene (Sanger's reagent) to give (±)-**11** in an overall yield of 36%. The relative stereochemistry of (±)-**11** was determined to be all *cis* by X-ray structure determination (Fig. 1, Table 1). The structure was stabilized by intermolecular hydrogen bonds from the alcohol to the carboxy oxygen. There are two independent but similar molecules in the asymmetric unit. In both sites disorder was found; the major components (75%) in both sites have the same chirality, whereas the minor



Scheme 4. Synthesis of regioisomer **11**.

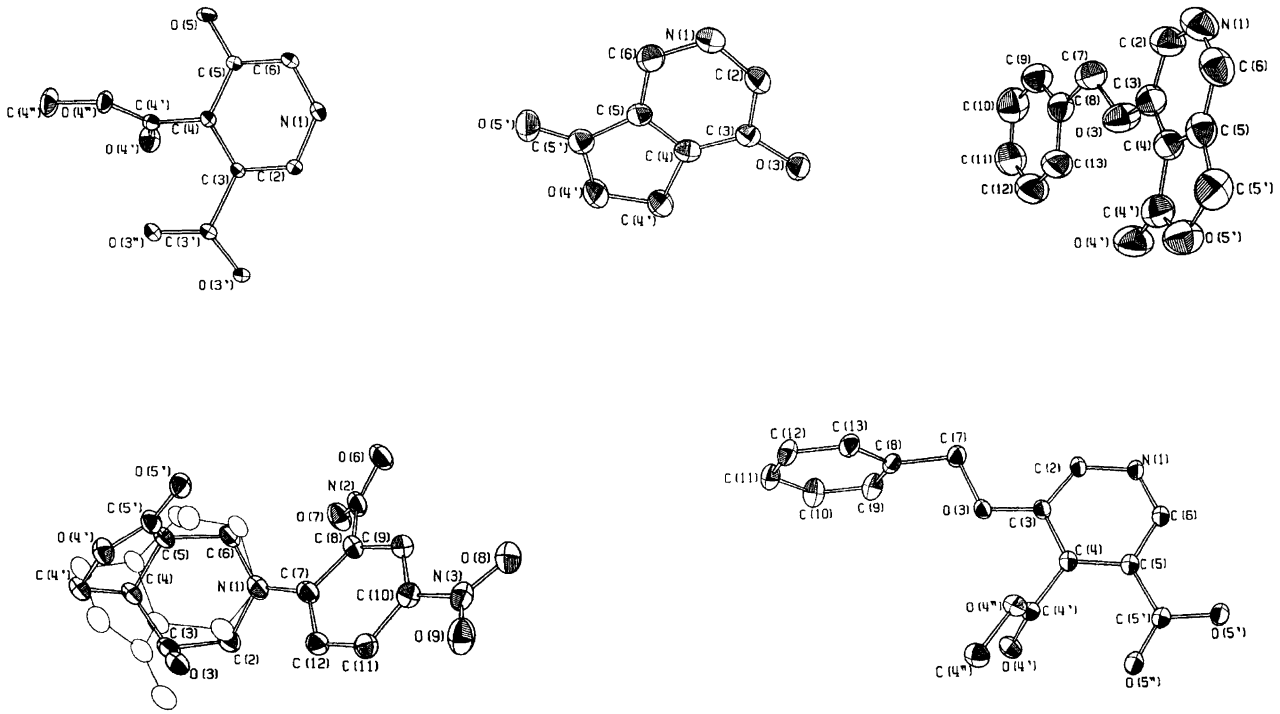


Fig. 1. View of **8**, **9**, **11**, **13** and **14** showing the labelling of the non-H atoms.[15] Thermal ellipsoids are shown at 50% probability levels; H atoms are omitted. For compound **11** only half the asymmetric unit is shown, and the minor orientation is shown in thin outline.

Table 1. Crystal data for compounds **8**, **9**, **11**, **13** and **14**. The coordinates can be obtained from the Cambridge Structural Database.[11] All distances and angles are in accordance with the formulas assigned to them.

	Compound				
	8	**9**	**11**	**13**	**14**
Formula	$C_8H_7NO_5$	$C_7H_5NO_3$	$C_{13}H_{13}N_3O_7$	$C_{15}H_{13}NO_5$	$C_{14}H_{11}NO_3$, 1/2 C_3H_6O
M_w	197.15	151.13	323.27	287.2+29	241.25
Appearance	Colourless	Colourless	Yellow	Colourless	Colourless
Crystal bond	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/n$	$Pna2_1$	$P2_1$	$Pccn$	$P2_1/c$
a/Å	7.9263(1)	10.3942(8)	10.827(5)	25.3676(8)	6.1968(3)
b/Å	10.2442(2)	9.5586(8)	12.828(6)	10.1589(9)	14.8224(8)
c/Å	10.3503(2)	6.3382(5)	10.889(5)	12.018(2)	12.6841(7)
β	85.094(1)	90	118.567(9)	90	97.803(1)
V/Å^3	837.35	629.73	1328(1)	3097.1(6)	1154.3(1)
Z	4	4	4	8	4
μ(Mo Kα)	0.133	0.127	0.13	0.103	0.099
D_x/Mg m^{-3}	1.56	1.59	1.62	1.36	1.39
Independent refl.	2259	672	3655	3599	2769
Significant refl.	1574	549	1691	1152	2157
No. parameters	156	120	136	109	164
R	0.033	0.027	0.077	0.066	0.040
wR	0.044	0.046	0.090	0.076	0.047
Goodness-of-fit	1.137	2.06	2.53	1.78	3.59
Shift/esd max	0.015	0.0001	0.0014	0.008	0.0003
Shift/esd mean	0.001	0.0000	0.0002	0.001	0.0000
$\Delta\rho_{max}$	0.37(5)	0.14(3)	0.54(9)	0.35(8)	0.21(3)
$\Delta\rho_{min}$	−0.22(5)	−0.13(3)	−0.48(9)	−0.50(8)	−0.16(3)

components are the opposite chirality. The dinitrobenzene rings show no disorder, and fit space group $P2_1/a$. The other 6-rings also conform to this symmetry, but the major positions of the 5-rings lower the symmetry to $P2_1$, the structure being stablized by intermolecular hydrogen bonds from the alcohol to the carboxy oxygen. The two 6-rings are twisted about 30° relative to one another, the nitro groups by 14 and 25°. The minor

component has the 5-ring on the same side of the molecular plane, but on the opposite side relative to the long axis of the molecule such that the minor component at one site is centrosymmetrically related to the major component at the other site. This gives no hydrogen bond and may even require some relaxation of the structure because of close contacts.

The assumption that the phenol group directed reduction to the C-4 carboxylic ester suggested that the phenol group should be protected. Therefore compound **3** was benzylated with benzyl bromide and Na_2CO_3 to form the benzyl ether **12** in 70% yield (Scheme 5). Selective saponification of **12** with 1 equivalent of NaOH gave only one product **13**, the structure of which was determined by X-ray methods. It is notable that while **8** was found in the zwitterionic form, **13** has the hydrogen atom on the carboxy group. The structure of **13** contained solvent, 1 molecule of acetone per 2 molecules of **13**, and was stabilized by intermolecular hydrogen bonds from the OH groups to nitrogen. The acid group was situated at C-3, and therefore the *O*-benzyl protection had no influence on the regioselectivity of the reaction. This rules out the possibility that the negative charge of the phenolate in compound **3** was the cause of the selectivity towards attack at C-3 by repelling hydroxide from C-4.

Reduction of **12** with $LiAlH_4$ was attempted in the hope that, when attachment to the phenol could not occur, preferential attack at C-3 would be seen. However no selectivity between the ester groups was observed.

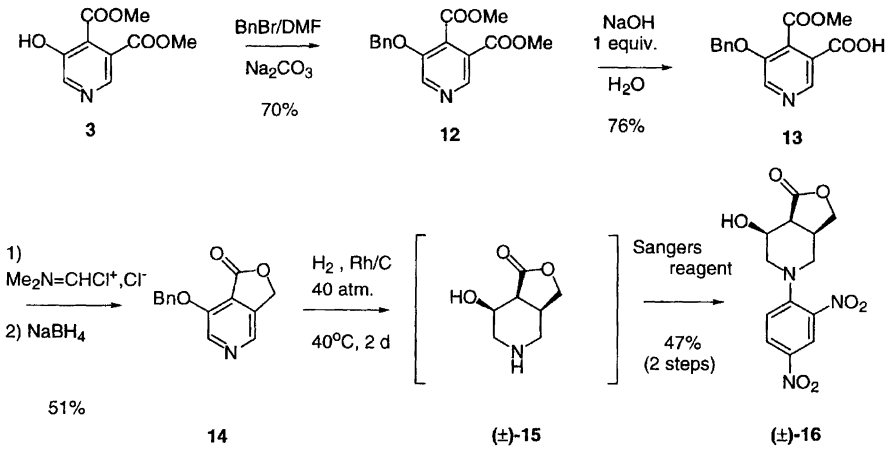
Knowing the structure of **13** we then decided to try to reduce the carboxylic acid group selectively. This could be done by a method which required that the acid be first converted into a reactive intermediate by reaction with *N,N*-dimethylchloromethyleneiminium chloride, and then subsequently treated with $NaBH_4$.[10] Thus **13** was treated with 2 equivalents of *N,N*-dimethylchloromethyleneiminium chloride in THF–MeCN, and then reduced with excess $NaBH_4$. This gave, after spontaneous lactonisation, **14** in 51% yield. The structure of **14** was elucidated by X-ray structure determination (Fig. 1, Table 1). The molecule is nearly planar, and it was confirmed that there is no possibility for hydrogen bonding, which explains the low melting point and the large atomic displacement parameters.

Lactone **14** was hydrogenated at 40 atm and 40 °C with rhodium-on-carbon as the catalyst. The resulting piperidine (±)-**15** was characterised by conversion into the *N*-2,4-dinitrophenyl derivative by reaction with Sanger's reagent. This gave (±)-**16** in 47% yield for the two steps. It was not possible to obtain **16** crystalline, so the relative stereochemistry could not be confirmed by X-ray analysis. However, since only one stereoisomer was observed in the reaction and since the very similar transformation **9** to **11** was stereoselective, it is very likely for chemical reasons that the stereochemistry of the product was the proposed one. The ^1H NMR spectrum of **16** was not completely elucidated, but the H-5 proton could clearly be seen, displaying 3 couplings of 6.5, 2.3 and 1.7 Hz. The H(5)–C(5)–C(4)–H(4) torsion angle in the crystal structure of **11** is 41°, while the H(5)–C(5)–C(6)–H(6a/6b) torsion angles are about ±60°. If **16** can be assumed to have a conformation similar to **11**, which is reasonable as they are very similar molecules, those couplings fit well with values one would expect: two small couplings for $J_{5,6a}$ and $J_{5,6b}$ and a large coupling for $J_{4,5}$.

In conclusion (±)-**1** was synthesised in its lactone form (±)-**15**. The overall yield of the derivative (±)-**16** was 13% from pyridine **3**. It was also observed that introduction of an oxy substituent into the 5-position changes the preference for basic hydrolysis of the two ester groups on the pyridine. This electronic preference for attack at C-3 contrasts what has been observed for **6**.[4] Obviously the electronic factors are quite small since it was not possible to reduce **12** preferentially, and there may also be some difference between the anhydride and diester.

Experimental

General. ^{13}C NMR and ^1H NMR spectra were recorded on a Varian Gemini 200 instrument. D_2O was used as



Scheme 5. Synthesis of **15** and **16**.

the solvent with DHO (^{1}H NMR: δ 4.7) and acetone (^{1}H NMR: δ 2.05; ^{13}C NMR: δ 29.8) as references. With $CHCl_3$ as the solvent tetramethylsilane (TMS) and $CHCl_3$ (^{13}C NMR: δ 76.93) were used as references. Mass spectra were obtained on a VG TRIO-2 instrument. Melting points are uncorrected. Solutions were concentrated on a rotary evaporator at a temperature below 40 °C. Dry tetrahydrofuran was prepared by distillation from sodium and benzophenone, dry MeCN by distillation from CaH_2 and dry CH_2Cl_2 by distillation from P_2O_5.

5-Hydroxypyridine-3,4-dicarboxylic acid 4-methyl ester (**8**). 5-Hydroxypyridine-3,4-dicarboxylic acid dimethyl ester (**3**, 1.50 g, 7.1 mmol) was dissolved in 12 ml water. NaOH (569 mg, 14.2 mmol) dissolved in 4 ml water, was added over a period of 5 min. The reaction was stirred for 2 h at 25 °C. HCl (1 M) was slowly added until the solution reached pH 2, and the water was removed under reduced pressure. The solid that remained after evaporation was boiled in 300 ml THF for 20 min. During boiling the THF phase turned yellow, and the remaining white solid was removed by filtration and discarded. The THF was removed under reduced pressure giving 5-hydroxypyridine-3,4-dicarboxylic acid 4-methyl ester (**8**). Yield 1.35 g (96%). M.p. 195–200 °C. ^{1}H NMR (DMSO): δ 8.62 (s, 1 H, =CH), 8.59 (s, 1 H, =CH) and 3.8 (s, 3 H, OCH_3). ^{13}C NMR (DMSO): δ 165.7, 165.4 (2 × C=O), 150.7, 141.6, 140.4, 129.8, 124.4 (Ar), 52.7 (OMe). MS (EI): *m/z* 197 (M^+).

5-Hydroxy-4-hydroxymethyl-3-pyridinecarboxylic acid 3,4′-lactone (**9**). Under a nitrogen atmosphere 500 mg (2.37 mmol) of 5-hydroxypyridine-3,4-dicarboxylic acid dimethyl ester (**3**) was dissolved in 5 ml of dry THF. The reaction was cooled in an ice bath and over a period of 5 min. $LiAlH_4$ (135 mg, 3.55 mmol) was added. The reaction was left at room temperature for 20 h after which time no hydrogen evolution was observed when two drops of water were added. The THF was separated from the solid by filtration and discarded. The remaining solid was stirred in 10 ml of water for 1.5 h. The lithium salts that did not dissolve in the water were removed by filtration and washed with 2 × 5 ml water. The pH was adjusted to pH 6 with 1 M HCl, after which the water was removed under reduced pressure. After purification by flash chromatography (ethyl acetate–pentane–formic acid, 40:60:1) 5-hydroxy-4-hydroxymethyl-3-pyridinecarboxylic acid 3,4′-lactone (**9**) was obtained. Yield: 176 mg (49%). M.p. >295 °C. ^{1}H NMR (DMSO): δ 8.55 (s, 1 H, =CH), 8.47, (s, 1 H, =CH), 5.40 (s, 2 H, CH_2). ^{13}C NMR (DMSO): δ 169.8 (C=O), 163.4, 149.0, 141.2, 140.9, 137.6 (Ar), 68.3 (CH_2). MS (EI): *m/z* 151 (M^+). IR (KBr): 1768 (C=O), 1585, 1309 cm^{-1}.

(3RS,4RS,5SR)-N-(2,4-Dinitrophenyl)-5-hydroxy-4-hydroxymethyl-3-piperidinecarboxylic acid (**11**). 5-Hydroxy-4-hydroxymethyl-3-pyridinecarboxylic acid 3,4′-lactone (**9**, 92 mg, 0.61 mmol) was dissolved in 5 ml 99% ethanol. Rhodium-on-carbon (100 mg, 5%) was added as a catalyst. The mixture was hydrogenated at 50 °C and 50 bar for 3 days. After hydrogenation the catalyst was removed by filtration over Celite, and the ethanol was removed by evaporation under reduced pressure. The yield of crude **10** was 89 mg (96%).

The crude product **10** (45 mg, 0.29 mmol) was dissolved in 2 ml of 99% ethanol. $NaHCO_3$ (25 mg) was added and after 2 min 1-fluoro-2,4-dinitrobenzene (110 mg, 0.59 mmol) was added. The reaction was stirred at room temperature for 2 h. The ethanol was removed by evaporation under reduced pressure. After purification by flash chromatography (EtOAc–pentane, 4:1) **11** was obtained. Yield: 43 mg (36%). ^{1}H NMR (DMSO): δ 8.59 (d, 1 H, ArH), 8.27 (dd, 1 H, ArH), 7.53 (d, 1 H, ArH), 5.48 (d, 1 H, $J_{OH,3}$ 4.0 Hz, OH), 4.35 (m, 2 H, *J* 8.7 Hz, *J* 6.5 Hz, H-4′), 4.07 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{2a,2b}$ 13.1 Hz, $J_{2a,3}$ 5.6 Hz, H-2a), 3.48 (dd, 1 H, $J_{2a,2b}$ 13.1 Hz, $J_{2b,3}$ 3.9 Hz, H-2b), 3.40 (dd, 1 H, $J_{6a,6b}$ 13.1 Hz, $J_{5,6a}$ 4.8 Hz, H-6a), 3.18 (dd, 1 H, $J_{6a,6b}$ 13.1 Hz, $J_{5,6b}$ 2.61 Hz, H-6b), 3.16 (m, 1 H, *J* 5.22 Hz, H-3), 2.88 (m, 1 H, H-4). ^{13}C NMR (DMSO): δ 177.5 (C=O), 149.5, 136.4, 135.9, 128.0, 123.9, 120.2 (ArH), 68.1 (C-5), 64.3 (C-4′), 53.4, 45.6 (C-2, C-6), 36.8, 36.3 (C-4, C-3). MS (EI) *m/z* 323 (M^+).

5-Benzyloxypyridine-3,4-dicarboxylic acid dimethyl ester (**12**). 5-Hydroxypyridine-3,4-dicarboxylic acid dimethyl ester (**3**, 2.66 g, 12.6 mmol) was dissolved in 10 ml DMF and 4 g Na_2CO_3 were added. Benzyl bromide (2.5 g, 15.1 mmol) was added, and the reaction was stirred at room temperature for 48 h. The DMF was removed under reduced pressure. After purification by flash chromatography (ethyl acetate–pentane, 1:6) 5-benzyloxypyridine-3,4-dicarboxylic acid dimethyl ester (**12**) was obtained. Yield 2.65 g (70%). M.p. 218–223 °C. ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 1 H, =CH), 8.52 (s, 1 H, =CH), 7.39–7.31 (m, 5 H, Ph), 5.26 (s, 2 H, OCH_2Ph), 3.97 (s, 3 H, CH_3O), 3.93 (s, 3 H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 166.1, 164.8 (2 × C=O), 151.2, 144.1, 139.9, 135.8, 133.1, 129.2, 128.9, 127.5, 123.4 (Ar), 72.0 (OCH_2Ph), 53.5, 53.4 (2 × CH_3O). MS (EI): *m/z* 301 (M^+).

5-Benzyloxypyridine-3,4-dicarboxylic acid 4-methyl ester (**13**). 5-Benzyloxypyridine-3,4-dicarboxylic acid dimethyl ester (**12**, 740 mg, 2.46 mmol) was dissolved in 10 ml THF. NaOH (97.6 mg, 2.44 mmol) dissolved in 10 ml water were added over a period of 2 min. The reaction was stirred for 3 h during which time the pH went from 13 to 10. The THF was removed under reduced pressure. The pH was raised to 12 with 1 M NaOH, and the water phase was extracted with 2 × 5 ml chloroform. The chloroform phases were discarded. The solid that was formed by adding 15 ml 4 M HCl to the water phase was recovered by filtration. The solid was for dried 24 h over P_2O_5, and **13** was obtained. Yield: 535 mg (75%). M.p.

182–185 °C. ^{1}H NMR (D_2O): δ 8.49 (s, 1 H, =CH), 8.35 (s, 1 H, =CH), 7.3 (m, 5 H, Bn), 5.12 (s, 2 H, CH_2Ph), 3.82 (s, 3 H, CH_3O). ^{13}C NMR (D_2O): δ 172.9, 171.6 (2 × C=O) 153.2, 145.5, 139.1, 138.3, 134.2, 133.5, 131.5, 130.9, 129.9 (Ar), 73.9 (OCH_2Ph), 56.0 (CH_3O). MS (EI): *m/z* 287 (M^+).

5-Benzyloxy-3-hydroxymethyl-4-pyridinecarboxylic acid 4,3′-lactone (**14**). 5-Benzyloxypyridine-3,4-dicarboxylic acid 4-methyl ester (**13**, 500 mg, 1.7 mmol) was dissolved in 75 ml dry THF and 25 ml dry acetonitrile. A suspension of 440 mg freshly made *N,N*-dimethylchloromethyleneiminium chloride (3.4 mmol) in 5 ml THF and 5 ml acetonitrile was added at −30 °C and stirred at the same temperature for 1 h. The temperature was lowered to −78 °C and 300 mg $NaBH_4$ (7.9 mmol) dissolved in 10 ml dry DMF were added. During a period of 3 h the temperature was raised to −30 °C. The reaction was quenched in 75 ml saturated $NaHCO_3$ and evaporated under reduced pressure to dryness. After flash chromatography (ethyl acetate–pentane–triethylamine 50:50:1) NMR spectroscopy showed a mixture of 5-benzyloxy-3-hydroxymethyl-4-pyridinecarboxylic acid 4,3′-lactone (**14**) and 5-benzyloxy-3-hydroxymethyl-4-pyridinecarboxylic acid methylester. The mixture was dissolved in 25 ml hot methanol, 1 ml 4 M HCl was added and water and methanol was removed under reduced pressure giving 5-benzyloxy-3-hydroxymethyl-4-pyridinecarboxylic acid 4,3′-lactone (**14**). Yield: 241 mg (50%). M.p. 114–117 °C. ^{1}H NMR (DMSO): δ 8.63 (s, 1 H, =CH), 8.57 (s, 1 H, =CH), 7.50–7.40 (m, 5 H, Ph), 5.47 (s, 2 H, H3 or H10), 5.45 (s, 2 H, H3′ or Bn). ^{13}C NMR (DMSO): δ 167.3 (C=O), 151.7, 143.7, 137.0, 136.2, 134.9, 128.8, 128.4, 127.8, 120.4 (Ar), 70.7, 68.2 (2 × CH_2). MS (EI): *m/z* 241 (M^+).

*(3*RS*,4*SR*,5*SR*)-5-Hydroxy-3-hydroxymethyl-4-piperidinecarboxylic acid 4,3′-lactone* (**16**). 5-Benzyloxy-3-hydroxymethyl-4-pyridinecarboxylic acid 4,3′-lactone (**14**, 164 mg, 0.68 mmol) was dissolved in 20 ml 99% ethanol. Rhodium-on-carbon (150 mg, 5%) was added as a catalyst. The mixture was hydrogenated at 40 °C and 40 atmosphere for 2 days. After hydrogenation the catalyst was removed by filtration over Celite. The ethanol was removed under reduced pressure. Yield: 105 mg (98%).

The crude product **15** (54 mg, 0.34 mmol) was dissolved in 2 ml of 99% ethanol. $NaHCO_3$ (30 mg) was added and after 2 min 1-fluoro-2,4-dinitrobenzene (115 mg, 0.62 mmol) was added. The reaction was stirred at room temperature for 2 h. The ethanol was removed by evaporation under reduced pressure. After purification by flash chromatography (ethyl acetate–pentane, 4:1) (*3RS,4SR,5SR*)-5-hydroxy-3-hydroxymethyl-4-piperidinecarboxylic acid 4,3′-lactone (**16**) was obtained. Yield: 52 mg (47%) ^{1}H NMR (DMSO): δ 8.60 (d, 1 H, ArH), 8.23 (dd, 1 H, ArH), 7.40 (d, 1 H, ArH), 5.75 (d, 1 H, $J_{OH,5}$ 3.8 Hz, OH) 4.32 (m, 2 H, H-3′), 3.97 (ddd, 1 H, H-5, *J* 6.5, *J* 2.3, *J* 1.7 Hz), 3.45 (br s, 2 H), 3.2 (m, 2 H), 3.0 (m, 2 H). ^{13}C NMR (DMSO): 176.4 (C-1), 149.8, 136.1, 135.8, 128.0, 124.0, 119.1 (Ar), 70.1, 63.6 (C-5, C-3′), 54.3, 47.4 (C-2, C-6), 41.9, 32.9 (C-4, C-3). MS (EI): *m/z* 323 (M^+).

X-ray structures. The structures of **8**, **9**, **11**, **13**, and **14** were determined by X-ray diffraction using a CCD area detector diffractometer[12] with Mo-Kα radiation monochromated by a graphite crystal. Omega rotation scans with narrow frames were used and integrated by means of SAINT and XPREP.[12] No absorption correction was employed. The datasets for **9** and **14** were collected at room temperature, the others at 120 K. The structures were solved by direct methods (SIR97).[13] Refinement proceeded by full matrix least squares but for **11** and **13** constraints had be introduced because too few reflections were available due to poor crystal quality and size, and for **11** also because of disorder and pseudosymmetry. **13** contains acetone of crystallisation, and the poor crystal quality is probably due to loss of solvent. Constraints were applied as described by Pawley.[14] For **13** the following model was used: phenyl group restrained to *mm*2 symmetry as was pyridine; atomic displacement parameters were described by the rigid body TLS model, one for the benzyl group and one for the rest of the molecule, with the same T for both. The extra oscillation of carboxyl groups was accounted for by two extra parameters. Hydrogen atoms were in calculated positions except for the one on O(1); for methyl groups a rotational parameter was refined, one of the ester groups was allowed two orientations with π/3 different torsion angle, and only the main component (86%) is given. For **11** pseudosymmetry was found (nearly space group $P2_1/a$) between the two molecules in the asymmetric unit, but at least for the small crystal used for data collection 75% of the molecules are of one chirality; the disorder parameters for the two sites were refined independently but gave nearly the same value, in agreement with the hydrogen bonds that connect the major components in the two sites and also the minor components amongst themselves. An ordered model in $P2_1$ refined to $R = 0.20$, and a difference map showed extra peaks where atoms would have been if the space group were $P2_1/a$. The disorder can be described as a molecule of the opposite chirality fitting in such a way that the dinitrophenyl group is exactly in the same place as in the main molecule, the C(4) carbon and 6-ring nearly overlap, and the 5-ring changes side with the hydroxyl group. This was modelled in the following way: the two dinitrophenyl groups were kept related by a centre of symmetry, the rest of the molecule was constrained to be the same for the two sites with the exception of the nitrogen atom, the disordered, minor, component was kept related to the major component by mirror symmetry; there was TLS for each site, with extra oscillation around the bond between 6-rings and for each nitro group. Hydrogens were in calculated positions except for the one on O(3). In this way the number of parameters was kept low to

correspond to the limited number of observations, and the geometry (common to all four molecules) could be determined with good accuracy. The structure of **14** refined to give good accuracy in spite of large atomic displacement parameters. The data were collected within a short counting time, which gave many small intensities and unreliable standard deviations. This resulted in a large goodness-of-fit, which could best be improved by removing the high theta reflexions. This flaw in the data reduction software has later been corrected.

Acknowledgements. We thank the Danish Natural Research Council for financial support through the THOR program. We also thank B. O. Pedersen for the mass spectra, and the Carlsberg Foundation for the SMART diffractometer.

References

1. Byrgesen, E., Nielsen, J., Willert, M. and Bols, M. *Tetrahedron Lett. 38* (1997) 5697.
2. Bach, P., Lohse, A. and Bols, M. *Tetrahedron Lett. 40* (1999) 367.
3. Ashcroft, W. R., Beal, M. G. and Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* (1981) 3012.
4. Krapcho, A. P., Maresh, M. J., Gallagher, C. E., Hacker, M. P., Menta, E., Oliva, A., Domenico, R. di, Re, G. da and Spinelli, S. *J. Heterocycl. Chem. 32* (1995) 1693.
5. Mühlradt, P. F., Morino, Y. and Snell, E. E. *J. Med. Chem. 10* (1967) 341.
6. Florent'ev, V. L., Drobinskaya, N. A., Ionova, L. V., Karpeiskii, M. Ya. and Turchin, K. F. *Dokl. Akad. Nauk SSSR (Engl. Transl.) 177* (1967) 617.
7. Florent'ev, V. L., Drobinskaya, N. A., Ionova, L. V. and Karpeiskii, M. Ya. *Khim. Get. Soedin. 5* (1969) 774.
8. van der Wal, B. de Boer, T. and Huisman, H. O. *Recl. Trav. Chim. Pays-Bas 80* (1961) 203.
9. Freifelder, R. M., Robinson, R. M. and Stone, G. R. *J. Org. Chem. 27* (1962) 284.
10. Fujisawa, T., Mori, T. and Sato, T. *Chem. Lett.* (1983) 835.
11. Allen, F. H., Davies, J. E., Galloy, J. J., Johnson, O., Kennard, O., Macrae, C. F., Mitchell, E. M., Mitchell, G. F., Smith, J. M. and Watson, D. G. *J. Chem. Inf. Comput. Sci.* (1991) 187.
12. Siemens SMART and SAINT Area-Detector Control and Integration Software, Bruker Analytical X-ray Instruments Inc., Madison, Winsconsin, USA 1995.
13. Cascarano, G., Altomare, A., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Siliqi, D., Burla, M. C., Polidori, G. and Camalli, M. *Acta Crystallogr., Sect. A 52* (1996) C50.
14. Pawley, G. S. *Adv. Struct. Res. Diffract. Methods 4* (1971) 1.
15. Burnett, M. N. and Johnson, C. K. ORTEP-III. Report ORNL-6895, Oak Ridge National Laboratory, TN 1996.

Received January 28, 1999.