CHAPTER 7

Pyridine Thiols as Models for HLADH.

Abstract: The zinc complex of pyridine dithiol 3.1f was tested as a model for the active site of the enzyme horse liver alcohol dehydrogenase and was found to be unsuccessful. The reason for this probably is the incapacity of zinc to coordinate the 1,4-dihydropyridine as well as the substrate at the same time. A mimic system 7.5 was designed in which a 1,4-dihydropyridine is attached to the pyridine thiol. This system indeed is capable of reducing ethyl phenylglyoxylate in moderate yield and low enantioselection. The results were compared to the model system 7.14 based on a pyridine alcohol. Like the thiol system 7.5 this system was found to reduction of the ketone 7.2, but the ketone is slowly oxidized back to the alcohol. The pyridinium salt 7.13, was also found to oxidize the alcohol 7.4 in the presence of Mg(ClO₄)₂. For the thiol and alcohol systems 7.5 and 7.13 it remains unclear whether or not the reaction goes to completion. It might be due to decomposition of the catalyst or to an equilibrium that has been reached in the reaction.
7.1 Introduction.

Horse liver alcohol dehydrogenase (HLADH) is a zinc-containing enzyme that is capable of reducing ketones and oxidizing alcohols making use of the coenzyme NADH. Mimicking the activity of HLADH has been a subject of study in our group for a number of years. Some interesting models, which mimic the activity of HLADH, have been developed. Most of these models are based on 1,4-dihydropyridines (as discussed in Chapter 1). These substituted dihydropyridines that have been used are capable of reducing activated carbonyl compounds like trifluoroacetophenone, pyridine-2-carboxaldehyde, benzophenone, and ethyl phenylglyoxylate. Of the dihydropyridines used, the N-alkylated 1,4-dihydronicotinamides show the greatest resemblance to NADH and have greater reactivity than others models. These compounds, however, are sensitive to side reactions. The combination of a 1,4-dihydronicotinamide derivative with ethyl phenylglyoxylate has been used as model reaction to study catalysts as models for the NADH system (Scheme 7.1). The reaction is usually carried out with a metal salt activator like Mg(ClO\textsubscript{4})\textsubscript{2} or Zn(ClO\textsubscript{4})\textsubscript{2}. Reactions with these metal ions, however, are stoichiometric rather than catalytic. With europium or neodymium the reaction proceeds catalytically. Reaction without a metal ion is minimal.

![Scheme 7.1 The model reaction.](image)

7.2 Model Compounds.

Models that mimic both the (re)activity as well as the structural aspects of the active site of the enzyme HLADH are not available. Attempts to use the monomeric zinc complex of pyridine dithiol failed due to the instability of this complex. A more stable monomeric zinc complex was formed with pyridine dithiol (for details see Chapter 4).

![4.5d,f](image)

d: \text{R}_1,\text{R}_2 = \text{fluorenyl}

f: \text{R}_1,\text{R}_2 = \text{fenchyl}
Application of this monomeric zinc complex as catalyst in the model reaction depicted in Scheme 7.1 using $N$-benzy-1,4-dihydronicotinicamide ($R^1$=Bz, $R$=H) as cofactor, however, did not lead to the reduction of ethyl phenylglyoxylate. One possible reason for the failure of this complex is that it is not able to coordinate with the substrate as well as with the 1,4-dihydropyridine. On the one hand the vicinity of the 1,4-dihydropyridine is necessary to accomplish reduction of the substrate. On the other hand substrate binding to the metal center is necessary to activate the carbonyl bond. In the natural enzyme NADH is closely situated to the zinc containing active site to which the substrate binds. All components are centralized in the active site and reaction therefore can take place. In our artificial system these components are close together and reaction cannot occur. In order for an artificial system to work like the enzyme the components should be brought together more efficiently. This can be accomplished by linking one or more components. By attaching the 1,4-dihydropyridine to a pyridine thiol a system (structure 7.5) is obtained in which the 1,4-dihydropyridine and the thiol functionality are always close together. Coordination of the substrate to the zinc complex of this system now should lead to the desired reduction of the substrate.

7.3 Synthesis of the Model Compounds.

The model system 7.5 was synthesized starting from 2-amino-picoline 7.7 and nicotinic acid 7.6. Attempted coupling of these starting materials to obtain the dipyridine 7.9 with DCC failed due to stability of the intermediate in which the acid is coupled to the DCC. To bypass the complication the nicotinic acid was converted to its acid chloride 7.8 and allowed to react with 2-amino-picoline in the presence of pyridine to trap the HCl formed (Scheme 7.2). The use of other bases instead of pyridine gave rise to lower yields of the bipyridine adduct 7.9.
The bipyridine adduct 7.9 was deprotonated using 2.5 equivalents of potassium diisopropylamide in order to deprotonate the methyl group. The deprotonation was followed by the addition of (R)-thiofenchone to give the pyridine thiol adduct 7.10 after hydrolysis (Scheme 7.3). Deprotonation of the bipyridine adduct 7.9 with n-butyllithium failed due to the directing ortho metalation effect of the amide functionality. This functionality effectuates deprotonation at positions adjacent to the amide at both pyridine rings. Using KDA no directing ortho metalation effect is present and deprotonation occurs selectively on the methyl group.

The pyridine thiol derivative 7.10 subsequently was alkylated in acetonitrile with methyl iodide in the presence of LiClO₄ to afford the soluble pyridinium perchlorate salt 7.11a (Scheme 7.4). Methylation of the nicotinic nitrogen occurred selectively. No methylation of the other pyridine nitrogen or the thiol group took place. This might be due to shielding of this pyridine ring by hydrogen bonding of the thiol group. Selective alkylation of the nicotinic nitrogen with benzyl bromide was accomplished at room temperature in dichloromethane afforded the pyridinium bromide 7.11b. Again no alkylation of the other pyridine nitrogen or thiol was observed under these conditions.
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Scheme 7.4 Reagents and conditions: i, MeI, Mg(ClO₄)₂, CH₃CN or benzylbromide, CH₂Cl₂; ii Na₂S₂O₄, phosphate buffer pH=7.00.

The pyridinium ion 7.11a was reduced to the corresponding 1,4-dihydropyridines 7.5a in a diluted buffered (pH = 7.0) solution using excess of Na₂S₂O₄ as reductant. Although Na₂S₂O₄ cleanly gives reduction to the 1,4-dihydropyridines at higher concentrations of 7.11 also the 1,6-dihydropyridines are formed. This probably is due to hydride exchange of the 1,4-dihydropyridine with the unreduced pyridine adducts present. The pyridinium adduct 7.11b was reduced with Na₂S₂O₄ in a buffered solution giving cleanly the 1,4-dihydropyridine 7.5b. Both dihydropyridines are relatively unstable and had to be used immediately after workup.

7.4 Test Results with the Model Compounds.

When 1,4-dihydropyridine 7.5a was applied in the reduction of ethyl phenylglyoxylate in the presence of Mg(ClO₄)₂, which is the most common metal salt activator, the reaction proceeded quickly and after only 15 min 30% of the substrate has been
reduced (Table 7.1). Stirring the mixture for a longer time did not lead to a higher conversion. Determination of the enantiomeric excess revealed a low ee of 9.6%. Reaction at a lower temperature led to a drop in reaction rate and to a small increase in the enantioselection. Compared to known examples in literature this system is relatively fast in the reduction reaction (for a summary see Chapter 1). Most systems require reaction times of days, whereas some are known to give an equally rapid reaction. When the reduction of the ketone was carried out in the presence of Zn(ClO$_4$)$_2$ at room temperature the reduction also took place, although it proceeded slower compared to the magnesium catalyzed reaction. The product, however, was formed as the other enantiomer in a slightly higher enantiomeric excess. This can be due to a different coordination of the zinc compared to the magnesium. Zinc easily binds sulfur, whereas magnesium tends to complex harder atoms like oxygen.$^9$ At 0°C a decrease in reaction rate is observed, whereas the enantioselectivity almost stays the same. Again, conversion of the ketone was not complete. The instability of the catalyst might be an explanation for this; it is also possible that an equilibrium was reached. When the benzyl-adduct 7.5b was applied in the reduction similar results were obtained, that is to say, a fast reduction and moderate yields with a low e.e. The combination of this system in the presence of zinc as metal salt activator give a fair, though not perfect, representation of the active site of HLADH.

Table 7.1 Results of the reduction of ethyl phenylglyoxylate.

<table>
<thead>
<tr>
<th>Dihydropyridine</th>
<th>metal</th>
<th>time</th>
<th>e.e.</th>
<th>yield</th>
<th>time</th>
<th>e.e.</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5a</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>15 min</td>
<td>9.6 (R)</td>
<td>30%</td>
<td>60 min</td>
<td>14.1 (R)</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Zn(ClO$_4$)$_2$</td>
<td>60 min</td>
<td>18.7 (S)</td>
<td>16%</td>
<td>2h</td>
<td>19.0 (S)</td>
<td>15%</td>
</tr>
<tr>
<td>7.5b</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>15 min</td>
<td>11.3 (R)</td>
<td>25%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

7.5 Other Derivatives as Models.

A model system that diverges more from the natural situation, was synthesized to investigate a possible positive effect of the thiol functionality in the model system 7.5. To this purpose a model system based on a pyridine alcohol was synthesized. The lack of the thiol group is expected to lead to a different behavior of the model system in the test reaction. The model system was synthesized starting from the dipyridine 7.9 by deprotonation with KDA and reaction with (R)-camphor to afford 7.12 (Scheme 7.5). At low temperatures (−70°C) the competitive enolization of the camphor is reduced. Reaction at higher temperatures gives rise to a substantial loss of the desired product because of enolization of the camphor.
The adduct 7.12 is methylated selectively at the nicotinic pyridine ring with methyl iodide to the pyridinium iodide salt 7.13 (Scheme 7.6). Conversion of this salt to the dihydropyridine was troublesome. Mixtures of 1,4 and 1,6-dihydropyridines were formed even when reduction was carried out in dilute solutions. However, conversion of the iodide salt 7.13 to the perchlorate salt prior to the reduction afforded the 1,4-dihydropyridine 7.14 selectively. The products was found to be unstable and had to be used in the test reaction immediately after the reduction.

Scheme 7.6 Reagents and conditions: i, MeI, Mg(ClO₄)₂, CH₃CN; ii Na₂S₂O₄, phosphate buffer pH=7.00.
Application of this model 7.14 in the reduction of ethyl phenylglyoxylate 7.2 in the presence of Zn(ClO₄)₂ did not lead to reduction of the substrate not even after 48h of stirring at room temperature. Reduction in the presence of Mg(ClO₄)₂ proceeded partly (15%) within 30 min, but after 2 h the alcohol began to be consumed and was converted to the ketone again. After 24 h only 5% of the alcohol was left. Addition of the pyridinium perchlorate salt 7.13 to a mixture of the alcohol and ketone (ratio 2:1) in the presence of Mg(ClO₄)₂ also led to the oxidation of the alcohol. After 18h the ratio was reduced to 1:1. The exact reason for the oxidation remains unclear, but it might be a consequence of the presence of perchloric acid after the formation of magnesium alkoxides.

7.6 Conclusions.

Attempts to obtain a model for the active site of HLADH based on the zinc complexes of pyridine dithiols 3.1 was not successful. The zinc seems to be incapable of coordinating the 1,4-dihydropyridine and substrate in the same time. Therefore a mimic 7.5 was designed in which a 1,4-dihydropyridine is attached to the pyridine thiol. This system indeed is able to reduce ethyl phenylglyoxyxylate in moderate yield and low enantioselection. The results were compared to the model system 7.14 based on a pyridine alcohol. This system was found to give scarcely any reduction of the ketone 7.2 but the pyridinium salt 7.13 was found to partly oxidize the alcohol 7.4. For the thiol and alcohol systems 7.5 and 7.13 it remains unclear whether the reaction stopped because of the decomposition of the catalyst or whether a equilibrium has been reached in the reaction. More research has to be carried out to get a clear picture of the process.

7.7 Experimental Section.

General Remarks: See chapter 2.

N-(6-methyl-2-pyridinyl)nicotinamide 7.9.

To a freshly prepared solution of nicotinic acid chloride 7.8 (17.7 g, 0.1 mol) in 250 mL of dichloromethane at 0 °C was added pyridine (11.9 g, 0.15 mol). After stirring for 15 min 2-amino-picoline 7.7 (10.8 g, 0.1 mol) in 25 mL of dichloromethane was added at such a rate that the temperature did not rise above 5 °C. Stirring continued for 1 h and the mixture was quenched with 2N NaOH. The organic layer was separated and washed with brine, dried over Na₂SO₄. After removal of the solvent the product was recrystallized from ethanol/water (1:1) affording 7.9 as colorless crystals (17.7 g, 0.8 mmol, 83%): mp 143-144 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.46 (s, 3H), 6.95 (d, J = 7.69 Hz, 1H), 7.42 (m, 1H), 7.65 (t, J = 7.69 Hz, 1H), 8.14 (d, J = 8.43 Hz, 1H), 8.21 (d, J = 5.86 Hz, 1H), 8.56 (br, NH), 8.77 (d, J = 5.12,
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1H), 9.14 (s, 1H); ^13^C NMR δ 23.52 (q), 111.36 (d), 119.78 (d), 123.36 (d), 129.99 (s), 135.11 (d), 138.94 (d), 148.39 (d), 150.40 (s), 152.60 (d), 156.73 (s), 163.94 (s); HRMS calcd 213.090, found 213.092. Anal. Calcd for C_{12}H_{11}N_{3}O: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.29; H, 5.22; N, 19.30.

Preparation of KDA.\textsuperscript{10}

To a cooled solution of 12.5 mmol potassium-t-butoxide and 12.5 mmol diisopropylamine in 50 mL of THF at –90 °C was slowly added 12.5 mmol n-BuLi (1.6M solution in hexane). This solution was stirred for 30 min at –80 °C and used immediately.


A solution of 7.9 (2.56 g, 12 mmol) in 200 mL of THF was cooled to –70°C and KDA (0.25 M in THF, 116 mL, 29 mmol) was added. After stirring for 10 min (R)-thiofenchone (2.1 g, 12.5 mmol) in 5 mL of THF was added. The solution was stirred for an additional hour allowing the mixture to reach room temperature. Then 25 mL of 2N NH_{4}Cl was added to the mixture and it was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_{2}SO_{4}. The product was purified by means of column chromatography (silica, ethyl acetate/hexane 1:2) affording 7.10 as a colorless solid (3.5 g, 9.2 mmol, 77%); mp 59-60 °C; ^1H NMR (300 MHz, CDCl_{3}) δ 0.86 (s, 3H), 1.16 (s, 3H), 1.21 (m, 2H), 1.23 (s, 3H), 1.40 (m, 1H), 1.71 (m, 2H), 1.93 (m, 1H), 2.18 (m, 1H), 3.28 (s, 2H), 3.10 (s, SH), 7.19 (d, J = 7.69 Hz, 1H), 7.45 (dd, J = 8.05 Hz, J = 7.68 Hz, 1H), 7.64 (dd, J = 8.05 Hz, J = 8.06 Hz, 1H), 8.12 (d, J = 8.06 Hz, 1H), 8.21 (m, 1H), 8.49 (br, NH), 8.78 (m, 1H), 9.14 (s, 1H); ^13^C NMR δ 18.08 (q), 24.35 (t), 27.44 (q), 28.94 (q), 33.65 (t), 40.21 (t), 45.42 (s), 47.97, (t), 50.76 (d), 54.59 (s), 62.39 (s), 110.98 (d), 121.37 (d), 123.36 (d), 129.96 (s), 135.02 (d), 138.16 (d), 148.05 (d), 149.25 (s), 152.45 (d), 160.50 (s), 163.70 (s); HRMS calcd 381.187, found 381.187. Anal. Calcd for C_{22}H_{27}N_{3}SO: C, 69.26; H, 7.13; N, 11.01; S, 8.40. Found: C, 68.74; H, 7.25; N, 10.71; S, 8.34.


The thiofenchone derivative 7.10 (0.85 g, 2.2 mmol) was dissolved in 25 mL of acetonitrile, LiClO_{4} (0.51 g, 4.8 mmol) and methyliodide (0.7 g, 4.8 mmol) were added. Stirring was continued overnight at 50°C. After removal of the solvent the product was purified by means of column chromatography (silica; acetonitrile / dichloromethane (1:2)) affording 7.11a as a white solid (1.0 g, 2.1 mmol, 95 %); ^1H NMR (300 MHz, CD_{3}OD) δ 0.41 (s, 3H), 0.74 (m, 1H), 0.77 (s, 3H), 0.81 (s, 3H), 1.01 (m, 1H), 1.22 (m, 1H), 1.34 (m, 1H), 1.63 (m, 1H), 1.80 (m, 1H), 2.95 (dd, J = 16.8 Hz, J = 26.0 Hz, 2H), 4.10 (s, 3H), 6.84 (d, J = 7.69 Hz, 1H), 7.31
(t, J = 7.68 Hz, 1H), 7.60 (d, J = 8.06 Hz, 1H), 7.81 (d, J = 6.23 Hz, 1H), 8.64 (m, 2H), 9.07 (s, 1H); ¹³C NMR (CD₃CN) δ 16.79, 23.41, 26.38, 27.84, 32.35, 39.01, 44.65, 46.79, 47.83, 49.83, 53.54, 61.27, 111.09, 121.54, 127.08, 133.56, 137.74, 142.87, 143.08, 144.31, 146.33, 147.98, 160.25; HRMS calcd 495.159, no proper HRMS could be obtained but CI(NH₃) gave a molecular ion at m/e 396. Anal. Calcd for C₂₃H₃₀N₃SO₅Cl: C, 55.69; H, 6.10; N, 8.47; S, 6.46. Found: C, 55.45; H, 6.05; N, 8.54; S, 6.41.


The thiofenchone derivative 7.10 (0.21 g, 0.55 mmol) was dissolved in 50 mL of dichloromethane and benzylbromide (0.43 g, 2.5 mmol) was added. After stirring for 18h the solution was concentrated in vacuo and the solid was washed with diethyl ether twice and recrystallized from 2-propanol affording 7.11b as a white solid (0.26 g, 0.47 mmol, 85 %): ¹H NMR (300 MHz, CDCl₃) δ 0.71 (s, 3H), 1.04 (m, 1H), 1.08 (s, 3H), 1.14 (s, 3H), 1.31 (m, 1H), 1.55 (m, 1H), 1.65 (m, 1H), 1.80 (m, 1H), 1.88 (m, 1H), 2.13 (s, 2H), 4.73 (s, SH), 6.15 (s, 2H), 7.00 (d, J = 7.3 Hz, 1H), 7.36 (m, 3H), 7.53 (t, J = 7.7 Hz, 1H), 7.58 (m, 2H), 7.77 (d, J = 8.1 Hz, 1H), 8.00 (m, 1H), 8.89 (d, J = 8.1 Hz, 1H), 9.32 (d, J = 5.9 Hz, 1H), 10.17 (br, NH); ¹³C NMR δ 18.29, 24.61, 25.27, 27.25, 29.32, 33.58, 10.41, 45.84, 48.09, 50.93, 54.64, 62.28, 64.65, 121.97, 127.51, 129.66, 129.72, 130.15, 131.95, 134.73, 138.13, 144.49, 145.29, 145.63, 149.18, 159.99; HRMS calcd 551.161, no proper HRMS could be obtained but CI(NH₃) gave a molecular ion at m/e 472. Anal. Calcd for C₂₉H₃₄N₃SOBr: C, 63.04; H, 6.20; N, 7.60; S, 5.80; Br, 14.46. Found: C, 63.15; H, 6.25; N, 7.70; S, 5.75.

1-methyl-N-\{(6-\{(1R,2R)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl\}-2-pyridinyl\}-1,4-dihydro-3-pyridinecarboxamide 7.5a.

To a stirred solution of pyridinium adduct 7.11a (0.20 g, 0.39 mmol) in 150 mL of methanol and 15 mL of a phosphate buffer (Merck Puffer-titrisol pH=7.00) was added Na₂S₂O₄ (0.44 g, 2.5 mmol) in 25 mL of water. The mixture was stirred for 5 min and then extracted with dichloromethane twice. The combined organic layers were dried over Na₂SO₄ and after concentration the product was flushed over a short column of silica with dichloromethane/acetonitrile (10:1). Product 7.5a was obtained as a yellow product that decomposed upon standing (0.15 g, 0.37 mmol, 96 %): ¹H NMR (300 MHz, CDCl₃) δ 0.85 (s, 3H), 1.14 (m, 1H), 1.17 (s, 3H), 1.21 (m, 1H), 1.24 (s, 3H), 1.40 (m, 1H), 1.65 (m, 1H), 1.73 (m, 1H), 1.90 (m, 1H), 2.16 (m, 1H), 2.98 (s, 3H), 3.24 (s, 2H), 3.30 (s, 2H), 3.73 (m, SH), 4.80 (m, 1H), 5.70 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 7.10 (s, 1H), 7.44 (br, NH), 7.53 (t, J = 8.1 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product.
1-benzyl-N-(6-[(1R,2R)-1,3,3-trimethyl-2-sulfanylbicyclo[2.2.1]hept-2-yl]methyl)-2-pyridinyl)-1,4-dihydro-3-pyridinecarboxamide 7.5b.

To a stirred solution of 7.11b (0.25 g, 0.45 mmol) in 100 mL of methanol and 25 mL of a phosphate buffer (Merck Puffer-titrisol pH = 7.00) was added Na₂S₂O₄ (0.53 g, 3.0 mmol) in 10 mL of water. The mixture was stirred for 5 min and extracted twice with dichloromethane. The organic layers were dried of Na₂SO₄ and concentrated. Column chromatography (silica; dichloromethene / acetonitrile (10:1)) afforded 7.5b as a yellow viscous oil (0.13 g, 0.27 mmol, 60 %): ¹H NMR (300 MHz, CDCl₃) δ 0.80 (s, 3H), 1.12 (s, 3H), 1.19 (s, 3H), 1.35 (m, 2H), 1.60 (m, 3H), 1.85 (m, 1H), 2.11 (m, 1H), 3.19 (s, 2H), 3.29 (s, 2H), 3.65 (s, SH), 4.28 (s, 2H), 4.76 (m, 1H), 5.72 (d, J = 6.1 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 7.2 (m, 6H), 7.48 (d, J = 7.3 Hz, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product.


To a stirred solution of 7.9 (1.5 g, 7.0 mmol) in 200 mL of THF at –70°C was added KDA (0.25 M solution in THF, 60 mL, 15 mmol) and stirring continued for 10 min before a solution of (R)-camphor (1.1 g, 7.2 mmol) in 25 mL of THF was added. The mixture was stirred at –70°C for 1h and at RT overnight. After addition of 2N NH₄Cl the mixture was extracted with ethyl acetate twice. The combined organic layers were washed with brine and dried over Na₂SO₄. The product was purified by means of column chromatography (silica, hexane/ethyl acetate 1:1) yielding a white solid, which was recrystallized from dichloromethene/hexane (1.1 g, 3.0 mmol, 43%): mp 130-131 °C; ¹H NMR (300 MHz, CDCl₃) δ 0.40 (s, 3H), 0.81 (s, 3H), 1.06 (s, 3H), 1.07 (m, 1H), 1.41 (m, 3H), 1.69 (m, 2H), 2.01 (m, 1H), 2.93 (s, 2H), 5.44 (br, OH), 7.02 (d, J = 7.32 Hz, 1H), 7.44 (dd, J = 7.69 Hz, J = 8.06 Hz, 1H), 7.71 (dd, J = 7.69 Hz, J = 8.06 Hz, 1H), 8.17 (m, 2H), 8.22 (d, J = 8.42 Hz, 1H), 8.64 (br, NH), 8.78 (d, J = 3.36 Hz, 1H), 9.13 (s, 1H); ¹³C NMR δ 10.98 (q), 20.77 (q), 21.13 (q), 26.92 (t), 30.48 (t), 44.69 (t), 44.98 (t), 46.71 (d), 49.27 (s), 52.25 (s), 81.15 (s), 111.98 (d), 120.77 (d), 123.27 (d), 129.93 (s), 135.09 (d), 138.04 (d), 148.30 (d), 149.81 (s), 152.42 (d), 158.75 (s), 164.09 (s); HRMS calcd 365.211, found 365.210. Anal. Calcd for C₂₂H₂₇N₃O₂: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.05; H, 7.49; N, 11.37.


To a stirred solution of 7.12 (0.50 g, 1.4 mmol) in 10 mL of acetonitrile was added methyl iodide (0.20 g, 1.4 mmol) and the mixture was stirred overnight at 50 °C. The solvent was evaporated and the product was recrystallized from 2-propanol yielding a white solid.
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(0.68 g, 1.3 mmol, 98%): ¹H NMR (300 MHz, CDCl₃) δ 0.34 (s, 3H), 0.67 (s, 3H), 0.90 (s, 3H), 0.96 (m, 1H), 1.17 (m, 1H), 1.34 (m, 2H), 1.58 (m, 2H), 1.82 (m, 1H), 2.65 (dd, J = 14.32 Hz, J = 14.32 Hz, 2H), 4.54 (s, 3H), 6.86 (br, OH), 6.85 (d, J = 7.32 Hz, 1H), 7.60 (dd, J = 7.68 Hz, J = 8.06 Hz, 1H), 7.94 (d, J = 8.06 Hz, 1H), 8.08 (m, 1H), 8.80 (d, J = 8.42 Hz, 1H), 9.45 (d, J = 6.23 Hz, 1H), 10.13 (s, 1H), 10.60 (br, NH); HRMS calcd 507.138, no proper HRMS could be obtained but CI(NH₃) gave a molecular ion at m/e 366 (-I, -CH₃).


1-methyl-N-(6-[(1R,2S)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]methyl)-2-pyridinyl)-1,4-dihydro-3-pyridinecarboxamide 7.14

To a stirred solution of 7.13 (0.66 g, 1.3 mmol) in 200 mL of methanol was added lithium perchlorate (0.14 g, 1.3 mmol). The mixture was stirred for 1 h and 50 mL of a phosphate buffer(Merck Puffer-titrisol pH=7.00) was added. Na₂S₂O₄ (1.5 g, 8.6 mmol) in 10 mL of water was added with vigorous stirring. After stirring for 30 min 200 mL of water was added and the mixture was extracted with dichloromethane twice. The combined organic layers were dried over Na₂SO₄ and after concentration in vacuo the product was flushed over a column of aluminum oxide with dichloromethane. A unstable yellow oil was obtained that was used as such for the reduction reactions (0.46 g, 0.9 mmol, 70 %): ¹H NMR (300 MHz, CDCl₃) δ 0.48 (s, 3H), 0.75 (s, 3H), 1.00 (m, 1H), 1.03 (s, 3H), 1.29 (m, 1H), 1.38 (m, 2H), 1.63 (m, 2H), 1.94 (m, 2H), 2.82 (s, 2H), 2.91 (s, 3H), 3.20 (s, 2H), 4.74 (m, 1H), 5.64 (d, J = 8.1 Hz, 1H), 5.80 (br, OH), 6.82 (d, J = 7.7 Hz, 1H), 7.01 (s, 1H), 7.36 (br, NH), 7.55 (t, J = 8.1 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H). No HRMS or elemental analysis could be obtained because of the instability of the product.

**General Procedure for the reduction of ethyl phenylglyoxylate.**

To a stirred solution of ethyl phenylglyoxylate (1.0 mmol) in 5 mL of acetonitrile was added the dihydropyridine adduct (1.2 mmol) followed by the addition of a zinc or magnesium perchlorate (1.2 mmol). The mixture was stirred in the dark for the given time and samples were taken to determine the conversion by means of GC analysis (HP-1; 30m x 0.25 mm x 0.25μm; flow He 1.3 mL/min; T(oven) 100°C 2 min, 20°C/min↑; T(det/inj) 350 °C; split ratio 150:1; Vinj = 0.2 μL. Tᵣ of ketone 5.91 min, Tᵣ of alcohol 5.75 min) After the reaction was complete the mixture was quenched with water and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over MgSO₄. The product was purified by means of column chromatography (silica; ether / hexane (1:3)) affording the alcohol. The enantiomeric excess was determined by means of HPLC (OB-H; hep:IPA (95:5); flow: 0.5 ml/min; Tᵣ of (S)-7.4 22.7 min and (R)-7.4 26.44 min)
7.8 References.


10 Pasquinet, E; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. Tetrahedron 1998, 54, 8771