

Chemistry of Bicyclic Endoperoxides Derived from Dihydropyridine Derivatives: Attempted Synthesis of Polyhydroxypiperidine Derivatives

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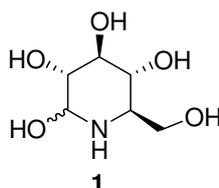
To achieve the synthesis of azasugar derivatives with the utilization of singlet oxygen, pyridine was used as the starting material. The reduction of pyridine followed by a singlet oxygen reaction afforded cyclic aza-endoperoxides (**14** and **16**). However, many attempts were made to convert the aza-endoperoxides to the corresponding di- and triacetates without success. However, the base-catalyzed rearrangement of **14** gave unprecedented rearrangement products **23** and **24**.

Key Words: Azasugar derivatives, amino sugars, singlet oxygen, bicyclic endoperoxides.

Introduction

Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and useful as potent glycosidase inhibitors.^{1–3} This discovery has stimulated interest in the development of effective procedures for the synthesis of various azasugars^{4–6} and analogues^{7–10} for the investigation of glycosidase reactions^{11–13} and the development of specific glycosidase inhibitors for treating metabolic disorders such as diabetes^{1–3,8,14,15} or as antiviral,^{1–3,16–18} antibacterial^{1–3,19} and anticancer^{1–3,20} agents.

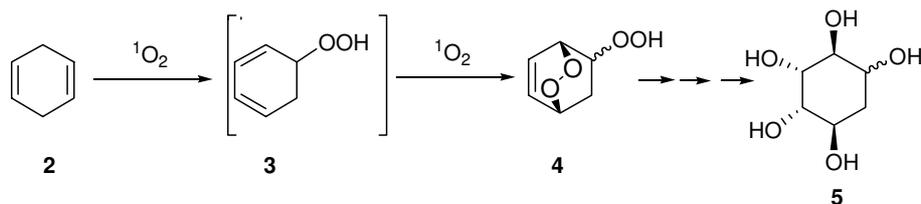
Many polyhydroxylated alkaloids have been shown to affect the processing of biologically important carbohydrate chains. In particular, some polyhydroxylated piperidines and pyrrolidines have recently been claimed to be a powerful set of inhibitors of glycosidase activity. Specifically, nojirimycin **1** and its 1-deoxy derivatives inhibit α - and β -glucosidases up to 10^5 times better than D-glucose.²¹



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Owing to the importance of these compounds, the main aim of this study was to develop a methodology leading to the synthesis of polyhydroxypiperidine derivatives starting from reduced pyridine derivatives.

In a previous study^{22,23} we showed that the photooxygenation of 1,4-cyclohexadiene **2** yielded the isomeric hydroperoxide **4** via the diene endoperoxide **3** (Scheme 1). The formed bicyclic hydroperoxy endoperoxides **4** were successfully converted to the corresponding quercitols **5**. We thought that the application of a photooxygenation reaction to appropriate dihydropyridine derivatives might give the corresponding polyhydroxy piperidine derivatives.

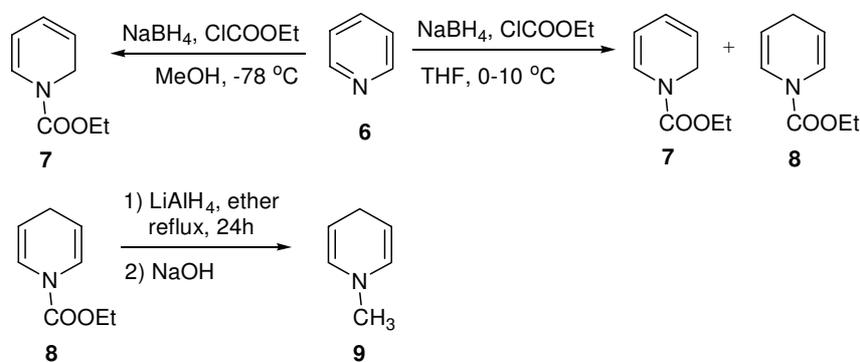


Scheme 1

In this work we report the reduction of pyridine and photooxygenation of the formed dihydropyridine derivatives.

Results and Discussion

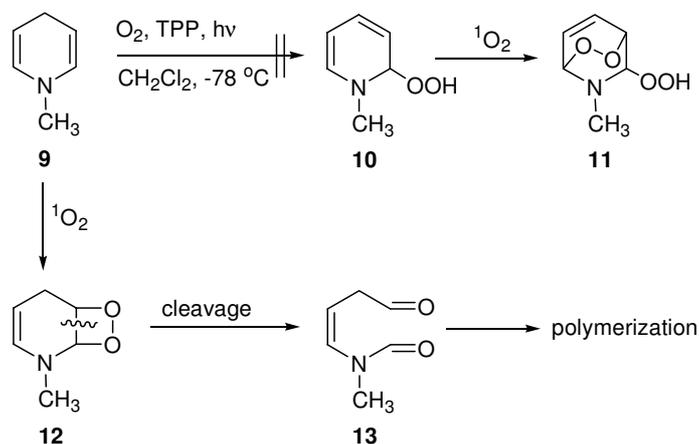
The starting material pyridine was reduced with sodium borohydride in the presence of ethyl chloroformate at different temperatures and solvents to give 2 different dihydropyridine derivatives, **7** and **8** (Scheme 2).²⁴



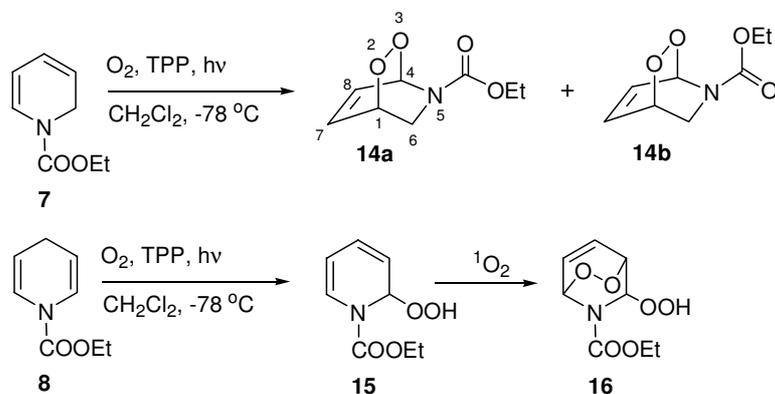
Scheme 2

The NMR spectrum of the 1,2-dihydropyridine derivative **7** shows that there are 2 isomers arising from the hindered rotation about the N-COOR bonds²⁵. On the other hand, the NMR spectrum of **8** showed only one isomer due to the symmetry plane in the molecule. N-carboethoxy-1,4-dihydropyridine **8** was then reduced with lithium aluminum hydride, followed by sodium hydroxide hydrolysis, to give N-methyl-1,4-dihydropyridine²⁴ **9** (Scheme 2). This compound is quite susceptible to atmospheric oxygen and decomposes at room temperature; therefore, the purification of this compound was not possible. The stability of **7** and **8** arises from the conjugation of the lone pair on nitrogen with the adjacent carbonyl group. However, even these dihydropyridines **7** and **8** decompose when exposed to atmospheric oxygen at room temperature for prolonged periods.

Tetraphenylporphyrin-sensitized photooxygenation of the obtained dihydropyridine derivatives **7**, **8** and **9** were carried out in methylene chloride at room temperature. Photooxygenation of N-methyl-1,4-dihydropyridine **9** at $-78\text{ }^{\circ}\text{C}$ gave only polymeric materials instead of the expected ene reaction followed by [2+4] cycloaddition product **11** (Scheme 3).



We assume that the enamine functional group in **9** undergoes a [2+2] cycloaddition reaction to afford a dioxetane. It is well documented that the electron-rich double bonds such as enol ethers and enamines would prefer a [2+2] cycloaddition reaction²⁶. With the knowledge that dioxetanes are immediately cleaved to 2 carbonyl compounds on gentle warming, we assume that the formed dialdehyde undergoes polymerization due to the high reactivity of the aldehyde groups.

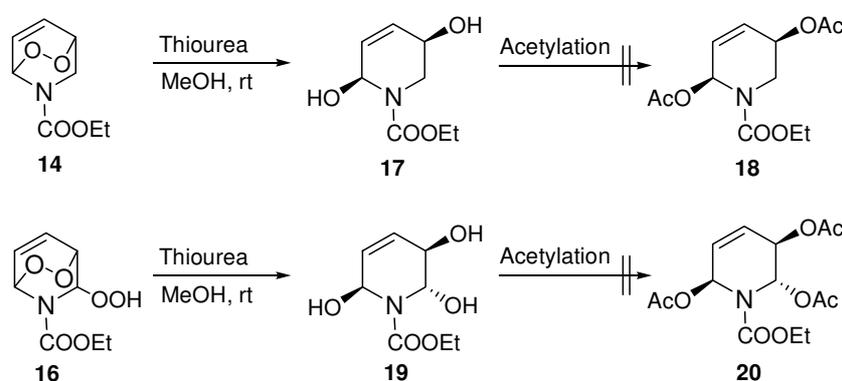


Because of the failure of this reaction, we turned our attention to the photooxygenation of N-carboethoxy-1,2-dihydropyridine **7**²⁷. The reaction was carried out in dichloromethane, using a 500-W halogen lamp, in the presence of TPP as sensitizer in a dry ice-acetone bath. A single and unstable product was obtained after work-up, and its chemical structure was deduced to be [2+4]cycloadduct between N-carboethoxy-1,2-dihydropyridine **7** and singlet oxygen. Analysis of the NMR spectra clearly indicated the formation of 2 isomers, **14a** and **14b**. The endoperoxide **14** can be stored at $-30\text{ }^{\circ}\text{C}$ for a limited period of time (Scheme 4).

Analysis of the $^1\text{H-NMR}$ spectrum of **14** (2:3 isomeric mixture) shows that olefinic protons H_7 and H_8 possess an AB-system in which the A-part proton resonates at δ 6.52 ppm and the B-part proton at δ 6.47 ppm, respectively. The bridgehead protons H_4 resonate at δ 5.96 and δ 5.82, respectively. The other bridgehead protons H_1 resonate at δ 4.63 and δ 4.57 as 2 separate broad signals for the 2 isomers. The coupling constants (for the 2 isomers) between H_4 and olefinic proton H_8 are $J = 5.4$ and $J = 5.2$ Hz. The closeness of the coupling constants indicates coinciding isomers. The ring methylene protons $-\text{CH}_2-$ exhibit different splitting patterns for each isomer. One set of $-\text{CH}_2-$ protons resonate at δ 2.97 ppm and give a broad doublet with $J = 9.6$ Hz. However, the other $-\text{CH}_2-$ protons resonate at δ 3.75 ppm as a multiplet. This difference can be attributed to the orientation of the ester group. $^{13}\text{C-NMR}$ spectral data are also in agreement with the proposed structure.

The same procedure for photooxygenation was applied to N-carboethoxy-1,4-dihydropyridine **8**. The expected hydroperoxy-endoperoxide **16** was obtained in 74% yield. 1,4-Dihydropyridine derivative **8** first underwent an ene reaction to give the hydroperoxide **15**, which is trapped by singlet oxygen, forming **16** as expected (Scheme 4). The carboethoxy group attached to the nitrogen atom prevents the formation of dioxetane because of the reduced electron density on the adjacent $\text{C}=\text{C}$ double bond.

The analysis of the $^1\text{H-NMR}$ spectrum of **16** revealed that only one type of product was formed. The olefinic protons exhibit an AB-system located at δ 6.75 (ddd, $J = 2.0$ Hz, $J = 5.1$ Hz and $J = 8.0$ Hz, 1H, H_8) and 6.54 as a multiplet. The bridgehead protons H_4 and H_1 resonate at 5.68 and 5.10, respectively. The signal belonging to proton H_6 coincides with the peaks of the methylene groups of the ester.



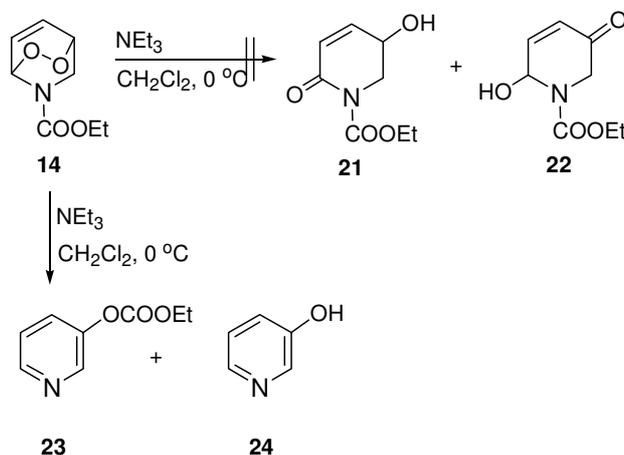
Scheme 5

Selective reduction of the peroxide linkage in **14** was performed with thiourea under very mild conditions to give diol **17** (Scheme 5). Since only the oxygen-oxygen bond breaks in this reaction, it preserves the configuration at 2 carbon atoms. For further structural proof, **17** was then subjected to acetylation. However, attempts with either acetic anhydride/pyridine or acetyl chloride/chloroform gave no trace of the expected acetates. The starting material was decomposed under these conditions.

The reduction of the peroxide linkage in **16** was also performed with thiourea. Again the formed triol could not be converted into the corresponding triacetates. The attempted hydroxylation of the double bonds in **17** and **19** resulted in the formation of polymeric materials.

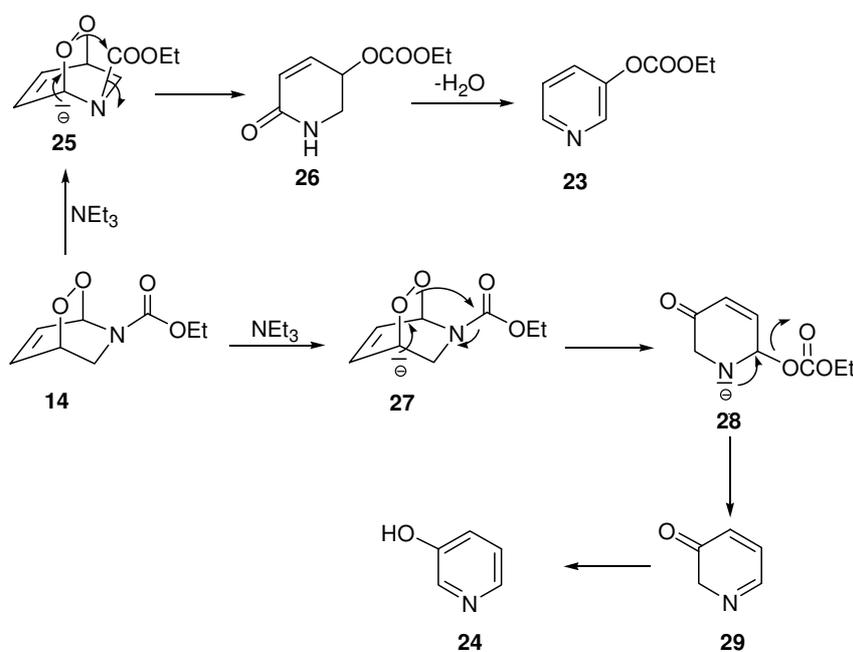
For further functionalization of the peroxide functionalities in **14** and **16**, the endoperoxides were treated with base. The base-catalyzed reactions of the bicyclic endoperoxides generally form monocyclic hydroxy ketones. The oxidation of the resulting hydroxy ketones should be an efficient way to obtain cyclic

1,4-diones.^{26,28,29} For this purpose, endoperoxide **14** was treated with NEt_3 in methylene chloride at $0\text{ }^\circ\text{C}$. Endoperoxide **14** gave the pyridine derivatives **23** and **24**, instead of the expected ring opening products **21** and **22** (Scheme 6). The formed products **23** and **24** were separated by column chromatography and their structures characterized thoroughly.



Scheme 6

For the formation of the unexpected products, **23** and **24**, we propose the following mechanism (Scheme 7). Base initially abstracts the bridgehead proton H_1 and H_4 . The formed carbanions **25** and **27** cleave the oxygen-oxygen bond where the carbonyl groups are formed. The formed alkoxide group attacks the ester carbonyl group, which leads to the breaking of the C-N bond to form **26**. On the other hand, **27** can easily form **28** by a similar mechanism. The elimination of the $-\text{OCOOEt}$ group followed by tautomerization can provide the hydroxypyridine derivative **24** (Scheme 7). To the best of our knowledge this base-catalyzed



Scheme 7

rearrangement of an endoperoxide is unprecedented. Treatment of **16** with base led to the formation of polymeric materials.

Experimental

General: Infrared spectra were recorded with a Mattson 1000 FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a 400 (100) MHz spectrometer and are reported in δ units with SiMe_4 as internal standard. All column chromatography was performed on silica gel (60 mesh, Fluka). TLC was carried out on Merck 0.2 mm silica gel 60 F₂₅₄ analytical aluminum plates.

Synthesis of ethyl pyridine-1(2H)-carboxylate (7)²⁴: Ethyl chloroformate (13.73 g, 0.127 mol) in 15 mL of ether was added to a mixture containing of 5.07 g (0.134 mol) of NaBH_4 and 10.0 g (0.127 mol) of pyridine in 50 mL of absolute methanol cooled in a dry ice-acetone bath. The rate of addition was controlled so that the temperature of the reaction mixture did not exceed $-69\text{ }^\circ\text{C}$ and the addition was completed over 1.5 h. Then the reaction mixture was stirred for an additional 1.5 h at this temperature and was poured into ice water. Water (200 mL) was added to dissolve the inorganic salts and the mixture was extracted with ether (4 x 50 mL). The ethereal layers were combined and washed with 15% HCl (3 x 30 mL) and then water, and dried over Na_2SO_4 . After removal of the solvent in vacuo (at $35\text{ }^\circ\text{C}$), N-carboethoxy-1,2-dihydropyridine (**7**) was obtained as an isomeric mixture (14.34 g, 74%, 2:3). ^1H -NMR (400 MHz, CDCl_3): δ ppm 6.67 (d, $J = 7.2\text{ Hz}$, 1H, olefinic H_6), 6.54 (d, $J=7.5\text{ Hz}$, 1H, olefinic H_6), 5.75 (m, 2H, olefinic H_4), 5.42 (m, 1H, olefinic H_3), 5.34 (m, 1H, olefinic H_3), 5.08 (m, 1H, olefinic H_5), 4.98 (m, 1H, olefinic H_5), 4.29 (m, 4H, ring methylenic protons H_2), 4.13 (q, $J = 7.1\text{ Hz}$, 4H, $-\text{CH}_2-$) and 1.35 (t, $J = 7.1$, 6H, $-\text{CH}_3$). ^{13}C -NMR (100 MHz, CDCl_3): δ ppm 153.5, 152.6 (C=O), 126.5, 125.7 (2C, C_6), 122.4, 121.9 (2C, olefinic C_4), 118.7, 118.0 (2C, C_3), 104.2 (2C, C_5), 61.9, 61.7 (2C), 43.6, 43.3 (2C, ring methylenic carbons C_2) and 14.5, 14.4 (2C). IR (CHCl_3 , cm^{-1}): 3643, 3030, 1702, 1678, 1421, 1243, 1217, 783, 757.

Synthesis of ethyl pyridine-1(4H)-carboxylate (8)²⁴: First 20 g (0.253 mol) of pyridine and 5.04 g (0.134 mol) of NaBH_4 were dissolved in 100 mL of fresh distilled THF and were brought to $0\text{--}10\text{ }^\circ\text{C}$ with an ice bath. Then 27.46 g (0.253 mol) of ethyl chloroformate was added to the reaction mixture at a rate so that the reaction temperature did not exceed $10\text{ }^\circ\text{C}$. Addition was completed in about 10 min. The reaction mixture was stirred for an additional 1.5 h at that temperature and water (200 mL) was added to dissolve inorganic salts and to decompose the excess unreacted NaBH_4 . Then the mixture was extracted with ether (5 x 30 mL). The ethereal extracts were combined, washed with water and dried over Na_2SO_4 . Evaporation of solvent in vacuo gave a mixture (22.14 g) of 1,2- and 1,4-dihydropyridines **7** and **8**. To obtain pure 1,4-isomer **8**, the obtained mixture was treated with 30.74 g of maleic anhydride and 125 mL of CH_2Cl_2 (previously purged with N_2) and refluxed for 14 h. The mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was dissolved in ether and washed with 15% NaOH solution (5 x 30 mL) and brine. The combined organic extracts were dried over Na_2SO_4 and the ether was evaporated. Finally, the product was further separated from the unreacted pyridine by vacuum distillation (10 mmHg) at room temperature. The total yield of **8** was 19%. ^1H -NMR (400 MHz, CDCl_3): δ 6.87 (d, $J = 7.4\text{ Hz}$, 1H, H_2), 6.68 (d, $J = 7.3\text{ Hz}$, 1H, H_6), 4.69 (m, 1H, H_3), 4.36 (m, 1H, H_5), 2.79 (m, 2H, H_4), 4.28 (q, $J = 7.1\text{ Hz}$, 2H) and 1.4 (t, $J = 7.1\text{ Hz}$, 3H). ^{13}C -NMR (100 MHz, CDCl_3): δ ppm 151.8 (C=O), 124.0, 123.8 (C_2 and C_6), 106.4, 105.8 (C_3 and C_5), 62.7 ($-\text{CH}_2-$), 22.8 (C_4) and 14.9 (CH_3). IR (CHCl_3 , cm^{-1}): 3030,

2978, 2953, 1702, 1421, 1395, 1243, 1217, 783, 758.

Synthesis of 1-methyl-1,4-dihydropyridine (8)²⁴: First 0.444 g (0.0117 mol) of LiAlH₄ in 10 mL of ether was placed in a flask and cooled to 0 °C with an ice bath. Then 1.0 g (0.0065 mol) of N-carboethoxy-1,4-dihydropyridine **8** in 5 mL of ether was added from the dropping funnel over 10 min. After the addition was completed, the reaction mixture was allowed to warm to room temperature and was then refluxed for 24 h. The mixture was cooled to 0 °C in an ice bath. The excess LiAlH₄ was decomposed with 1.8 mL of 20% NaOH solution. The salts were removed by filtration and washed with ether. The ethereal solution was dried over Na₂SO₄ and the product was concentrated in vacuo (at 30 °C). As the product was unstable to atmospheric oxygen, purification did not give observable results. The crude yield was 76%. ¹H-NMR (400 MHz, CDCl₃): δ ppm 5.52 (dt, A part of the AB system, J = 8.1 Hz and ⁴J = 1.4 Hz, 2H, H₂, H₆), 4.2 (m, B part of the AB system, 2H, H₃, H₅), 2.8 (br.s, 2H, methylenic protons, H₄) and 2.68 (s, 3H, CH₃).

Photooxygenation of 1-methyl-1,4-dihydropyridine (8): First 0.1 g of N-methyl-1,4-dihydropyridine **8** (0.0011) and a catalytic amount of *meso*-tetraphenylporphyrin (TPP) (20 mg) were dissolved in 50 mL of CH₂Cl₂. The reaction mixture was cooled by dry ice-acetone bath to -78 °C. Then the mixture was irradiated with a projection lamp (150 W) for 2 h while the dry oxygen gas was bubbled through the reaction mixture. The starting material was consumed after 2 h. The solvent was evaporated in vacuo (at 35 °C). The ¹H-NMR spectral studies showed the formation of undefined polymeric materials instead of the expected product **11**.

Synthesis of ethyl 2,3-dioxa-5-azabicyclo[2.2.2]oct-7-ene-5-carboxylate (14): First 5 g of N-carboethoxy-1,2-dihydropyridine **7** (0.0327 mol) was dissolved in 200 mL of CH₂Cl₂. A catalytic amount of TPP (20 mg) was added with constant stirring. The reaction mixture was brought to -78 °C by dry ice-acetone cooling bath. While this solution was irradiated by 2 projection lamps (150 W), the dry oxygen gas was bubbled through the solution. The reaction was monitored by TLC and it was completed after 5 h. The product was concentrated in vacuo by rotary evaporator. The crude yield was about 93% for the 2 isomers. The product was eluted from the column containing 40 g of silica gel (ether:hexane, 5:1). ¹H-NMR (400 MHz, CDCl₃): δ ppm 6.52 (m, A part of the 2 AB system, 2H, H₈), 6.47 (m, B part of the 2 AB system, 2H, H₇), 5.96 (d, J = 5.4 Hz, 1H, H₄), 5.82 (d, J = 5.2 Hz, 1H, H₄), 4.62 (m, 1H, H₁), 4.57 (m, bridgehead proton, 1H, H₁), 4.0 (m, 4H), 3.75 (m, 2H, H₆), 2.97 (d, J = 9.6 Hz, 2H, H₆) and 1.09 (m, 6H). ¹³C-NMR (100 MHz, CDCl₃): δ ppm 154.7, 154.0 (C=O), 131.4, 130.8 (2C, C₈), 129.3, 128.9 (2C, C₇), 76.7, 77.4 (2C, C₄), 70.7, 70.2 (2C, C₁), 62.1, 62.0 (2C), 45.4, 45.2 (2C, C₆), 15.03, 14.90 (2C). IR (CHCl₃, cm⁻¹): 3030, 1726, 1656, 1243, 1217, 783, 757, 681.

Synthesis of ethyl 6-hydroperoxy-2,3-dioxa-5-azabicyclo[2.2.2]oct-7-ene-5-carboxylate (16): First 0.5 g of N-carboethoxy-1,4-dihydropyridine **8** (0.0033 mol), 20 mg of TPP and 125 mL of CH₂Cl₂ were placed in a flask cooled by dry ice-acetone bath. The flask was irradiated with 2 projection lamps (150 W) at the given temperature while oxygen was bubbled through the mixture. The reaction was completed after 30 min and then the solvent was removed in vacuo. The crude yield was 74%. The compound was highly sensitive to column materials. ¹H-NMR (400 MHz, CDCl₃): δ ppm 6.75 (ddd, A part of the AB-system, J = 2.0 Hz, 5.1 Hz, and 8.0 Hz, 1H, H₈), 6.54 (m, B part of the AB-system, 1H, H₇), 5.68 (d, J = 5.1 Hz, 1H, H₄), 5.10 (dd, J = 4.4 Hz, J = 5.7 Hz, 1H, H₁), 4.0-4.20 (m, 3H, -CH₂- and H₆) and 1.1-1.33 (m, 3H, -CH₃). IR (CHCl₃, cm⁻¹): 3030, 1728, 1702, 1396, 1294, 1243, 1217, 1064, 783, 753, 681.

Synthesis of ethyl (3R(S),6R(S))-3,6-dihydroxy-3,6-dihydropyridine-1(2H)- carboxylate (17): First 0.5 g of endoperoxide **14** (0.0027 mol) was dissolved in 20 mL of methanol and brought to 0 °C with an ice bath. Thiourea (0.206 g, 0.0027 mol) in 10 mL of methanol was added to the reaction mixture. The reaction mixture was stirred at room temperature for 1 h. The formed solid particles were filtrated and the methanol was evaporated. Then the residue was dissolved and washed with ether. The removal of the solvent gave the cis-diol **17**. The crude yield was 79%. ¹H-NMR (400 MHz, CDCl₃): δ ppm 5.92 (dd, A part of the AB system, J = 10.2, 1.4 Hz, 1H, H₅), 5.75 (d, B part of the AB system, J = 10.2 Hz, 1H, H₄), 5.69 (br.s, 1H, H₆), 3.44 (br.s, 2H, H₂), 4.88 (m, 1H, alkoxide proton H₃), 4.23 (m, 2H, -CH₂-), 1.70 (br.s, -OH proton). 1.23 (t, 3H, -CH₃). IR (CHCl₃, cm⁻¹): 3311, 3183, 2698, 2264, 1702, 1626, 1498, 1345, 1243, 1064, 783, 681.

Synthesis of ethyl (2S(R),3R(S),6S(R))-2,3,6-trihydroxy-3,6-dihydro-pyridine-1 (2H)- carboxylate (19):

The hydroperoxy endoperoxide **16** (0.56 g, 0.0026 mol) in 20 mL of methanol was placed in a flask and brought to -6 °C with an ice-salt bath. At this temperature, thiourea (0.216 g, 0.0028 mol) in 10 mL of methanol was added to this solution. At the end of the addition, the reaction mixture was stirred at 0 °C for 30 min and then it was warmed to room temperature and stirred for an additional 1 h. The precipitated solid particles were filtered and the methanol was removed in vacuo. The residue was dissolved and washed with ether. Finally, concentration of the product in vacuo gave a mixture of 0.536 g of insoluble material, which was reacted with acetic anhydride and pyridine to transfer the product into the soluble triacetate **20**. The ¹H-NMR spectral studies of the reaction mixture did not reveal the formation of the triacetate **20**.

The reaction of endoperoxide 14 with NEt₃: The endoperoxide **14** (0.126 g, 0.68 mmol) in 30 mL of CH₂Cl₂ was placed in a flask cooled by an ice bath. NEt₃ (0.068 g, 0.67 mmol) in 10 mL of CH₂Cl₂ was added to the solution. After the addition was completed, the reaction mixture was stirred at 0 °C for 19 h. Then the solvent and NEt₃ were removed by rotary evaporator to give a crude mixture (0.135 g) consisting of **23** and **24** in a ratio of 1:3. The compounds were separated by silica gel (32.0 g) column chromatography, eluting with ether:hexane (1:5). Spectral data for **ethyl pyridin-3-yl carbonate (23)**: ¹H-NMR (400 MHz, CDCl₃): δ ppm 8.42 (d, J = 2.6 Hz, 1H, H₂), 8.35 (dd, J = 4.6, 1.3 Hz, 1H, H₆), 7.47 (ddd, A part of the AB-system, J = 8.3, 2.6, 1.3 Hz, 1H, H₄), 7.22 (dd, B part of the AB system, J = 8.3, 4.6 Hz, 1H, H₅), 4.22 (q, J = 7.1 Hz, 2H), 1.31 (t, ³J = 7.1 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ ppm 153.16 (C=O), 148.2 (C₃), 147.1 (C₆), 143.3 (C₂), 128.5 (C₄), 123.8 (C₅), 65.2 (-CH₂-) 14.50 (-CH₃). IR (CHCl₃, cm⁻¹): 3030, 1698, 1268, 1242, 1217, 808, 783, 681. Spectral data for **pyridin-3-ol (24)**: ¹H-NMR (400 MHz, CDCl₃): δ ppm 8.28 (d, J = 1.7 Hz, 1H, H₂), 8.09 (d, J = 4.4 Hz, 1H, H₆), 7.36-7.25 (m, 2H, H₄, H₅). ¹³C-NMR (100 MHz, d-DMSO): δ ppm 155.4 (C₃), 140.3 (C₆), 139.2 (C₂), 124.8 (C₄), 122.9 (C₅). IR (CHCl₃, cm⁻¹): 3463, 3412, 3030, 1677, 1651, 1626, 1268, 1242, 1217, 1069, 1038, 1013, 834, 783, 757, 681.

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