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# SYNTHESIS OF *CIS*-FUSED PYRANOPYRAN AND PYRANOPYRIDINE TEMPLATES BY RING REARRANGEMENT METATHESIS

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**Abstract** – A short, racemic and multigram scale synthesis of two novel templates is described. The key steps of the synthesis are ring rearrangement metathesis of strained tropane-derivatives into *cis*-fused pyranopyrans and pyranopyridines and subsequent functionalisation via cross metathesis and stereoselective dihydroxylation.

## INTRODUCTION

The need for large collections of compounds that can be screened for biological activity in the constant search for new drugs has led organic chemists to the strategy of combinatorial synthesis.[1] This strategy includes the synthesis of compound libraries which are based on small organic molecules (templates[2]). Those molecules may serve as building blocks for the synthesis of various derivatives in order to find new therapeutic agents or to improve therapeutic properties. Therefore a template needs to conform to requirements of a central building block: many functional groups should be available and the template structure should be carefully selected by pharmacological prospects.

Molecules **1** and **2** (*Figure 1*) are highly functionalised templates which are based on pharmacological interesting structures: *cis*-Fused pyrano[3,2-*b*]pyrans of type **1** occur as part of a few natural products like the marine polyethers maitotoxin (a highly active neurotoxin)[3] and halichondrin (an antitumor agent)[4] or the phytotoxin diplopyrone.[5] c*is*-Fused pyrano[3,2-*b*]pyridines of type **2** are non natural structures. Recent studies have shown biological activity in glycosidase inhibition, which is an important feature in HIV- and diabetes-therapy.[6] Hence, derivatives which are based on central building blocks **1** and **2** may be potential candidates in many fields of pharmacological application.

We would like to report an inexpensive and short synthesis of these new template structures. Many functional groups have been introduced so that various reactions may be possible for the synthesis of further derivatives.

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This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

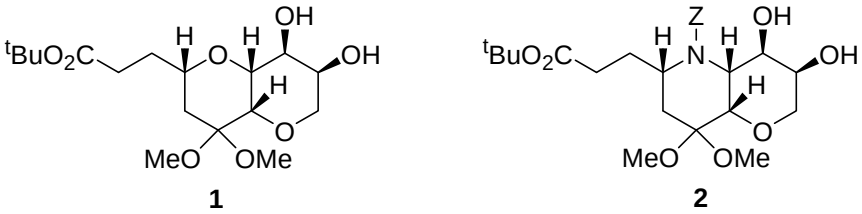
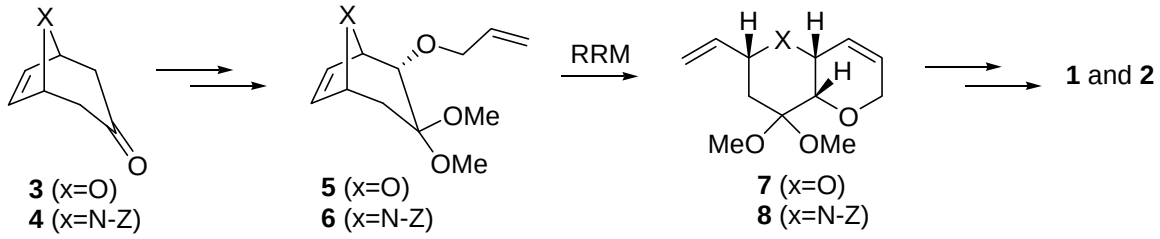



**Figure 1.** *Cis*-fused pyrano[3,2-*b*]pyran **1** and pyrano[3,2-*b*]pyridine **2** (Z=benzyloxycarbonyl).

As a key step in our synthesis we planned the construction of the pyranopyran/-pyridine skeleton of the target structures by a ring rearrangement metathesis[7] (RRM) of strained tropane-derivatives **5** and **6** (*Scheme 1*). These substituted bicycles are accessible by zinc-mediated [4+3] cycloaddition between tetrabromoacetone and furan or N-protected pyrrole respectively,[8] followed by attachment of an allylic side-chain on the resulting bicycles **3** and **4**. We envisioned that substitution of **3**/**4** could be achieved by α-hydroxylation using a method described by Moriarty[9] and subsequent etherification with allyl bromide. The hydroxylation should be directed to the less hindered endo-side of the bicycles hence the obtained stereochemistry allows the synthesis of *cis*-fused pyranopyrans/-pyridines **7** and **8** in the ring rearrangement metathesis. From **7** and **8** cross metathesis on the mono-substituted double bond followed by dihydroxylation on the disubstituted double bond would finally lead to the desired templates **1** and **2**.




**Scheme 1**. Synthetic strategie towards templates **1** and **2**.

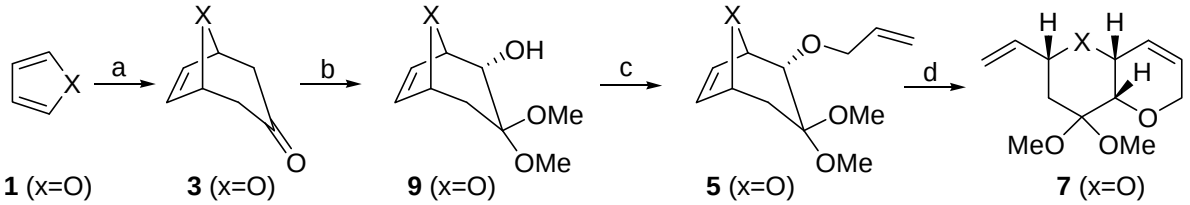
## RESULTS AND DISCUSSION

Tetrabromoacetone was synthesized from acetone, HBr and bromine in a 300 g scale following a modified procedure published by Kim and Hoffmann.[10] During the reaction the product normally precipitates from the reaction solution and is suction-filtered and washed several times with hexane in order to separate from steaming and stinking bromination by-products. We discovered that simple washing with water resulted in white crystals and therefore avoiding the use of copious amounts of hexane. Galling by-products have been dissolved in the aqueous phase and could be easily neutralised.

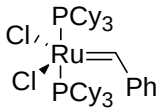
Following literature procedures,[8] compounds **3** and **4** could be prepared from tetrabromoacetone and

furan either Z-protected pyrrole in a 20-30 gram scale. After treating with KOH in MeOH, the resulting enolates were further oxidised into alcohols **9** and **10** (*Scheme 2*) with iodosobenzenediacetate. The oxidation proceeded under formation of a racemic mixture of the desired *endo*-alcohols. Furthermore the carbonyl moiety was simultaneously protected as dimethyl ketal. The *endo*-alcohols underwent smooth allylation with allyl bromide in the presence of NaH to give ethers **5** and **6** in up to 70 % yield.

When the metathesis precursors **5** and **6** were exposed to 5 mol% of catalyst **Ru-1** in $CH_2Cl_2$ at rt, the projected RRM proceeded with incomplete conversion of the starting material. Using refluxing $CH_2Cl_2$ as well as an increased amount of **Ru-1** (10 to 15 mol%) did not improve the yield. Further examination of various reaction conditions led us to the need of ethylene to drive the metathesis into completion. This was in agreement to results described by Grubbs[11] for tandem metathesis reactions. The consequence of ethylene may be the avoidance of oligomerisation products and a better turnover of the catalyst.[11] However, RRM of **5** and **6** in $CH_2Cl_2$ at rt under an atmosphere of ethylene gave the desired products **7** and **8** in over 90 % yield.




**1** (x=O) **2** (x=N-Z) **3** (x=O) **4** (x=N-Z) **9** (x=O) **10** (x=N-Z) **5** (x=O) **6** (x=N-Z) **7** (x=O) **8** (x=N-Z)




**Ru-1**

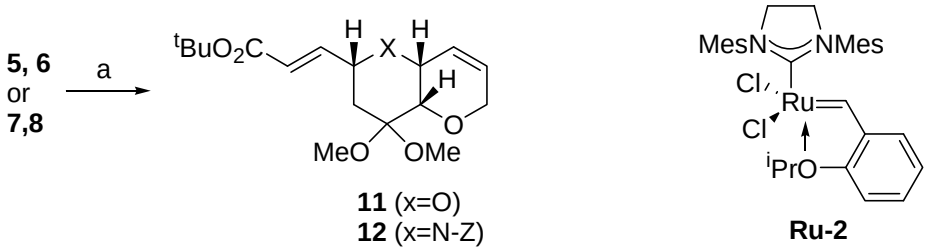
**Scheme 2**. Synthesis of pyranopyrans and pyranopyridines, *reagents and conditions*: (a) 1. tetrabromoacetone, $Et_2Zn$, toluene, 0 °C to rt, 2. Zn/Cu, MeOH, 0 °C, yield: 51 % (**3**), 36 % (**4**); (b) KOH, iodosobenzenediacetate, MeOH, rt, yield: 22 % (**9**), 34 % (**10**); (c) NaH, allylbromide, THF, reflux, yield: 69 % (**5**), 68 % (**6)**; (d) 5 mol% **Ru-1**, $CH_2Cl_2$, ethylene, rt, yield: 94 % (**7**), 92 % (**8**).

With the pyranopyrans/-pyridines **7** and **8** in hands we focused on a final functionalisation of the double bonds. For the introduction of the ester unit we envisaged a cross metathesis with acrylic acid tert-butyl ester. In order to reduce the number of synthetic steps we planned the combination of the RRM and CM into one domino metathesis step. Ruthenium catalyst **Ru-2** (*Scheme 3*) has been proofed to be an efficient catalyst for the cross metathesis with electron deficient olefins.[12] On the other hand these olefins are generally less reactive towards metathesis catalysts[12] than electron rich olefins like allylic ethers **5** and **6**. A metathesis reaction mixture containing **5** or **6** and acrylic acid tert-butyl ester would perform the RRM

as a first step and undergo the cross metathesis afterwards with the vinyl moiety of intermediate RRM products **7** and **8**.

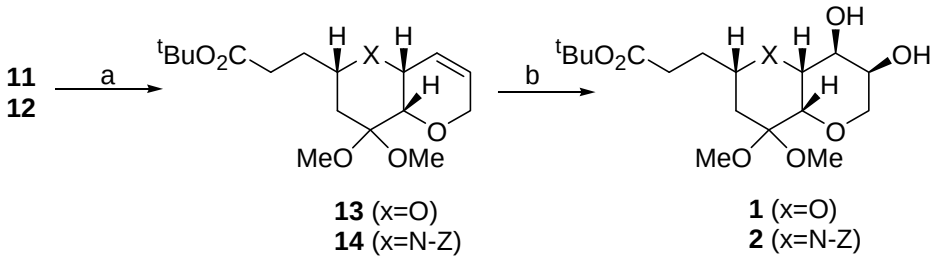
Examination of the combined RRM-CM reaction has been done by utilizing the same reaction conditions used for the ring rearrangement metathesis. Unfortunately no cross metathesis could be achieved under these conditions but when the metathesis was performed without ethylene esters **11** and **12** were obtained in 31 % yield. Efforts to increase the yield of the one-pot tandem metathesis reaction were unsuccessful.

Thus we used isolated **7** and **8** for separate CM steps, which were performed with 5 mol% **Ru-2** in refluxing $CH_2Cl_2$ and yielded **11** and **12** in 48 % and 63 % respectively. A final optimisation was achieved by additional purification of RRM products **7**/**8**: a slightly brown colour of the materials after chromatography pointed to traces of **Ru-1** as residues from the previous step and may caused catalyst inhibition in the cross metathesis. Purification was done by treatment with charcoal as described by Cho and Kim[13] and finally cross metathesis of the purified materials gave **11** and **12** in over 95 % yield.




**Scheme 3**. Functionalisation by cross metathesis, *reagents and conditions*: (a) 5 mol% **Ru-2**, $CH_2Cl_2$, acrylic acid tert-butyl ester, reflux, yield: 31 % (**11**, from **5),** 99 % (**11**, from **7)**, 31 % (**12**, from **6**), 96 % (**12**, from **8**).

Having established the cross metathesis of the terminal olefin we next determined whether the internal olefin could be functionalised by hydroboration or dihydroxylation. Our initial attempts to achieve this goal were unsuccessful: hydroboration did not occur under various conditions and we were not able to perform a dihydroxylation selectively on the internal double bond. Consequently we decided to remove the conjugate olefin by a selective reduction using Stryker's copperhydride catalyst[14] to obtain **13** and **14** (*Scheme 4*) in over 90 % yield. Fortunately the remaining olefin could be converted into diols **1** and **2** by treatment with $OsO_4/K_3[Fe(CN)_6]$. The *cis*-dihydroxy groups were found to have an *endo*-orientation as revealed by $^1$H-NMR spectroscopic analysis and NOE experiments (*Figure 2*). The compounds **1** and **2** showed strong NOE correlations between H-8a and H-$2^{ax}$, H-8a and H-4a as well as H-4a and H-6. Also the *trans*-coupling ($^3J$=10 Hz) between H-$2^{ax}$ and H-3 confirmed with the determined stereochemistry.




**Scheme 4**. Dihydroxylation, *reagents and conditions*: (a) tris(triphenylphosphine) copperhydride hexamer, PMHS, tert-butanol, toluene, rt, yield: 98 % (**13**), 91 % (**14**); (b) $OsO_4$, $K_3[Fe(CN)_6]$, $K_2CO_3$, tert-butanol /$H_2O$ 1:1, yield: 88 % (**1**), 75 % (**2**).

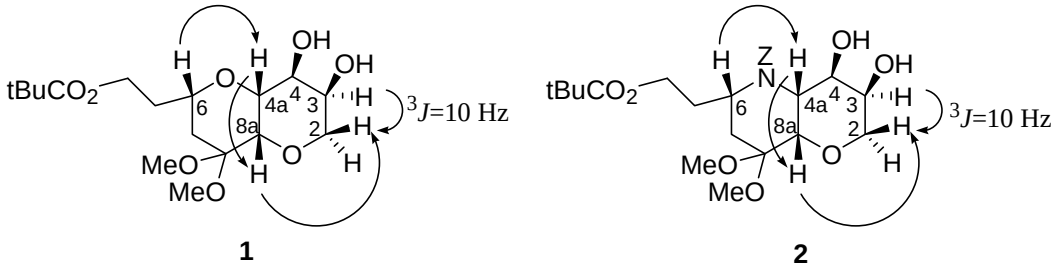
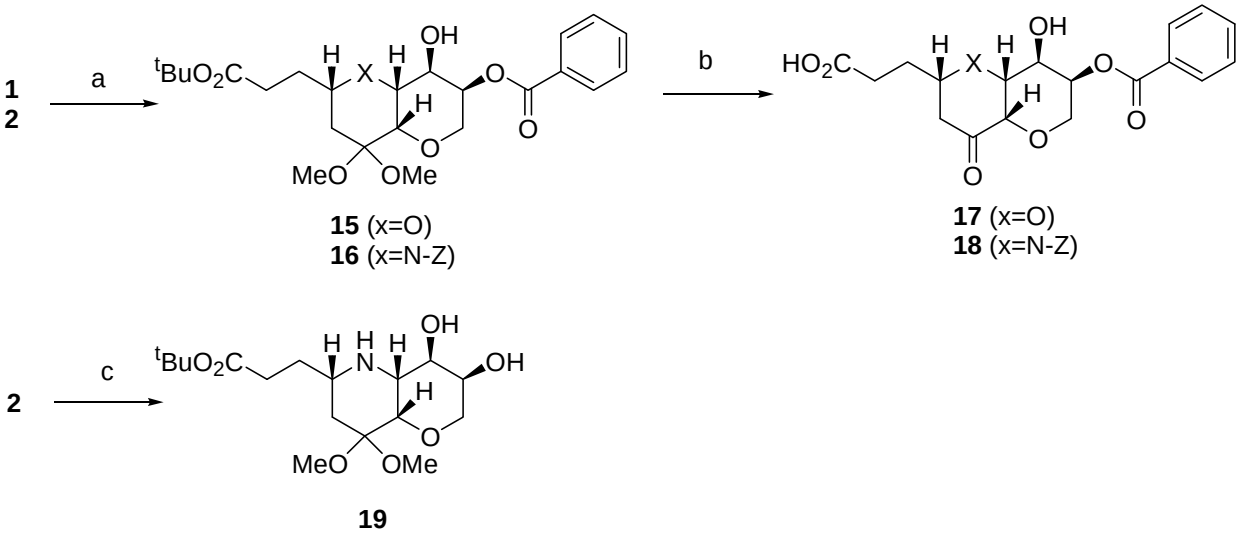



**Figure 2**. Relative stereochemistry of **1** and **2**, NOE interactions and $^3J$-couplings marked by arrows.

To further consider the applicability of the synthesized templates we examined the selective transformation of the functional groups (*Scheme 5*). Esterification with benzoyl chloride proceeded exclusively under conversion of the C-3 hydroxyl group. Therefore the opportunity of a selective conversion of both hydroxyl groups is confirmed. Considerable pathways may be protection of the C-3 alcohol, substitution at C-4 followed by deprotection and derivatisation steps at C-3.

On the other hand, treatment of the diesters **15** and **16** with TFA in $CH_2Cl_2$ yielded free acids **17** and **18** under simultaneously cleavage of the dimethyl ketal. Finally cleavage of the Z-protective group of **2** worked smoothly with hydrogen and an Pd/C catalyst. Free amine **19** was performed in 98 % yield in this step.

In summary we have performed a short, racemic and multigram scale synthesis of two novel *cis*-fused pyrano[3,2-*b*]pyran and pyrano[3,2-*b*]pyridine templates from inexpensive starting materials. The concept of ring rearrangement metathesis was used for the construction of the main skeletons. Several chemical specifiable functional groups were inserted offering access to a wide range of derivatives from these core structures. Further applications of these new templates are in progress.




**Scheme 5**. Double bond functionalisation, *reagents and conditions*: (a) benzoylchloride, DMAP $Et_3N$, $CH_2Cl_2$, yield: 89 % (**15**), 49 % (**16**); (b) TFA, $CH_2Cl_2$, yield: 96 % (**17**), 83 % (**18**); (c) Pd/C, $H_2$, MeOH, yield: 98 % (**19**).

## EXPERIMENTAL

Melting points were measured with a Leica Galen III melting point apparatus and are uncorrected. Infrared spectra (Attenuated Total Reflectance) were obtained on a Perkin-Elmer 881 spectrophotometer and are reported in wave numbers ($cm^{-1}$). $^1H$ and $^{13}C$-NMR spectra were recorded at 500 and 125 MHz on a Bruker DRX 500 in $CDCl_3$ and chemical shifts are given in ppm relative to the internal solvent peak. The samples for high resolution mass spectra (HRMS) were ionized at an ionization potential of 70 eV using a Finnigan MAT 95 SQ or Varian MAT 711. Elemental analyses were performed on an Elementar Vario EI analyser.

### 3,3-Dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-2-ol (9)

To a solution of 25.42 g (453 mmol) KOH in 450 mL of MeOH was added dropwise a solution of 18.80 g (151 mmol) **3** in 150 mL MeOH at 0 °C. After stirring for 30 min 53.50 g (166 mmol) iodosobenzenediacetate was added portion wise over a period of 20 min at ambient temperature and the mixture was stirred additional 16 h at rt and evaporated in vacuo. The black residue was dissolved in 200 mL of water, saturated with solid $NH_4Cl$ and extracted with $CH_2Cl_2$ (1*200 mL, 3* 100 mL). The extracts were dried over $Na_2SO_4$ and evaporated in vacuo. Flash chromatography in Hexane/methyl tert-butyl ether (6:4) gave 6.15 g (22 %) **9** as a yellow oil.

**RF** (hexane/EtOAc 1:1) = 0.31; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.62-1.65 (d, J = 15 Hz, 1H), 1.71-1.75 (dd, J = 15, 4 Hz, 1H), 2.72 (s, 3H), 2.87-2.89 (d, J = 10 Hz, 1H), 3.15 (s, 3H), 4.03-4.06 (dd, J = 10. 5 Hz, 1H), 4.37-4.38 (m, 1H), 4.68-4.69 (dd, J = 5, 1 Hz, 1H), 5.71-5.72 (dd, J = 6, 1 Hz, 1H), 6.00-6.01 (dd, J = 6, 1 Hz); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 32.36 ($CH_2$), 46.90 (CH), 49.80 (CH),

73.54 (CH), 77.73 (CH), 80.28 (CH), 98.13 (C), 133.28 (CH), 133.81 (CH); **IR** (ATR): ν = 2962 (m), 2925 (w), 2853 (w), 1260 (s), 1087 (s), 1062 (s), 1025 (s), 799 (s); **MS** (EI, 25 °C): m/z (%) = 186 ($M^+$, 1), 173 (4), 154 (30), 139 (3), 125 (3), 109 (4), 97 (28), 87 (100), 81 (36), 77 (4), 68 (88); **HR-MS** ($C_9H_{14}O_4$, $M^+$): calcd. 186.0892, found 186.0899; **Anal.** Calcd for $C_9H_{14}O_4$: C 58.05 %, H 7.58. Found C 57.87 %, H 7.57 %

**2-Hydroxy-3,3-dimethoxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester (10)**

Following the procedure described above gave 11.64 g **10** (34 %) as a brown oil.

**RF** (hexane/EtOAc 6:4) = 0.17; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.67-1.71 (m, 1.5H), 1.90-1.93 (m, 0.5H), 2.66 (s, 3H), 3.05 (s, 3H), 3.10-3.12 (m, 1H), 4.04-4.05 (br d, 0.5H), 4.27 (br s, 1H), 4.56 (br s, 0.5H), 4.70 (br s, 0.5H), 4.92 (br s, 0.5H), 5.00-5.10 (m, 2H), 5.56-5.60 (m, 1H), 5.85-5.90 (m, 1H), 7.03-7.08 (m, 3H), 7.15-7.18 (m, 2H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 31.07, 32.02 ($CH_2$), 47.03 (CH), 49.70 (CH), 57.09, 57.17 (CH), 61.37 (CH), 66.92, 67.04 ($CH_2$), 72.94, 73.59 (CH), 98.58 (C), 127.88-128.82 (CH), 131.18, 131.72 (CH), 132.92, 133.50 (CH), 137.40 (C), 152.99 (C, C=O); **IR** (ATR): ν = 3516 (br m), 3089 (w), 3066 (w), 3032 (w), 2965 (m), 2945 (m), 2834 (w), 1702 (s), 1420 (s), 1294 (s), 1103 (s), 1076 (s), 1036 (s); **MS** (EI, 150 °C): m/z (%) = 319 ($M^+$, <1), 201 (4), 157 (8), 124 (4), 105 (12), 91 (100), 88 (8), 65 (10); **HR-MS** ($C_{17}H_{21}NO_5$, $M^+$): calcd. 319.1419, found 319.1427; **Anal.** Calcd for $C_{17}H_{21}NO_5$: C 63.94%, H 6.63 %, N 4.39 %. Found C 63.53 %, H 6.64 %, N 4.17 %

**2-Allyloxy-3,3-dimethoxy-8-oxabicyclo[3.2.1]oct-6-ene (5)**

A solution of 2.86 g (15.36 mmol) **9** in 20 mL THF was added dropwise to a suspension of 0.68 g (16.90 mmol) NaH in 30 mL THF and stirred 30 min at rt. Then 2.66 mL (30.72 mmol) allylbromide was added and refluxed for 16 h. After cooling to rt water was added carefully and the reaction mixture was extracted with EtOAc (3*50 mL), dried over $Na_2SO_4$ and evaporated in vacuo. Purification by flash chromatography gave 2.40 g (69 %) **5** as a yellow oil.

**RF** (hexane/EtOAc 1:1) = 0.45; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.64-1.67 (dd, J = 14, 1 Hz, 1H), 1.77-1.81 (dd, J = 14, 4 Hz, 1H), 3.08 (s, 3H), 3.20 (s, 3H), 3.81-3.82 (d, J = 4 Hz, 1H), 3.85-3.89 (dd, J = 13, 5 Hz, 1H), 3.95-3.98 (dd, J = 13, 5 Hz, 1H), 4.49-4.50 (m, 1H), 4.66-4.67 (dd, J = 4, 1 Hz, 1H), 4.95-4.97 (dd, J = 10, 2 Hz, 1H), 5.15-5.18 (dd, J = 17, 2 Hz, 1H), 5.72-5.77 (ddt, J = 17, 10, 5 Hz, 1H), 5.92-5.93 (dd, J = 6, 1 Hz, 1H), 6.21-6.23 (dd, J = 6, 1 Hz, 1H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 36.19 ($CH_2$), 48.10 (CH), 49.77 (CH), 72.13 ($CH_2$), 78.09 (CH), 78.24 (CH), 84.02 (CH), 99.95 (C), 116.09 ($CH_2$), 130.87 (CH), 133.61 (CH), 135.61 (CH); **IR** (ATR): ν = 3080 (w), 2946 (s), 2832 (m), 1137 (s), 1103 (s), 1080 (s), 1047 (s); **MS** (EI, 25 °C): m/z (%) = 226 ($M^+$, 1), 197 (4), 185 (100), 155 (24), 138 (10), 127 (28), 110 (20), 103 (30), 97 (50), 88 (68), 69 (80); H**R-MS** ($C_{12}H_{18}O_4$, $M^+$): calcd. 226.1205, found 226.1210

**2-Allyloxy-3,3-dimethoxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester (6)**

Following the procedure above gave 5.48 g (68 %) **6** as a yellow oil.

**RF** (hexane/EtOAc 1:1) = 0.34; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.65-1.70 (m, 1H), 1.74-1.77 (dd, J = 14, 2 Hz, 0.5H), 2.00-2.03 (dd, J = 14, 2 Hz, 0.5H), 3.00-3.04 (br d, 3H), 3.11-3.14 (br d, 3H), 3.75 (s, 0.5H), 3.92-4.02 (m, 2.5H), 4.37 (s, 0.5H), 4.65 (br s, 1H), 4.91-4.94 (m, 1H), 4.98-5.24 (m, 3.5H), 5.70-5.81 (m, 2H), 6.05-6.12 (m, 1H), 7.02-7.19 (m, 5H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 34.58, 35.29 ($CH_2$), 48.27, 48.46 (CH), 49.50,49.78 (CH), 57.25, 57.28 (CH), 58.77, 58.92 (CH), 66.91, 66.94 ($CH_2$), 71.59, 71.73 ($CH_2$), 82.97, 83.56 (CH), 100.20, 100.29 (C), 116.34, 116.51 ($CH_2$), 127.88-128.69 (CH), 130.59, 131.32 (CH), 133.10, 133.78 (CH), 135.31, 135.37 (CH), 137.44 (C), 152.59, 152.80 (C); **IR** (ATR): ν = 3067 (w), 3032 (w), 2959 (m), 2942 (m), 2901 (w), 2832 (w), 1705 (s), 1421 (m), 1296 (m), 1132 (m), 1104 (s), 1092 (s), 1047 (m), 995 (m); **MS** (EI, 160 °C): m/z (%) = 359 ($M^+$, <1), 271 (8), 158 (8), 145 (4), 103 (4), 91 (100), 89 (4), 65 (4); **HR-MS** ($C_{20}H_{25}NO_5$, $M^+$): calcd. 359.1732, found 359.1730; **Anal.** Calcd for $C_{20}H_{25}NO_5$: C 66.84 %, H 7.01 %, N 3.90 %. Found C 66.73 %, H 7.03 %, N 3.81 %.

**4,4-Dimethoxy-2-vinyl-2,3,4,4a,6,8a-hexahydropyrano[3,2-*b*]pyran (7)**

1.86 g (8.22 mmol) **5** was dissolved in 500 mL $CH_2Cl_2$, cooled to 0 °C and saturated with ethylene. 338 mg (0.41 mmol) **Ru-1** was added to the solution and stirred for 5 h under an atmosphere of ethylene (balloon). Afterwards the mixture was evaporated in vacuo and the residue was purified by flash chromatography in hexane/methyl tert-butyl ether 6:4. The resulting light yellow oil was dissolved in $CH_2Cl_2$, treated with 4 g of active carbon and stirred 24 h at rt. Filtration over celite and evaporation in vacuo gave 1.75 g (94 %) **7** as colorles oil.

**RF** (hexane/EtOAc 1:1) = 0.45; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.88-1.91 (d, J = 14 Hz, 1H), 2.06-2.11 (dd, J = 14, 12 Hz, 1H), 2.96 (s, 3H), 3.14 (s, 3H), 3.34 (s, 1H), 3.71-3.75 (dd, J = 17, 2 Hz, 1H), 3.95-3.96 (d, J = 6 Hz, 1H), 3.99-4.05 (m, 2H), 4.94-4.97 (dd, J = 10, 1 Hz, 1H), 5.28-5.31 (dd, J = 17, 1 Hz, 1H), 5.43-5.46 (m, 1H), 5.84-5.92 (m, 2H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 34.47 ($CH_2$), 46.77 (CH), 47.35 (CH), 66.10 ($CH_2$), 67.81 (CH), 72.64 (CH), 74.32 (CH), 99.16 (C), 114.81 ($CH_2$), 124.96 (CH), 131.00 (CH), 139.07 (CH); **IR** (ATR): ν = 3078 (w), 3040 (w), 2962 (m), 2942 (m), 2873 (m), 2830 (m), 2708 (w), 1098 (s), 1076 (s); **MS** (EI, 25 °C): m/z (%) = 211 ($M^+$, 2), 195 (6), 145 (24, 139 (16), 127 (6), 117 (10), 103 (30), 97 (8), 88 (70), 82 (100), 75 (20); **HR-MS** ($C_{11}H_{15}O_4$, $M^+$-$CH_3$): calcd. 211.0970, found 211.0971

**8,8-Dimethoxy-6-vinyl-2,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyridine-5-carboxylic acid benzyl ester (8)**

Following the procedure above gave 2.98 g (92 %) **8** as a yellow oil.

**RF** (hexane/EtOAc 1:1) = 0.34; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.86-1.90 (dd, J = 14, 5 Hz, 1H), 2.31-2.36 (dd, J = 14, 12 Hz, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.91-3.93 (d, J = 6 Hz, 1H), 4.07-4.10 (d, J =

16 Hz, 1H), 4.25-4.28 (d, J = 16 Hz, 1H), 4.48 (br s, 1H), 4.80-4.85 (m , 1H), 4.92-4.94 (d, J = 10 Hz, 1H), 5.02-5.06 (d, J = 17 Hz, 1H), 5.12-5.19 (m, 2H), 5.88-5.90 (m, 1H), 5.93-5.98 (m, 1H), 6.00-6.03 (m, 1H), 7.25-7.33 (m, 5H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 30.38 ($CH_2$), 47.55 (CH), 48.22 (CH), 48.62 (CH), 51.60 (CH), 64.16 ($CH_2$), 67.20 ($CH_2$), 70.50 (CH), 99.72 (C), 114.44 ( $CH_2$), 125.96 (CH), 127.65, 127.74, 127.90, 128.49 (CH), 136.95 (C), 140.00 (CH), 155.68 (C); **IR** (ATR): ν = 3248 (w), 3067 (w), 3033 (w), 2961 (m), 2898 (w), 2830 (w), 1692 (s), 1407 (m), 1294 (m), 1097 (s), 1057 (s), 1028 (s); **MS** (EI, 120 °C): m/z (%) = 359 ($M^+$, 2), 271 (8), 236 (8), 224 (8), 180 (12), 146 (4), 136 (10), 127 (12), 91 (100), 88 (16), 65 (4); **HR-MS** ($C_{20}H_{25}NO_5$, $M^+$): calcd. 359.1732, found 359.1740; **Anal.** Calcd for $C_{20}H_{25}NO_5$: C 66.84 %, H 7.01 %, N 3.90 %. Found C 66.15 %, H 6.96 %, N 3.50 %

**3-(4,4-Dimethoxy-2,3,4,4a,6,8a-hexahydropyrano[3,2-*b*]pyran-2-yl)acrylic acid tert-butyl ester (11)**

1.75g (7.73 mmol) **7** was dissolved in 80 mL $CH_2Cl_2$, 4.53 mL (30.93 mmol) acrylic acid tert-butyl ester and 242 mg (0.39 mmol) **Ru-2** were added and the solution was refluxed for 2 days. Evaporation in vacuo and flash chromatography in hexane/methyl tert-butyl ether 7:3 gave a light brown oil, which was dissolved again in $CH_2Cl_2$, treated with 4 g of active carbon and stirred at rt overnight. Filtration over celite and evaporation in vacuo resulted in 2.50 g (99 %) **11** as colourless oil.

RF (hexane/EtOAc 1:1) = 0.48; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.36 (s, 9H), 1.71-1.74 (d, J = 14 Hz, 1H), 1.87-1.92 (dd, J = 14, 12 Hz, 1H), 2.86 (s, 3H), 3.08 (s, 3H), 3.27 (s, 1H), 3.69-3.72 (dd, J = 17, 2 Hz, 1H), 3.82-3.84 (d, J = 6 Hz, 1H), 3.97-4.01 (m, 2H), 5.45-5.47 (dd, J = 10, 2 Hz, 1H), 5.82-5.85 (m, 1H), 6.31-6.35 (dd, J = 16, 2 Hz, 1H), 6.97-7.01 (dd J = 16, 4 Hz, 1H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 28.14 (3x CH), 33.73 ($CH_2$), 46.79 (CH), 47.40 (CH), 66.05 ($CH_2$), 67.76 (CH), 72.22 (CH), 72.59 (CH), 79.69 (C), 98.94 (C), 122.89 (CH), 124.55 (CH), 131.23 (CH), 146.13 (CH), 165.61 (C); **IR** (ATR): ν = 3041 (w), 2975 (m), 2941 (m), 2877 (m), 2830 (m), 2711 (w), 1713 (s), 1660 (m), 1368 (m), 1156 (s), 1137 (s), 1098 (s), 1074 (s); **MS** (EI, 140 °C): m/z (%) = 326 ($M^+$, <1), 295 (4), 269 (4), 253 (4), 237 (8), 221 (8), 182 (30), 171 (30), 139 (24), 117 (20), 103 (36), 88 (40), 82 (100); **HR-MS** ($C_{17}H_{26}O_6$, $M^+$): calcd. 326.1729, found 326.1725; **Anal.** Calcd for $C_{17}H_{26}O_6$:C 62.56 %, H 8.03. Found C 62.09 %, H 8.13 %.

**6-(2-tert-Butoxycarbonylvinyl)-8,8-dimethoxy-2,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyridine-5-carboxylic acid benzyl ester (12)**

Following the procedure above gave 3.60 g (96 %) **12** as colourless oil.

**RF** (hexane/EtOAc 1:1) = 0.48; **$^1$H-NMR** (500 MHz, $C_6D_6$): δ (ppm) = 1.38 (s, 9H), 1.93-1.97 (dd, J = 14, 6 Hz, 1H), 2.06-2.11 (dd, J = 14, 11 Hz, 1H), 2.88 (s, 3H), 2.98 (s, 3H), 3.56-3.59 (dd, J = 16, 2 Hz, 1H), 3.67-3.68 (d, J = 6 Hz, 1H), 3.90-3.93 (dd, J = 16, 2 Hz, 1H), 4.60 (br s, 1H), 5.05-5.08 (m, 3H, H-8), 5.38-5.41 (m, 1H), 6.00-6.07 (m, 2H, H-5), 6.99-7.17 (m, 5H), 7.25-7.30 (dd, J = 16, 7 Hz, 1H); **$^{13}$C-NMR** (125 MHz, $C_6D_6$): δ (ppm) = 28.18 (CH), 30.29 ($CH_2$), 47.97, 48.07, 48.14 (CH), 50.39 (CH), 63.92 ($CH_2$), 67.48 ($CH_2$), 70.61 (CH), 79.67 (C), 99.88 (C), 122.63 (CH), 126.00 (CH), 127.87-128.68

(CH), 137.48 (C), 148.80 (CH), 155.73 (C), 165.80 (C); **IR** (ATR): ν = 3090 (w), 3064 (w), 3035 (w), 2975 (m), 2940 (m), 2902 (m), 2832 (m), 2715 (w), 1699 (s), 1410 (s), 1292 (s), 1152 (s), 1057 (s), 1029 (m); **MS** (EI, 140 °C): m/z (%) = 459 ($M^+$, 4), 402 (4), 358 (4), 324 (10), 315 (20), 280 (8), 268 (10), 256 (8), 236 (10), 224 (16), 180 (16), 91 (100), 81 (16); **HR-MS** ($C_{25}H_{33}NO_7$, $M^+$): calcd. 459.2257, found 459.2260; **Anal.** Calcd for $C_{25}H_{33}NO_7$: C 65.34 %, H 7.24 %, N 3.05 %. Found C 65.62 %, H 7.40 %, N 2.73 %

**3-(4,4-Dimethoxy-2,3,4,4a,6,8a-hexahydropyrano[3,2-*b*]pyran-2-yl)propionic acid tert-butylester (13)**

To a solution of 2.42 g (7.41 mmol) **11** in 74 mL toluene was added 0.78 mL (8.15 mmol) tert-butanol, 1.94 mL (29.64 mmol) polymethylhydrosiloxane and 121 mg (0.06 mmol) tris(triphenylphosphin) copperhydrid-hexamer and stirred for 2 days at rt. The solution was evaporated in vacuo and purified by flash chromatography in hexane/methyl tert-butyl ether 7:3 to give 2.21 g (98 %) **13** as a white solid.

**RF** (hexane/EtOAc 6:4) = 0.31; **MP** 73 °C; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.43 (s, 9H), 1.60-1.65 (d, J = 11 Hz, 1H), 1.74-1.88 (m, 3H), 2.30-2.35 (m, 1H), 2.39-2.44 (m, 1H), 3.21 (s, 3H), 3.27 (s, 3H), 3.41 (s, 1H), 3.45-3.48 (m, 1H), 3.83 (s, 1H), 4.18-4.21 (d, J = 17 Hz, 1H), 4.40-4.43 (d, J = 17 Hz, 1H), 6.00 (br s, 2H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.15 ($CH_3$), 30.86 ($CH_2$), 31.77 ($CH_2$), 34.03 ( $CH_2$), 47.29 ($CH_3$), 47.57 ($CH_3$), 66.52 ($CH_2$), 67.51 (CH), 72.36 (CH), 72.45 (CH), 80.12 (C), 98.75 (C), 124.26 (CH), 131.40 (CH), 172.83 (C); **IR** (ATR): ν = 3040 (w), 2974 (m), 2939 (m), 2872 (w), 2829 (w), 2711 (w), 1728 (s), 1367 (m), 1154 (m), 1098 (s), 1075 (m); **MS** (EI, 140 °C): m/z (%) = 328 ($M^+$, <1), 278 (6), 255 (8), 241 (12), 223 (12), 173 (68), 159 (12), 139 (10), 117 (76), 103 (16), 88 (40), 82 (100); **HR-MS** ($C_{17}H_{28}O_6$, $M^+$): calcd. 328.1885, found 328.1887; **Anal.** Calcd for $C_{17}H_{28}O_6$: C 62.18 %, H 8.59. Found C 61.87 %, H 8.33 %

**6-(2-tert-Butoxycarbonylethyl)-8,8-dimethoxy-2,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyridine-5-carboxylic acid benzyl ester (14)**

Following the procedure above gave 3.45 g (91 %) **14** as colourless oil.

**RF** (hexane/EtOAc 1:1) = 0.40; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.40 (s, 9H), 1.68-1.71 (dd, J = 14, 4 Hz, 1H), 1.74-1.78 (m, 1H), 2.07-2.17 ( m, 3H), 2.30-2.35 (dd, J = 14, 12 Hz, 1H), 3.15 (s, 3H), 3.25 (s, 3H), 3.91-3.93 (d, J = 6 Hz, 1H), 4.08-4.11 (br d, J = 16 Hz, 1H), 4.28-4.33 (dd, J = 16, 3 Hz, 1H), 4.41-4.44 (m, 1H), 4.49 (br s, 1H), 5.12-5.21 (m, 2H), 5.92-5.95 (br d, J = 10 Hz, 1H), 5.98-6.00 (br d, J = 10 Hz, 1H), 7.30-7.37 (m, 5H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.14 ($CH_3$), 29.90 ($CH_2$), 31.75 ($CH_2$), 32.37 ($CH_2$), 47.41 (CH), 47.98 (CH), 48.25 ($CH_3$), 48.44 ($CH_3$), 64.30 ($CH_2$), 67.20 ($CH_2$), 70.36 (CH), 80.01 (C), 99.98 (C), 125.77 (CH), 127.69 (CH), 127.75 (CH), 127.92 (CH), 128.50 (CH), 137.02 (C), 156.09 (C), 172.70 (C); **IR** (ATR): ν = 3088 (w), 3068 (w), 3034 (w), 2976 (m), 2940 (m), 2894 (w), 2830 (w), 1727 (s), 1695 (s), 1415 (m), 1151 (m), 1119 (m), 1099 (m), 1069 (m), 1054 (m);

**MS** (EI, 140 °C): m/z (%) = 461 ($M^+$, <1), 429 (4), 380 (4), 332 (12), 288 (12), 256 (6), 236 (12), 192 (10), 173 (12), 156 (4), 103 (6), 91 (100), 69 (12); **HR-MS** ($C_{25}H_{35}NO_7$, $M^+$): calcd. 461.2413, found 461.2419; **Anal.** Calcd for $C_{25}H_{35}NO_7$: C 65.06%, H 7.64 %, N 3.03 %. Found C 64.76 %, H 7.52 %, N 2.78 %.

**3-(7,8-Dihydroxy-4,4-dimethoxyoctahydropyrano[3,2-*b*]pyran-2-yl)propionic acid tert-butyl ester (1)**

2.14 g (6.52 mmol) **13** was dissolved in 66 mL tert-butanol/$H_2$0 1:1, treated with 2.70 mg (19.56 mmol) $K_2CO_3$, 6.44 g (19.56 mmol) $K_3[Fe(CN)_6]$ and 165 mg (0.65 mmol) $OsO_4$ and stirred 2 days at rt. Water and solid $Na_2SO_3$ was added and the brown suspension was extracted with EtOAc (5*50 mL), dried over $Na_2SO_4$ and evaporated in vacuo. Purification by flash chromatography in methyl tert-butyl ether gave 2.08 g (88 %) **1** as a white solid.

**RF** (methyl tert-butyl ether) = 0.30; **MP** 116.1 °C; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 9H), 1.56 (d, J = 12 Hz, 1H), 1.71-1.77 (m, 3H), 2.24-2.38 (m, 2H), 2.62 (br s, 1H), 2.79 (br s, 1H), 3.16 (s, 3H), 3.22 (s, 3H), 3.38-3.42 (ddd, J = 12, 6, 6 Hz, 1H), 3.49 (d, J = 10 Hz, 1H), 3.60 (s, 1H), 3.70 (s, 1H), 3.79-3.81(dd, J = 10, 5 Hz, 1H), 4.00 (br s, 2H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.15 ($CH_3$), 30.67 ($CH_2$), 31.62 ($CH_2$), 33.71 ($CH_2$), 47.40 ($CH_3$), 47.52 ($CH_3$), 64.57 (CH), 65.65 ($CH_2$), 68.71 (CH), 68.83 (CH, C-1), 72.74 (CH), 74.91 (CH), 80.45 (C), 98.70 (C), 173.18 (C); **IR** (ATR): ν = 3438 (br m), 2971(m), 2938 (m), 2907 (m), 2832 (w), 1728 (s), 1368 (m), 1257 (m), 1155 (s), 1103 (s), 1093 (s), 1049 (m); **MS** (EI, 150 °C): m/z (%) = 362 ($M^+$, <1), 289 (6), 275 (10), 257 (8), 239 (10), 233 (20), 189 (10), 172 (16), 117 (100), 88 (60), 85 (12), 73 (12); **HR-MS** ($C_{17}H_{30}O_8$, $M^+$): calcd. 362.1940, found 362.1946; **Anal.** Calcd for $C_{17}H_{30}O_8$: C 56.34 %, H 8.34 %. Found C 56.38 %, H 8.24 %

**6-(2-tert-Butoxycarbonylethyl)-3,4-dihydroxy-8,8-dimethoxyoctahydropyrano[3,2-*b*]pyridine-5-carboxylic acid benzyl ester (2)**

Following the procedure above and flash chromatography in hexane/methyl tert-butyl ether 1:1 gave 2.46 g (75 %) **2** as a white solid.

**RF** (methyl tert-butyl ether) = 0.27, **MP** 45.7 °C; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.41 (s, 9H), 1.75-1.83 (m, 2H), 2.04-2.11 (m, 2H), 2.24-2.27 (m, 2H), 3.22 (s, 6H), 3.66-3.70 (dd, J = 12, 5 Hz, 1H), 4.02-4.05 (m, 2H), 4.08-4.10 (dd, J = 7, 3 Hz, 1H), 4.14-4.18 (dd, J = 12, 5 Hz, 1H), 4.25-4.30 (ddd, J = 15, 8, 7 Hz, 1H), 4.47 (d, J = 7 Hz, 1H), 5.11-5.19 (m, 2H), 7.25-7.36 (m, 5H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.14 ($CH_3$), 30.78 ($CH_2$), 32.43 ($CH_2$), 32.69 ($CH_2$), 48.14 (CH), 49.25 ($CH_3$), 49.71 ($CH_3$), 55.26 (CH), 67.11 (CH), 67.81 ($CH_2$), 68.06 ($CH_2$), 70.41 (CH), 71.02 (CH), 80.59 (C), 99.37(C), 127.77 (CH), 128.15 (CH), 128.61 (CH), 136.42 (C), 157.80 (C), 172.77(C); **IR** (ATR): ν = 3438 (br m), 3091 (w), 3065 (w), 3033 (w), 2974 (m), 2940 (m), 2833 (m), 1727 (s), 1695 (s), 1299 (s), 1152 (s), 1118 (s), 1070 (s), 1054 (s); **MS** (EI, 180 °C): m/z (%) = 495 ($M^+$, <1), 480 (1), 408 (2), 380 (6), 372 (10), 366

(16), 322 (12), 304 (8), 272 (30), 236 (6), 216 (6), 173 (12), 91 (100), 73 (4); **HR-MS** ($C_{25}H_{37}NO_9$, $M^+$): calcd. 495.2468, found 495.2477; **Anal.** Calcd for $C_{25}H_{37}NO_9$: C 60.59 %, H 7.53 %, N 2.83 %. Found C 60.41 %, H 7.55 %, N 3.05 %

**Benzoic acid-6-(2-tert-butyloxycarbonylethyl)-4-hydroxy-8,8-dimethoxyoctahydropyrano[3,2-*b*]-pyran-3-yl ester (15)**

0.016 mL (0.14 mmol) benzoylchloride, 0.029 mL (0.21 mmol) triethylamin and 17 mg (0.07 mmol) DMAP were added sequentially to a solution of 50 mg (0.14 mmol) **1** in 1.4 mL $CH_2Cl_2$ and stirred for 1.5 h at rt. The reaction mixture was evaporated in vacuo an purified by chromatography in hexane/methyl tert-butyl ether = 7:3 to give 58 mg (89%) **15** as a colourless oil.

**RF** (hexane/EtOAc 1:1) = 0.43; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.45 (s, 9H), 1.63-1.68 (dd, J = 14, 12 Hz, 1H), 1.76-1.82 (m, 3H), 2.00 (s, 1H), 2.29-2.35 (m, 1H), 2.38-2.44 (m, 1H), 3.20 (s, 3H), 3.27 (s, 3H), 3.45-3.50 (m, 1H), 3.74 (s, 1H), 3.79-3.83 (m, 2H), 4.00-4.03 (dd, J = 10, 5 Hz, 1H), 4.29-4.30 (d, J = 2 Hz, 1H), 5.37-5.41 (ddd, J = 11, 5, 3 Hz, 1H), 7.43-7.47 (m, 2H), 7.57-7.60 (m, 1H), 8.00-8.02 (m, 2H); **$^{13}$C- NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.16 (3x CH), 30.67 ($CH_2$), 31.54 ($CH_2$), 33.83 ($CH_2$), 47.40 (CH), 47.54 (CH), 62.57 ($CH_2$), 67.36 (CH), 68.64 (CH), 68.97 (CH), 72.88 (CH), 74.92 (CH), 80.23 (C), 98.63 (C), 128.52 (2x CH), 129.73 (2x CH), 133.38 (2x CH), 165.32 (C), 172.96 (C); **IR** (ATR): ν = 3485 (br m), 3064 (w), 2974 (m), 2939 (m), 2907 (m), 2875 (m), 2831 (m), 1723 (s), 1602 (w), 1452 (m), 1367 (m), 1320 (m), 1269 (m), 1099 (s), 1000 (m); **MS** (EI, 160 °C): m/z (%) = 409 (M-$C_4H_9$), 393 (24), 379 (20), 344 (60), 239 (40), 221 (16), 207 (12), 189 (20), 183 (30), 173 (44), 137 (189, 117 (100), 88 (100), 69 (38); **HR-MS** ($C_{20}H_{25}O_9$,M-$C_4H_9$): calcd. 409.1498, found 409.1503

**3-Benzoyloxy-6-(2-tert-butoxycarbonylethyl)-4-hydroxy-8,8-dimethoxyoctahydropyrano[3,2-*b*]-pyridine-5-carboxylic acid benzyl ester (16)**

Following the procedure above gave 41 mg (49 %) **16** as colourless oil.

**RF** (hexane/EtOAc 1:1) = 0.29; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 9H), 1.84-2.00 (m, 3H), 2.16-2.20 (m, 1H), 2.31-2.40 (m, 2H), 3.04 (br s, 1H), 3.24 (s, 3H), 3.34 (s, 3H), 3.87-3.90 (dd, J = 13, 4 Hz, 1H), 4.06-4.08 (d, J = 7 Hz, 1H), 4.36-4.41 (m, 2H), 4.45-4.48 (dd, J = 13, 4 Hz, 1H), 4.86-4.89 (dd, J = 10, 7 Hz, 1H), 5.13-5.23 (m, 2H), 5.40-5.42 (m, 1H), 7.25-7.35 (m, 5H), 7.37-7.42 (m, 2H), 7.54-7.57 (m, 1H), 8.01-8.03 (m, 2H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.16 (3x CH), 31.52, 31.63 ($CH_2$), 32.68 ($CH_2$), 48.19 (CH), 49.88, 50.01 (CH), 54.17 (CH), 67.19 ($CH_2$), 67.90 ($CH_2$), 68.83 (CH), 71.84 (CH), 73.46 (CH), 80.53 (C), 99.81 (C), 127.80 (2x CH), 128.19 (2x CH), 128.56 (2x CH), 128.65 (2x CH), 129.79 (2x CH), 129.87 (CH), 133.27 (CH), 136.33 (C), 157.61 (C), 166.11 (C); **IR** (ATR): ν = 3477 (br w), 3090 (w), 3065 (w), 3033 (w), 2972 (m), 2939 (m), 2834 (w), 1721 (s), 1696 (s), 1392 (m), 1269 (s), 1151 (s), 1106 (s), 1070 (m), 1051 (m), 1027 (m); **MS** (EI, 150 °C): m/z (%) = 574 (40), 530 (40), 512 (44), 494 (M-$C_7H_5O$, 30), 470 (90), 464 (60), 426 (100), 408 (50), 376 (100), 316 (30), 272

(249, 236 (20), 173 (40), 105 (40), 91 (100); **HR-MS** ($C_{25}H_{36}NO_9$,M-$C_7H_5O$): calcd. 494.2390, found 494.2399

**Benzoic acid 6-(2-carboxyethyl)-4-hydroxy-8-oxooctahydropyrano[3,2-*b*]pyran-3-yl ester (17)**

10 mg (0.02 mmol) **15** was dissolved in 0.2 mL of a 1:1 mixture of $CH_2Cl_2$ and TFA and stirred 1 h at rt. Evaporation of the solvents in vacuo resulted in 7 mg (96%) **17** as colourless oil.

**RF** (methyl tert-butyl ether) = 0.26; **$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.97-2.10 (m, 2H), 2.29-2.33 (dd, J = 13, 1 Hz, 1H), 2.51-2.64 (m, 2H), 2.88-2.94 (dd, J = 13, 12 Hz, 1H), 3.64-3.74 (m, 1H), 3.79-3.80 (d, J = 4 Hz, 1H), 3.84-3.90 (t, J = 11 Hz, 1H), 3.97-4.01 (dd, J = 11, 5 Hz, 1H), 4.03 (br s, 1H), 4.38-4.39 (m, 1H), 5.45-5.50 (m, 1H), 7.42-7.48 (m, 2H), 7.58-7.62 (m, 1H), 8.00-8.04 (m, 2H); **$^{13}$C-NMR** (125 MHz, DMSO): δ (ppm) = 29.54 ($CH_2$), 30.73 ($CH_2$), 44.66 ($CH_2$), 46.87, 62.03, 64.82, 68.11 (CH), 76.17, 76.26, 78.24 (CH), 128.73 (2x CH), 129.60 (2x CH), 133.60 (CH), 165.17 (C), 174.13 (C), 203.79 (C); **IR** (ATR): ν = 3066(w), 3035 (w), 2971 (m), 2929 (m), 2880 (m), 1719 (s), 1602 (w), 1452 (m), 1319 (m), 1271 (s), 1098 (s), 1028 (m), 1001 (w); **MS** (EI, 200 °C): m/z (%) = 347 (M-OH, <1), 224 (6), 207 (3), 183 (69, 171 (49, 117 (6), 105 (100), 77 (30); **HR-MS** ($C_{18}H_{19}O_7$, M-OH): calcd. 347.1130, found 347.1156

**3-Benzoyloxy-6-(2-carboxyethyl)-4-hydroxy-8-oxooctahydropyrano[3,2-*b*]pyridine-5-carboxylic acid benzyl ester (18)**

Following the procedure above gave 7 mg (83 %) **18** as colourless oil.

**RF** (methyl tert-butyl ether) = 0.34; **$^1$H-NMR** (500 MHz, 60 °C, $CDCl_3$): δ (ppm) = 1.91-1.97 (m, 1H), 2.03-2.07 (m, 1H), 2.39-2.42 (dd, J = 14, 1 Hz, 1H), 2.48-2.59 (m, 2H), 2.84-2.88 (dd, J = 14, 9 Hz, 1H), 3.89-3.93 (dd, J = 12, 3 Hz, 1H), 4.05-4.08 (dd, J = 14, 2 Hz, 1H), 4.25-4.29 (d, J = 14 Hz, 1H), 4.65-4.66 (d, J = 8 Hz, 1H), 4.89-4.94 (m, 1H), 5.15-5.28 (m, 2H), 5.33 (s, 1H), 5.42-5.45 (m, 1H), 7.25-7.28 (m, 3H), 7.31-7.33 (m, 2H), 7.38-7.40 (m, 2H), 7.56-7.59 (m, 1H), 8.03-8.07 (m, 2H); **IR** (ATR): ν = 3063 (w), 3035 (w), 2964 (m), 2927 (m), 2854 (w), 1721 (s), 1703 (s), 1601 (w), 1452 (m), 1420 (m), 1272 (s), 1113 /m), 1070 (m), 1025 (m), 982 (w); **MS** (EI, 200 °C): m/z (%) = 497 ($M^+$, <1), 392 (10), 301 (10), 181 (16), 167 (4), 105 (10), 91 (100), 69 (10); **HR-MS** ($C_{26}H_{27}NO_9$, $M^+$): calcd. 497.1685, found 497.1693

**3-(3,4-Dihydroxy-8,8-dimethoxyoctahydropyrano[3,2-*b*]pyridin-6-yl)propionic acid tert-butyl ester (19)**

26 mg (0.05 mmol) **2** was dissolved in 1 mL MeOD, treated with 3 mg Pd/C and was stirred under hydrogen atmosphere for 1 h. The catalyst was separated by filtration over celite and the solution was evaporated in vacuo to obtain 18 mg (98%) **19** as colourless oil.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ (ppm) = 1.25-1.31 (dd, J = 14, 12 Hz, 1H), 1.43 (s, 9H), 1.58-1.72 (m, 2H), 1.84-1.87 (d, J = 14 Hz, 1H), 2.27-2.36 (m, 2H), 2.56-2.63 (m, 1H), 3.06 (br s, 1H), 3.15 (s, 3H),

3.23 (s, 3H), 3.47-3.51 (t, J = 11 Hz, 1H), 3.67 (s, 1H), 3.83-3.91 (m, 2H), 3.97 (br s, 1H); **$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 28.06 (CH), 31.04 ($CH_2$), 32.12 ($CH_2$), 34.57 ($CH_2$), 47.22 (CH), 47.40 (CH), 52.11 (CH), 57.48 (CH), 64.17 (CH), 66.60 ($CH_2$), 69.07 (CH), 69.33 (CH), 80.47 (C), 99.17 (C), 172.99 (C); **IR** (ATR): ν = 3407 (br m), 2974 (m), 2935 (m), 2871 (m), 2831 (w), 1726 (s), 1458 (m), 1367 (m), 1154 (s), 1101 (s), 1087 (s), 1049 (s), 994 (m), 946 (m); **MS** (EI, 160 °C): m/z (%) = 361 ($M^+$, 4), 304 (12), 274 (40), 258 (30), 239 (54), 232 (100), 200 (36), 190 (20), 182 (30), 173 (16), 156 (20), 144 (12), 102 (50), 91 (24), 81 (30), 69 (58); **HR-MS** ($C_{17}H_{31}NO_7$, $M^+$): calcd. 361.2100, found 361.2124.

## REFERENCES


1. S. D. Lindell and J. Scherkenbeck, *Combinatorial Chemistry and High Throughput Screening*, 2005, **8**, 555; K. C. Nicolaou, R. Hanko, and W. Hartwig, *Handbook of Combinatorial Chemistry*. Wiley-VCH Verlag GmbH: 2005; R. E. Dolle and K. H. Nelson, *J. Comb. Chem.*, 1999, **1**, 235; E. M. Gordon, M. A. Gallop, and D. V. Patel, *Acc. Chem. Res.*, 1996, **29**, 144; D. L. Boger, C. M. Tarby, P. L. Myers, and L. H. Caporale, *J. Am. Chem. Soc.*, 1996, **118**, 2109.
2. A. F. Katritzky, J. S. Kiely, N. Herbert, and C. Chassaing, *J. Comb. Chem.*, 2000, **2**, 2; F. Balkenhohl, C. Bussche-Hünnefeld, A. Lansky, and C. Zechel, *Angew. Chem. Int. Ed.*, 1996, **35**, 2288; F. Diederich and P. J. Stang, *Templated Organic Synthesis*. Wiley-VCH: Weinheim, 2000; p. 410.
3. A. Yokoyama, M. Murata, Y. Oshima, T. Iwashita, and T. Yasumoto, *J. Biochem.*, 1988, **104**, 184; M. Murata and T. Yasumoto, *Nat. Prod. Rep.*, 2000, **17**, 293.
4. D. Uemura, K. Takahashi, and T. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 4796; Y. Hirata and D. Uemura, *Pure Appl. Chem.*, 1986, **58**, 701.
5. A. Evidente, L. Maddau, E. Spanu, A. Franceschini, S. Lazzaroni, and A. Motta, *J. Nat. Prod.*, 2003, **66**, 313.
6. B. G. Reddy and Y. D. Vankar, *Angew. Chem. Int. Ed.*, 2005, **44**, 2001.
7. For a recent review see: N. Holub and S. Blechert, Ring Rearrangement Metathesis in Alkaloid Synthesis. In *Asymmetric Synthesis - The Essentials*, Wiley-VCH: Weinheim, 2007; pp. 230-235; for selected examples see: C. Stapper and S. Blechert, *J. Org. Chem.*, 2002, **67**, 6456; A. Rückert, P. Deshmukh, and S. Blechert, *Tetrahedron Lett.*, 2006, **47**, 7977; Z. Liu and J. D. Rainier, *Org. Lett.*, 2006, **6**, 459; A. H. Hoveyda, R. R. Schrock, G. S. Weatherhead, J. G. Ford, and E. J. Alexanian, *J. Am. Chem. Soc.*, **2000**, **122**, 1828; J. Haltsclaw and M. Koreeda, *Org. Lett.*, 2004, **6**, 3719; T. L. Choi and R. H. Grubbs, *Chem. Commun.*, 2001, 2648; N. Buschmann, A. Rückert, and S. Blechert, *J. Org. Chem.*, 2002, **67**, 4325; V. Boersch and S. Blechert, *Chem. Commun.*, 2006, **18**, 1968.
8. J. Mann and L. C. de Almeida Barbosa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 787.

9. R. M. Moriarty, O. Prakash, P. R. Vavilikolanu, R. K. Vaid, and W. A. Freeman, *J. Org. Chem.*, 1989, **54**, 4008.
10. H. Kim and H. M. R. Hoffmann, *Eur. J. Org. Chem.*, 2000, 2195.
11. W. J. Zuercher, M. Hashimoto, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, **118**, 6634; G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock, and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 1828.
12. S. Gessler, S. Randl, and S. Blechert, *Tetrahedron Lett.*, 2000, **41**, 9973; D. Dewi, S. Randl, and S. Blechert, *Tetrahedron Lett.*, 2005, **46**, 577; S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.*, 2003, **17**, 1900.
13. J. H. Cho and B. M. Kim, *Org. Lett.*, 2003, **5**, 531.
14. W. S. Mahoney and J. M. Stryker, *J. Am. Chem. Soc.*, 1989, **111**, 8818; W. S. Mahoney, D. M. Brestensky, and J. M. Stryker, *J. Am. Chem. Soc.*, 1988, **110**, 291.