Enantioselective Synthesis of α,α'-Disubstituted Piperidines via Ruthenium-Catalyzed Ring Rearrangement

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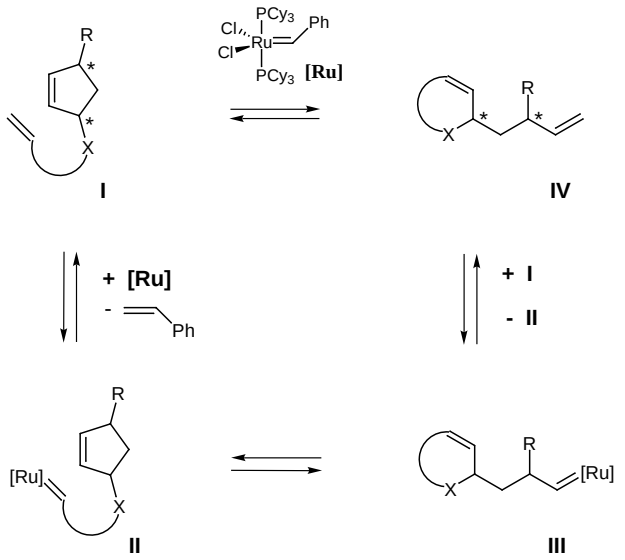
Abstract: A new method for the enantioselective synthesis of α,α'-disubstituted piperidines is described. Easily available cyclopentenones **5a,b** rearrange via Ru-catalyzed RCM-ROM to heterocycles. Compound **6a** is converted to the indolizidine **13**.

Key words: metathesis, rearrangements, piperidines, indolizidines, azasugars, ruthenium, osmium, dihydroxylations

Transition metal-catalyzed olefin metathesis is a very powerful tool in organic synthesis. Variations of this valuable transformation like ring closing metathesis (RCM), ring opening metathesis (ROM) and cross metathesis (CM) have been investigated during recent years.[1] RCM has found many applications. Its efficiency has been proven in the synthesis of various carbo- and heterocycles and especially in the synthesis of natural products.[2] The less frequently applied ROM is mainly known as partial step in the polymerization (ROMP) of strained rings like norbornene and cyclooctene.[3] However, in the presence of acyclic olefins it is possible to combine the ROM with a selective cross metathesis and, thus, to suppress the polymerization.[4] Such ROM can also be combined with RCM and CM to domino processes.[5] Unstrained rings can be opened using a RCM-ROM-RCM sequence.[6] Reactions are driven by a loss of ring strain or by the release of a volatile olefin like ethylene. Currently, we are interested in RCM-ROM combinations of type **I** ⇆ **IV**, which offer interesting opportunities for ring rearrangements. A special aspect of this reaction is the catalytic transfer of stereocenters from easily available carbocyclic olefins to heterocycles with substituted side chains. Based on earlier work, we assume, that Grubbs' pre-catalyst **[Ru]**[7] first reacts with the better accessible terminal double bond of cyclopentene derivative **I** forming ruthenium carbene complex **II** (Scheme 1). Subsequent reaction between **I** and **II** would lead to dimeric products. As we did not observe any dimerization, it has to be assumed, that an intramolecular [2+2] cycloaddition reaction with the cyclic double bond and subsequent cycloreversion proceeds much faster.

The resulting metal carbene-complex **III** reacts in a cross metathesis reaction with another molecule of **I** under formation of product **IV**. In principle, the dimerization is also possible at this stage. However, NMR-analyses of the reaction did not reveal the formation of any dimerization products.



Scheme 1

The equilibrium in this novel reaction sequence should depend on the relative thermodynamic stabilities of substrate and product. Recently, we have applied this concept to the synthesis of the piperidine alkaloid (−)-halosalin.[8]

Now, we report about the extension of this concept towards the synthesis of α,α'-disubstituted piperidines and subsequent products, which are interesting as azasugars. As shown in the case **1**→**2** (Scheme 2) the application of metathesis ring rearrangement **I**→**IV** to heterocycles with an olefinic side chain should lead to *cis*- or *trans*- α,α'-disubstituted derivatives of defined configuration depending on the chiral centre highlighted. Besides the equilibrium problem we were also interested in relative rearrangement rates of the two diastereomers of **1**.

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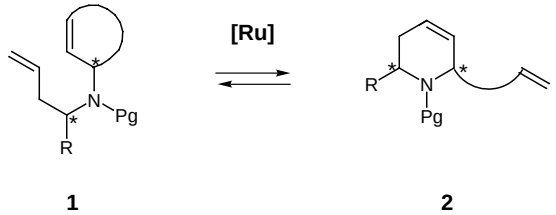
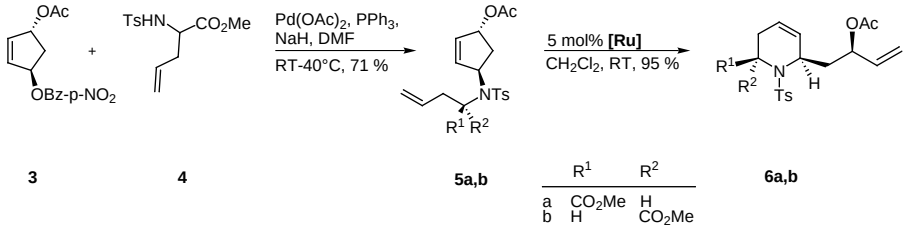


Scheme 2



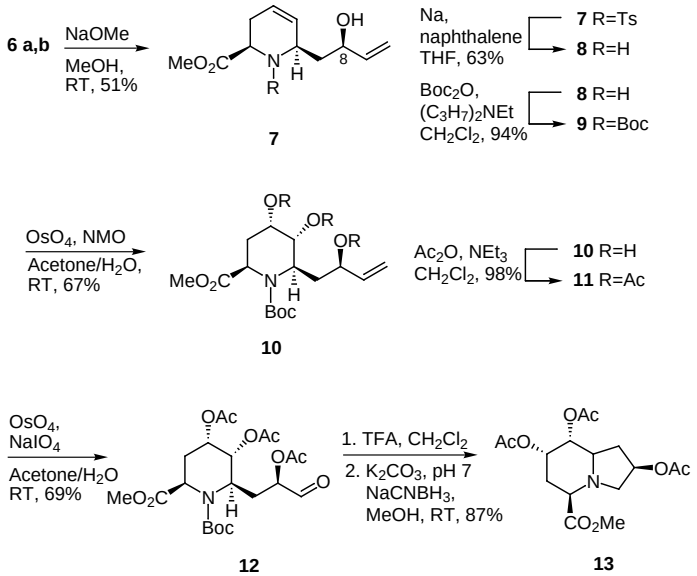
Scheme 3

An ester function, i.e. an allylglycine derivative, was chosen as a substituent offering a high flexibility for subsequent reactions. Allylglycine derivatives have been used in metathesis reactions several times.[1,9] Racemization is not to be expected under the mild, neutral conditions of metathesis. As a starting material for the synthesis of a suitable precursor we used *p*-nitrobenzoate **3**, which is easily available in high overall yield by enzymatic hydrolysis[10] and Mitsunobu reaction of *cis*-1,3 diacetoxycyclopentadiene. A Pd(0)-catalyzed allylation of *rac*-allylglycine ester **4** with **3** gives rise to the desired 1:1 mixture of diastereomers **5a** and **5b**, which should be investigated and compared in their ability to react as metathesis precursors.

Different rates of rearrangement of **5a** and **5b** could lead to kinetic separation of diastereomers. Therefore, the mixture (0.1 mol/L in CH_2Cl_2) was treated with 5 mol% of **[Ru]**. At room temperature both compounds are rearranged equally fast. After 15 hours the transformation has reached the equilibrium, which is characterized by the practically complete formation of pipecolic acid derivative **6a** and **6b**. After filtration on silica gel **6a,b** was obtained almost quantitatively and in pure form. Since racemization can be excluded under the reaction conditions, it should be feasible to obtain stereochemically uniform *cis*- or *trans*-α,α'-disubstituted N-heterocycles starting from enantiomerically pure D- or L- allylglycine ester. As a proof, (+)-**4** or (−)-**4** was treated with **3** and we exclusively obtained the *cis*-ester **6a** or the thermodynamically more labile *trans*-ester **6b** in the same yield.

In the next step, we wanted to apply this new procedure to the preparation of polyhydroxypiperidine derivatives, representing azasugar analogs. As inhibitors of glycosidases and glycosyltransferases and consequently, as potential antibacterial, antiviral, antimetastatic and antidiabetic agents polyhydroxylated indolizidines have drawn considerable attention.[11]

We have used the new concept of ring rearrangement for the synthesis of the novel indolizidine **13**. The transformation of alkenyl-substituted piperidines of type **6** into an indolizidine requires a cyclization to a five-membered ring. It was planned to cleave oxidatively the terminal double bond and to cyclize the resulting aldehyde in a reductive amination with the deprotected secondary amine. During the synthesis of the required enantiomerically pure *cis*-disubstituted piperidine it is not necessary to start from the expensive D-allylglycine. Instead, we treated the 1:1 diastereomeric mixture of **6a** and **6b**, obtained from the racemic amino acid ester, with a catalytic amount of NaOMe



Scheme 4

in methanol. After workup and chromatography on silica gel the completely isomerized, thermodynamically more stable compound **7** was isolated. Under the isomerization conditions the acetyl group at C-8 was cleaved.

During the preparation of precursor **5** a tosyl group proved favourable with regard to the Pd(0)-catalyzed step. Unfortunately, the deprotection conditions are not compatible with the functional groups required for the reductive amination. Therefore, in the next step the sulfonyl group was reductively removed using sodium naphthalide and the resulting free amine **8** was protected with a Boc-group cleavable under acidic conditions. Moreover, the introduction of this group in contrast to the tosyl group enables a highly selective oxidation of the cyclic olefin. *cis*-Dihydroxylation of **9** using a catalytic amount of OsO_4 and 1.0 equivalent of NMO (*N*-methylmorpholine *N*-oxide) surprisingly resulted in the formation of the triol **10**, which was obtained in 67% yield after chromatography. Besides 19% of starting material only traces of completely hydroxylated product were isolated.

The free hydroxyl groups in **10** were acetylated to give triacetate **11**. Oxidative double bond cleavage using catalytic amounts of OsO_4 and 5.0 equivalents of $NaIO_4$ yielded aldehyde **12** suitable for planned cyclization. The Boc group was carefully removed using trifluoroacetic acid (TLC control) and the resulting imine was reduced with $NaBH_3CN$ at pH 7. The reductive amination afforded the desired indolizidine **13** in 7% overall yield over 10 steps.

In conclusion, we have presented a domino ring opening-ring closing metathesis terminated by a methylene transfer. This concept enables the preparation of enantiomerically pure *cis*- or *trans*- α,α'-disubstituted piperidines, which can be transformed into indolizidines using easily available racemic or enantiomerically pure starting materials. This synthetic principle is applicable to other members of the indolizidine family by simple modifications of the route described above. Further studies in this direction are currently being performed in our group.

^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100.6 MHz) were recorded on a Bruker AM 400 spectrometer using the indicated solvents. ^{1}H NMR spectra (500 MHz) were recorded on a Bruker DRX 500 spectrometer. ^{13}C NMR spectra (67.5 MHz) were recorded on a Bruker AM 270 spectrometer. NMR chemical shifts are expressed in ppm upfield, relative to the internal solvent peak. HRMS were recorded on a Finnigan MAT 95 SQ and IR spectra on a Nicolet FT-IR 750 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Leica Galen III heater tablemicroscope and are uncorrected. Elemental analyses were recorded on a Elementar Vario El Fa. Analytik Jena. Analytical TLC was performed using silica gel 60 F254 precoated plates Merck, 0.25 mm thickness with a fluorescent indicator. Flash column chromatography was performed on Merck silica gel 60 (0.040−0.063 mm) using the indicated solvent. Chemicals were purchased from Aldrich or Merck and used without further purification. Metathesis reactions were performed in a Braun MB 150B-G glove box under N_2. Solvents were distilled under N_2 from sodium/benzophenone (THF) or CaH_2 (CH_2Cl_2, DMF).

***p*-Nitrobenzoic Acid (1*R*,4*R*)-4-Acetoxycyclopent-2-en-1-yl Ester (3)**

To an ice-cooled solution of (1*R*,3*S*)-(+)-*cis*-4-cyclopentene-1,3-diol-1-acetate (700 mg, 4.9 mmol), Ph_3P (5.1 g, 19.5 mmol) and *p*-nitrobenzoic acid (3.3 g, 20 mmol) in anhyd THF (25 mL) under N_2 was slowly added diethyl azodicarboxylate (3.5 g, 20 mmol) via a syringe. The mixture was stirred overnight at r.t., concentrated in vacuum, diluted with Et_2O (50 mL) and stirred again for 18 h at r.t. A white precipitate appeared. The precipitation was completed by addition of hexane (10 mL). It was filtered off and washed with a mixture of hexane/Et_2O (1:1, 50 mL). The solvent was removed under vacuum and the residue was chromatographed on silica gel [10:1 hexane/methyl *tert*-butyl ether (MTBE)] to give **3** as a yellow solid (1.30 g, 90%); mp 47 °C; $[\alpha]_D^{25}$ +257.0 (*c* = 1.445, $CHCl_3$).

IR (KBr): ν = 3112 (w), 3081 (w), 2954 (w), 1723 (s), 1528 (s), 1274 (s), 1238 (s), 1103 (m), 1027 (m), 719 (m) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 9 Hz, 2 H, Ar-H), 8.18 (d, *J* = 9 Hz, 2 H, Ar-H), 6.24 (m, 2 H, C^2-H, C^3-H), 6.10 (m, 1 H, C^1-H), 5.90 (m, 1 H, C^4-H), 2.45 (ddd, *J* = 15, 7, 4 Hz, 1 H, C^5-H), 2.38 (ddd, *J* = 15, 6, 4 Hz, 1 H, C^5-H), 2.08 (s, 3 H, $COCH_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.8, 164.4, 150.5, 136.4, 134.6, 135.3, 130.6, 123.5, 79.9, 78.1, 37.4, 21.0.

MS (EI): *m*/*z* (%) = 232 ($[M - OAc]^+$, 24), 150 (100), 82 (48).

HRMS: *m*/*z* calcd for $C_{12}H_{10}NO_4$ $(M - OAc)^+$ 232.0609; found 232.0608.

Anal. calcd for $C_{14}H_{13}NO_6$: C, 57.76; H, 4.46; N, 4.81; found C, 57.37; H, 4.72; N, 5.06.

2-(Toluene-4-sulfonylamino)pent-4-enoic Acid Methyl Ester (4)

To a solution of allylglycine methyl ester (2.0 g, 15.4 mmol) in CH_2Cl_2 (20 mL) was added sat. aq $NaHCO_3$ (15 mL) and *p*-toluenesulfonyl chloride (3.0 g,16.9 mmol, 1.1 equiv). After stirring strongly overnight the organic layer was separated, washed with brine (2 × 25 mL), dried ($MgSO_4$) and concentrated in vacuum. The resulting oil was chromatographed on silica gel (10:1 hexane/MTBE) to give **4** as a colourless solid (3.2 g, 73%) after recrystallization from MTBE.

IR (KBr): ν = 3277 (w), 3080, 3029 (w), 2982,2954 (w), 1741 (s), 1343 (s), 1163 (s), 1092 (m), 815 (m), 665 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8 Hz, 2 H, Ar-H), 7.30 (d, *J* = 8 Hz, 2 H, Ar-H), 5.62 (m, 1 H, C^4-H), 5.12 (d, *J* = 10 Hz, 1 H, C^5-H), 5.08 (d, *J* = 17 Hz, 1 H, C^5-H), 4.04 (m, 1 H, C^2-H), 3.53 (s, 3 H, CO_2CH_3), 2.48 (dd, *J* = 6.5, 6.5 Hz, 2 H, C^3-H), 2.44 (s, 3 H, Ar-CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ = 171.2, 143.5, 136.7, 131.2, 129.4, 127.0, 119.4, 55.1, 52.2, 37.3, 21.3.

MS (EI): *m*/*z* (%) = 283 ($[M]^+$, 1), 242 (60), 155 (100), 91 (84).

HRMS: *m*/*z* calcd for $C_{13}H_{17}NO_4S$ $(M)^+$ 283.0878; found 283.0877.

Anal. calcd for $C_{12}H_{14}N_2O_6S$ (nosyl-protected derivative): C, 45.86; H, 4.46; N, 8.92; found C, 45.62; H, 4.55; N, 8.92.

(*R*) *and* (*S*) -2-{[(1*R*,4*R*)-4-Acetoxycyclopent-2-enyl](toluene-4-sulfonyl)amino}pent-4-enoic Acid Methyl Ester (5a,b)

To an ice-cooled solution of racemic **4** (486 mg, 1.72 mmol) in DMF (20 mL) was added NaH (75 mg as a 60% dispersion in oil, 1.87 mmol). The mixture was stirred for 20 min at 0 °C and 20 min at r.t. A mixture of $Pd(OAc)_2$ (22 mg, 0.1 mmol), Ph_3P (131 mg, 0.4 mmol) and **3** (488 mg, 1.75 mmol) in anhyd DMF (20 mL) was added in two portions. After 15 h the mixture was concentrated in vacuum, diluted with MTBE (30 mL), washed with aq sat. NH_4Cl (50 mL), dried ($MgSO_4$) and concentrated. The resulting oil was chromatographed on Al_2O_3 (1:1 hexane/MTBE) to give **5** as a

colourless oil (1:1 mixture of two inseparable diastereomers; 496 mg, 71%).

IR (film): ν = 3075 (w), 2953 (w), 2924 (w), 1736 (s), 1341 (m), 1241 (s), 1157 (s), 664 (m) cm^{-1}.

MS (EI): *m*/*z* (%) = 347 ($[M - C_2H_4O]^+$, 8), 192 (22), 155 (68), 125 (100), 91 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{21}O_4NS$ $(M - C_2H_4O)^+$ 347.1191; found 347.1192.

Anal. calcd for $C_{20}H_{25}NO_6S$: C, 58.97; H, 6.14; N, 3.44; found C, 58.63; H, 6.30; N, 3.57.

(*R*)-2-{[(1*R*,4*R*)-4-Acetoxycyclopent-2-enyl](toluene-4-sulfonyl)amino}pent-4-enoic Acid Methyl Ester (5a)

Reaction of (+)-**4** (200 mg, 0.75 mmol) with **3** (216.5 mg, 0.63 mmol) was carried out analogous to the synthesis of **5a,b** as above [NaH (37 mg as a 60% dispersion in oil, 0.93 mmol); $Pd(OAc)_2$ (11 mg, 0.05 mmol), Ph_3P (65.5 mg, 0.2 mmol), DMF (20 mL)] and worked up to give **5a** as a colourless oil (198 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 9 Hz, 2 H, Ar-H), 7.27 (d, *J* = 9 Hz, 2 H, Ar-H), 5.98 (m, 2 H, $C^{2'}$-H, $C^{3'}$-H), 5.78 (m, 2 H, C^4-H, $C^{4'}$-H), 5.13 (d, *J* = 10 Hz, 1 H, C^5-H), 5.11 (d, *J* = 17 Hz, 1 H, C^5-H), 4.84 (m, 1 H, $C^{1'}$-H), 4.22 (dd, *J* = 8, 6 Hz, 1 H, C^2-H), 3.64 (s, 3 H, CO_2CH_3), 2.88 (m, 1 H, C^3-H), 2.52 (m, 1 H, C^3-H), 2.42 (s, 3 H, Ar-C*H*$_3$), 2.39 (m, 1 H, $C^{5'}$-H), 2.06 (ddd, *J* = 15, 8, 2 Hz, 1H, $C^{5'}$-H), 2.01 (s, 3 H, $COCH_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.1, 170.7, 143.2, 138.3, 136.9, 133.7, 132.8, 129.3, 127.4, 118.4, 78.6, 63.1, 59.4, 52.2, 37.1, 35.8, 21.4, 21.0.

(*S*)-2-{[(1*R*,4*R*)-4-Acetoxycyclopent-2-enyl](toluene-4-sulfonyl)amino}pent-4-enoic Acid Methyl Ester (5b)

Reaction of (−)-**4** (200 mg, 0.75 mmol) with **3** (216.5 mg, 0.63 mmol) was carried out analogous to the synthesis of **5a,b** as above [NaH (37 mg as a 60% dispersion in oil, 0.93 mmol); $Pd(OAc)_2$ (11 mg, 0.05 mmol), Ph_3P (65.5 mg, 0.2 mmol), DMF (20 mL)] and worked up to give **5b** as a colourless oil (209 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8 Hz, 2 H, Ar-H); 7.29 (d, *J* = 8 Hz, 2 H, Ar-H), 6.02 (m, 1 H, $C^{3'}$-H), 5.88 (m,1 H, $C^{2'}$-H), 5.70 (m, 2 H, C^4-H, $C^{4'}$-H), 5.05 (d, *J* = 10 Hz, 1 H, C^5-H), 5.02 (d, *J* = 17 Hz, 1 H, C^5-H), 4.98 (m, 1 H, $C^{1'}$-H), 3.85 (dd, *J* = 7, 7 Hz, 1 H, C^2-H), 3.74 (s, 3 H, CO_2CH_3), 2.86 (m, 1 H, C^3-H), 2.48 (m, 2 H, C^3-H, $C^{5'}$-H), 2.43 (s, 3 H, Ar-C*H*$_3$), 2.11 (ddd, *J* = 16, 8, 3 Hz, 1H, $C^{5'}$-H), 2.01 (s, 3 H, $COCH_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.9, 170.4, 143.3, 138.3, 136.6, 134.1, 133.6, 129.3, 127.3, 117.8, 78.0, 63.1, 58.1, 52.2, 35.6, 35.4, 21.2, 20.8.

(*R*)-6-[(*R*)-2-Acetoxybut-3-enyl]-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (6)

Compound **5a,b** (360 mg, 0.88 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL). **[Ru]** (36 mg, 0.043 mmol) was added and the mixture was stirred for 20 h at r.t. in a glovebox. The solvent was removed under vacuum and the residue was chromatographed on silica gel (1:1 hexane/MTBE) to give **6a,b** as a colourless solid (1:1 mixture of two inseparable diasteromers; 340 mg, 95%); mp 58 °C.

IR (KBr): ν = 3034 (w), 2951 (w), 2925 (w), 1740 (s), 1346 (m), 1235 (s), 1161 (s), 717 (m), 659 (m) cm^{-1}.

MS (EI): *m*/*z* (%) = 407 ($[M]^+$, 1), 294 (48), 234 (42), 192 (44), 155 (28), 138 (44), 91 (84), 80 (100).

HRMS: *m*/*z* calcd for $C_{20}H_{25}NO_6S$ $(M)^+$ 407.1402; found 407.1411.

Anal. calcd for $C_{20}H_{25}NO_6S$: C, 58.97; H, 6.14; N, 3.44; found C, 59.02; H, 6.10; N, 3.63.

(2*R*, 6*R*)-6-[(*R*)-2-Acetoxybut-3-enyl]-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (6a)

Transformation of **5a** (180 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) with **[Ru]** (18 mg, 0.021 mmol) was carried out analogous to the synthesis of **6a,b** as above and worked up to give **6a** as a colourless solid (173 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8 Hz, 2 H, Ar-H), 7.28 (d, *J* = 8 Hz, 2 H, Ar-H), 5.80 (ddd, *J* = 17, 10, 6 Hz, 1 H, $C^{3'}$-H), 5.65 (m, 1 H, C^4-H), 5.60 (m, 1 H, C^5-H), 5.40 (m, 1 H, $C^{2'}$-H), 5.30 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.22 (d, *J* = 10 Hz, 1 H, $C^{4'}$-H), 4.72 (d, *J* = 7 Hz, 1 H, C^2-H), 4.41 (m, 1 H, C^6-H), 3.70 (s, 3 H, CO_2CH_3), 2.48 (dd, *J* = 17, 6 Hz, 1H, C^3-H), 2.42 (s, 3 H, Ar-C*H*$_3$), 2.08 (s, 3 H, $COCH_3$), 1.85 (m, 3 H, C^3-H, $C^{1'}$-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.3, 169.9, 143.5, 136.7, 136.0, 129.5, 126.9, 126.2, 122.8, 116.9, 71.8, 52.4, 51.3, 49.8, 39.5, 26.7, 22.9, 21.3.

(2*S*, 6*R*)-6-[(*R*)-2-Acetoxybut-3-enyl]-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (6b)

Transformation of **5b** (180 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) with **[Ru]** (18 mg, 0.021 mmol) was carried out analogous to the synthesis of **6a,b** as above and worked up to give **6b** as a colourless solid (166 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8 Hz, 2 H, Ar-H), 7.26 (d, *J* = 8 Hz, 2 H, Ar-H), 5.75 (ddd, *J* = 17, 11, 6 Hz, 1H, $C^{3'}$-H), 5.70 (m, 1 H, C^4-H), 5.65 (m, 1 H, C^5-H), 5.22 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.18 (d, *J* = 10 Hz, 1 H, $C^{4'}$-H), 5.12 (m, 1 H, $C^{2'}$-H), 4.37 (m, 1 H, C^6-H), 4.10 (dd, *J* = 10, 5 Hz, 1 H, C^2-H), 3.80 (s, 3 H, CO_2CH_3), 2.58 (ddd, *J* = 18, 10, 2 Hz, 1 H, C^3-H), 2.43 (s, 3 H, Ar-C*H*$_3$), 2.24 (ddd, *J* = 18, 5, 5 Hz, 1 H, C^3-H), 1.98 (s, 3 H, $COCH_3$), 1.90 (m, 2 H, $C^{1'}$-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.5, 169.7, 143.8, 137.4, 136.0, 129.4, 128.3, 127.7, 124.9, 117.0, 71.5, 54.1, 53.0, 52.4, 38.8, 26.1, 21.5, 21.0.

(2*R*,6*R*)-6-[(*R*)-2-Hydroxybut-3-enyl]-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (7)

To a solution of **6** (40mg, 0.1 mmol) in anhyd MeOH (3 mL) was added NaOMe (2 mg, 0.037 mmol). The mixture was stirred overnight, diluted with brine (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The resulting oil was chromatographed on silica gel (1:1 hexane/MTBE) to give **7** (18 mg, 51%) as a colourless oil; $[\alpha]_D^{25}$ −27.3 (*c* = 0.3, $CHCl_3$).

IR (film): ν = 3532 (w), 3036 (w), 2954 (w), 2926 (w), 1741 (s), 1332 (m), 1162 (s), 659 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8 Hz, 2 H, Ar-H), 7.28 (d, *J* = 8 Hz, 2 H, Ar-H), 5.88 (ddd, *J* = 17, 11, 6 Hz, 1 H, $C^{3'}$-H), 5.59 (m, 1 H, C^4-H), 5.50 (m, 1 H, C^5-H), 5.34 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.12 (d, *J* = 10 Hz, 1 H, $C^{4'}$-H), 4.75 (d, *J* = 7 Hz, 1 H, C^2-H), 4.62 (m, 1 H, $C^{2'}$-H), 4.53 (m, 1 H, C^6-H), 3.72 (s, 3 H, CO_2CH_3), 2.48 (dd, *J* = 18, 6 Hz, 1 H, C^3-H), 2.43 (s, 3H, Ar-C*H*$_3$), 1.76 (ddd, *J* = 18, 8, 2 Hz, 1 H, C^3-H), 1.52 (m, 2 H, $C^{1'}$-H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.4, 144.1, 140.0, 136.5, 129.4, 126.9, 126.7, 122.7, 114.3, 67.8, 52.8, 51.6, 50.7, 42.1, 22.3, 21.6.

MS (EI): *m*/*z* (%) = 306 ($[M - C_2H_3O_2]^+$, 4), 294 (84), 155 (36), 138 (100), 91 (60), 80 (82). HRMS: *m*/*z* calcd for $C_{16}H_{20}O_3NS$ $(M - C_2H_3O_2)^+$ 306.1163; found 306.1166.

Anal. calcd for $C_{18}H_{23}NSO_5.H_2O$: C, 56.40; H, 6.53; N, 3.65; found C, 56.51; H, 6.23; N, 3.82.

(2*R*,6*R*)-6-[(*R*)-2-Hydroxybut-3-enyl]-1,2,3,6-tetrahydropyridine-2-carboxylic Acid Methyl Ester (8)

To a solution of **7** (200 mg, 0.55 mmol) in THF (5 mL) was added a 0.8 M solution of sodium naphthalide in DME until complete cleavage of the tosyl group (TLC control). The mixture was diluted with MTBE (50 mL) and extracted with 0.1 M HCl (2 × 30 mL). The aqueous layer was neutralized and concentrated in vacuum. The residue was chromatographed on silica gel (8:1 EtOAc/MeOH) to give **9** as a colourless solid (73 mg, 63%); $[\alpha]_D^{25}$ −40.8 (*c* = 1.08, $CHCl_3$).

IR (KBr): ν = 3316 (m), 2951 (m), 2928 (m), 1740 (s), 1436 (m), 1219 (s), 997 (m), 921 (m) cm^{-1}.

^1H NMR (400 MHz, MeOD): δ = 5.88 (dd, *J* = 17, 11, 6 Hz, 1 H, $C^{3'}$-H), 5.82 (ddd, *J* = 10, 3, 3 Hz, 1 H, C^4-H), 5.62 (m, 1 H, C^5-H), 5.23 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.05 (d, *J* = 10 Hz, 1 H, $C^{4'}$-H), 4.27 (m, 1 H, $C^{2'}$-H), 3.74 (s, 3 H, CO_2CH_3), 3.69 (m, 1 H, C^6-H), 3.58 (dd, *J* = 11, 4 Hz, 1 H, C^2-H), 2.34 (m, 1 H, C^3-H), 2.20 (m, 1 H, C^3-H), 1.66 (m, 2 H, $C^{1'}$-H).

^{13}C NMR (67.5 MHz, MeOD): δ = 139.8, 128.3, 123.0, 111.9, 68.2, 53.7, 50.6, 50.0, 39.9, 26.4.

MS (EI): *m*/*z* (%) = 211 ($[M]^+$, 4), 152 (52), 140 (72), 80 (100).

HRMS: *m*/*z* calcd for $C_{11}H_{17}NO_3$ $(M)^+$ 211.1208; found 211.1209.

(2*R*,6*R*)-6-[(*R*)-2-Hydroxybut-3-enyl]-3,6-dihydro-2*H*-pyridine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (9)

To a solution of **8** (300 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) were added di-*tert*-butyl dicarbonate (372 mg, 1.7 mmol) and diisopropylethylamine (920 mg, 7.1 mmol). The mixture was stirred overnight at r.t., diluted with CH_2Cl_2 (20 mL), washed with aq sat. NH_4Cl solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (MTBE) to give **9** as a colourless oil (423 mg, 94%); $[\alpha]_D^{25}$ −40.0 (*c* = 0.66, $CHCl_3$).

IR (film): ν = 3447 (m), 2978 (m), 2953 (m), 1745 (s), 1678 (s), 1409 (s), 1366 (m), 1205 (m), 1170 (s), 1034 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.88 (dd, *J* = 17, 11, 5 Hz, 1 H, $C^{3'}$-H), 5.79 (m, 1 H, C^4-H), 5.71 (m, 1 H, C^5-H), 5.28 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.06 (d, *J* = 10 Hz, 1 H, $C^{4'}$-H), 4.93 (m, 1 H, C^2-H), 4.61 (m, 1 H, C^6-H), 4.26 (m, 1 H, $C^{2'}$-H), 3.67 (s, 3 H, CO_2CH_3), 2.61 (m, 1 H, C^3-H), 2.38 (m, 1 H, C^3-H), 1.66 (m, 1 H, $C^{1'}$-H), 1.56 (dd, *J* = 10, 5 Hz, 1 H, $C^{1'}$-H), 1.48 (s, 9 H, C_4H_9).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.5, 156.3, 140.2, 128.7, 122.4, 113.8, 81.8, 68.0, 52.3, 51.3, 48.4, 42.5, 28.4, 24.8.

MS (EI): *m*/*z* (%) = 211 ($[M - C_4H_8]^+$, 1), 240 (16), 152 (12), 140 (100), 80 (62), 57 (58).

HRMS: *m*/*z* calcd for $C_{12}H_{17}NO_5$ $(M - C_4H_8)^+$ 255.1106; found 255.1109.

(2*R*,4*S*,5*R*,6*R*)-4,5-Dihydroxy-6-[(*R*)-2-hydroxybut-3-enyl]piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (10)

To an ice-cooled solution of **9** (100 mg, 0.32 mmol) in acetone/H_2O (2:1 v/v; 3 mL) was added OsO_4 (2 mg, 0.0078 mmol). After 5 min, *N*-methylmorpholine *N*-oxide (43 mg, 0.32 mmol) was added to the brown solution in two portions. The mixture was allowed to warm up to r.t. and stirred overnight. EtOAc (15 mL) and brine (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The resulting dark brown oil was chromatographed on silica gel (EtOAc) to give **10** as a colourless oil (60 mg, 67% based on 81% of conversion); $[\alpha]_D^{25}$ +27.5 (*c* = 1.26, $CHCl_3$).

IR (film): ν = 3407 (m), 2976 (m), 2952 (m), 2929 (m), 1741 (s), 1668 (s), 1406 (s), 1366 (s), 1203 (m), 1166 (s), 1085 (m), 1020 (m) cm^{-1}.

^1H NMR (400 MHz, MeOD, 60 °C): δ = 5.85 (ddd, *J* = 17, 11, 6 Hz, 1H, $C^{3'}$-H), 5.23 (d, *J* = 17 Hz, 1 H, $C^{4'}$-H), 5.05 (d, *J* = 11 Hz, 1 H, $C^{4'}$-H), 4.96 (dd, *J* = 6, 4 Hz, 1 H, C^2-H), 4.44 (ddd, *J* = 9, 6, 2 Hz, 1 H, C^4-H), 4.18 (m, 1 H, $C^{2'}$-H), 3.84 (ddd, *J* = 10, 6, 2 Hz, 1 H, C^5-H), 3.80 (m, 1 H, C^6-H), 3.68 (s, 3 H, CO_2CH_3), 2.12 (m, 2 H, C^3-H), 1.66 (ddd, *J* = 14, 10, 4 Hz, 1 H, $C^{1'}$-H), 1.48 (s, 9 H, C_4H_9), 1.40 (m, 1 H, $C^{1'}$-H).

^{13}C NMR (100.6 MHz, MeOD, 60 °C): δ = 173.6, 157.5, 141.0, 114.0, 81.5, 71.0, 69.5, 64.0, 56.2, 53.6, 52.2, 39.1, 27.8, 26.8.

MS (EI): *m*/*z* (%) = 289 ($[M - C_4H_8]^+$, 1), 186 (84), 174 (52), 168 (24), 150 (16), 57 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{19}O_7N$ $(M - C_4H_8)^+$ 289.1161; found 289.1167.

(2*R*,4*S*,5*R*,6*R*)-4,5-Diacetoxy-6-[(*R*)-2-acetoxybut-3-enyl]piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (11)

To a solution of **10** (60 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added Ac_2O (100 mg, 1.0 mmol), Et_3N (200 mg, 2.0 mmol) and 4-dimethylaminopyridine (5 mg, 0.045 mmol). After 30 min, the mixture was concentrated in vacuum, diluted with MTBE (10 mL) and the organic layer was washed with aq satd NH_4Cl solution. The organic layer was dried ($MgSO_4$), concentrated in vacuum and the resulting oil was chromatographed on silica gel (1:1 hexane/MTBE) to give **11** as a colourless oil (81 mg, 98%); $[\alpha]_D^{25}$ −6.9 (*c* = 0.91, $CHCl_3$).

IR (film): ν = 2954 (m), 2925 (m), 1742 (s), 1697 (s), 1368 (m), 1231 (s), 1215 (s), 1025 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 70 °C): δ = 5.80 (ddd, *J* = 17, 11, 6 Hz, 1 H, $C^{3'}$-H); 5.32−5.10 (m, 6 H, C^2-H, C^4-H, C^5-H, $C^{2'}$-H, $C^{4'}$-Ha,b), 4.50 (m, 1 H, C^6-H), 3.74 (s, 3 H, CO_2CH_3), 2.30 (dd, *J* = 12, 4 Hz, 1 H, C^3-H), 2.20 (ddd, *J* = 12, 12, 7 Hz, 1 H, C^3-H), 2.05 (s, 6 H, $COCH_3$), 2.00 (s, 3 H, $COCH_3$), 1.86 (m, 2 H, $C^{1'}$-Ha,b), 1.47 (s, 9 H, C_4H_9).

^{13}C NMR (100.6 MHz, MeOD): δ = 172.4, 170.2, 170.0, 169.9, 155.5, 135.7, 117.4, 81.4, 72.2, 69.5, 65.0, 53.9, 52.6, 51.4, 35.2, 28.2, 24.6, 21.3, 20.9.

MS (EI): *m*/*z* (%) = 412 ($[M - C_2H_3O_2]^+$, 4), 312 (24), 252 (100), 192 (52), 132 (38); 57 (90).

HRMS: *m*/*z* calcd for $C_{20}H_{30}NO_8$ $(M - C_2H_3O_2)^+$ 412.1971; found 412.1977.

(2*R*,4*S*,5*R*,6*R*)-4,5-Diacetoxy-6-[(*R*)-2-acetoxy-3-oxopropyl]piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (12)

To an ice-cooled solution of **11** (18 mg, 0.038 mmol) in acetone/phosphate puffer pH 7 (3:1 v/v, 2 mL) was added OsO_4 (1 mg, 0.0039 mmol). After 10 min $NaIO_4$ (42 mg, 0.19 mmol) was added to the brown solution in two portions. The mixture was allowed to warm up to r.t. and stirred overnight. EtOAc (15 mL) and brine (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. The resulting dark brown oil was chromatographed on silica gel (EtOAc) to give **12** as a colourless oil (12.4 mg, 69%).

IR (film): ν = 2976 (m), 2935 (m), 1744 (s), 1699 (s), 1369 (m), 1244 (s), 1219 (s), 1047 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 70 °C): δ = 9.50 (s, 1 H, CHO), 5.15−5.09 (m, 4 H, C^2-H, C^4-H, C^5-H, $C^{2'}$-H), 4.60 (m, 1 H, C^6-H), 3.77 (s, 3 H, CO_2CH_3), 2.34 (dd, *J* = 13, 4 Hz, 1 H, C^3-H), 2.26 (dd, *J* = 13, 7 Hz, 1 H, C^3-H), 2.20 (s, 3 H, $COCH_3$), 2.12 (dd, *J* = 15, 10 Hz, 1 H, $C^{1'}$-H), 2.07 (s, 3 H, $COCH_3$), 2.00 (s, 3 H, $COCH_3$), 1.78 (ddd, *J* = 15, 11, 5 Hz, 1 H, $C^{1'}$-H), 1.46 (s, 9 H, C_4H_9).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 197.0, 172.3, 169.9, 81.6, 75.5, 69.5, 65.1, 53.0, 52.6, 52.0, 29.6, 28.1, 24.5, 20.8.

MS (EI): *m*/*z* (%) = 353 ([M − 2 × $C_2H_4O_2$]$^+$, 16), 201 (100), 133 (42), 113 (42), 89 (80), 81 (68), 59 (40).

HRMS: *m*/*z* calcd for $C_{17}H_{23}NO_7$ (M − 2 × $C_2H_4O_2$)$^+$ 353.1474; found 353.1477.

(2*R*,5*R*,7*S*,8*R*,8a*R*)-2,7,8-Triacetoxyoctahydroindolizine-5-carboxylic Acid Methyl Ester (13)

To a solution of **12** (10 mg, 0.021 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.1 mL) until complete cleavage of the *tert*-butoxycarbonyl group, monitored by TLC. The mixture was diluted with MeOH (1 mL) and neutralized with solid K_2CO_3 and then $NaBH_3CN$ (3 mg, 0.047 mmol) was added. After stirring overnight, trifluoroacetic acid was added until pH 2 was reached and then the mixture was stirred for further 2 h. The solution was neutralized, concentrated in vacuum and the residue was chromatographed on silica gel (MTBE) to give **13** (6.5 mg, 87%) as a colourless oil; $[\alpha]_D^{25}$ +24.6 (*c* = 1.20, MeOH).

IR (film): ν = 2926, 2853 (m), 1740 (s), 1242 (s), 1221(s), 1053 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (m, 1 H, C^7-H), 5.12 (m, 1 H, C^2-H), 4.86 (dd, *J* = 10, 3 Hz, 1 H, C^8-H), 3.74 (s, 3 H, CO_2CH_3), 3.34 (d, *J* = 11 Hz, 1 H, C^3-H), 3.16 (dd, *J* = 11, 4 Hz, 1 H, C^5-H), 2.60 (ddd, *J* = 10, 10, 6 Hz, 1 H, C^{8a}-H), 2.48 (m, 2 H, C^1-H, C^3-H), 2.12 (m, 2 H, C^6-H), 2.12, 2.07, 2.02 (3 s, 9 H, $COCH_3$), 1.67 (ddd, *J* = 16, 10, 6 Hz, 1 H, C^1-H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 73.4, 71.4, 67.2, 60.3, 59.6, 58.7, 52.4, 36.1, 33.4, 21.2, 21.0, 20.8.

MS (EI): *m*/*z* (%) = 358 ([M + H]$^+$, 1), 297 (20), 238 (100), 178 (80), 118 (72).

HRMS: *m*/*z* calcd for $C_{16}H_{24}O_8N$ (M + H)$^+$ 358.1501; found 358.1523.

NOE (500 MHz, $CDCl_3$): 5.45 ppm (C^7-H) with 4.86 ppm (C^8-H) 4%; 3.16 ppm (C^5-H) with 2.60 ppm (C^{8a}-H) 3%; no NOE between (C^8-H) and (C^{8a}-H).

References

(1) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(b) Schuster, M., Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036.
(c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, *371*.
(d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37.

(2) (a) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 166.
(b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem.Soc*. **1999**, *121*, 5653.
(c) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424.
(d) Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 426.

(3) (a) Grubbs, R. H. *J. Macromol. Sci. Chem*. **1994**, *A31*,1829.
(b) Schrock, R. R. *Pure Appl. Chem.* **1994**, *66*, 1447.

(4) (a) Schneider, M. F.; Lucas, N., Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 257.
(b) Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 410.

(5) Stragies, R.; Blechert, S. *Synlett* **1998**, 169.

(6) (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **1996**, *118*, 6634.
(b) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem* **1998**, *63*, 8626.

(7) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039.

(8) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179.

(9) For example Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett*. **1997**, *38*, 677.

(10) (a) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.
(b) Johnson, C. R.; Bis, S. J., *Tetrahedron Lett*. **1992**, *33*, 7287.

(11) *Iminosugars as Glucosidaseinhibitors*, Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1998.

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