Hydroxylated α-Vinylpyrrolidines from Sugar-Derived 2,5-Dihydrofurans. Synthesis of (1*S*,2*S*,8a*R*)-1,2-Dihydroxyindolizidine by Ring Closing Olefin Methathesis

Claudio Paolucci,* Lorenzo Musiani, Francesca Venturelli, Antonino Fava

Dipartimento de Chimica Organica "A: Mangini"-Università di Bologna, Viale Risorgimento, 4, I-40136 Bologna, Italy
Fax +39(51)644-3654; E-mail: fava@antlab.cineca.it

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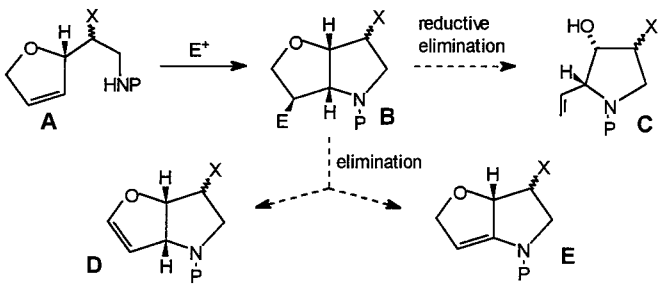
Sugar-derived dihydrofurans carrying an amino function at the terminus of a two-carbon branch undergo Hg(II)-promoted cyclization to give mercury substituted oxa-aza bicyclic compounds. Thiol promoted deoxymercuration results in cleavage of the tetrahydrofuran ring and formation of hydroxylated 2-vinylpyrrolidines. These appear to be convenient precursors for the synthesis of indolizidines via ring-closing olefin metathesis. As an example the synthesis of a new lentiginosine epimer is reported.

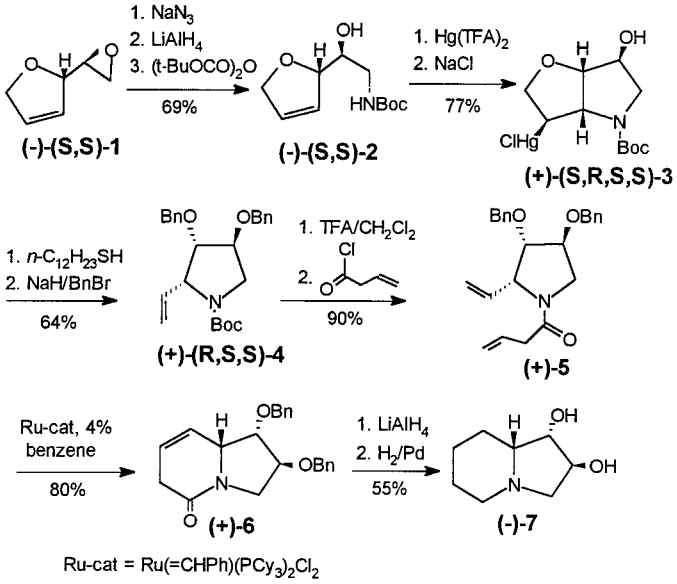
Due to the enzyme inhibitory properties possessed by many polyhydroxylated nitrogen heterocycles ("aza-sugars") their synthesis has attracted a great deal of interest recently.[1] Enantiomerically pure hydroxylated pyrrolidines, piperidines, and bicyclic systems containing these moieties with a nitrogen atom at the bridgehead have been the target of a multitude of preparations featuring a variety of synthetic approaches, most of which are based on the elaboration of chiral pool precursors (sugars and amino acids in particular).[2,3]

In this paper an approach is presented for the synthesis of hydroxylated pyrrolidines which, although based on a conventional intramolecular electrophilic addition of a (protected) amine onto a double bond, is peculiar insofar as the starting materials are 2,5-dihydrofurans (obtained from common sugars, however)[4] carrying a functionalized two-carbon branch at C2. The approach is outlined in Scheme 1 showing the amino- or amino-alcohol-branched dihydrofuran **A** (X=H, OH) undergoing electrophile-promoted cyclization to form the oxa-aza bicyclic system **B**. This may be subsequently manipulated regioselectively at the tetrahydrofuran ring moiety to eventually yield, depending on the nature of the electrophile and reaction conditions, different elimination products, **C**–**E**, all susceptible to further useful transformations. Thus, when an Hg(II) salt is used as the electrophile, **B** is a mercurial that can be deoxymercurated to form an hydroxylated α-vinylpyrrolidine **C**. On the other hand when the E-substituent in **B** is an iodine atom (arising from iodination of the mercurial), base-catalyzed elimination leads to either **D** or **E** depending on the stereochemistry, α or β, of the iodine substituent.[5,6]



Scheme 1

As part of a project aimed at the synthesis of new aza-sugars, we have now implemented this approach and report the synthesis of the hydroxylated α-vinylpyrrolidines derivatives **4** (Scheme 2), **8**, and **10** (Scheme 3) from, respectively, dihydrofurans (*S*,*S*)-**1**, (*S*,*R*)-**1**, and **9**, in turn obtained from mannitol or sorbitol as described previously.[4] In this paper we also show how these vinylpyrrolidines can be exploited for the synthesis of indolizidine alkaloids via ring closing olefin metathesis. As an example of this application, the synthesis is described, starting from the hydroxylated 2-vinylpyrrolidine **4**, of the 8a-epimer, **7**, of natural lentiginosine,[7] an isomer which had not been previously prepared.

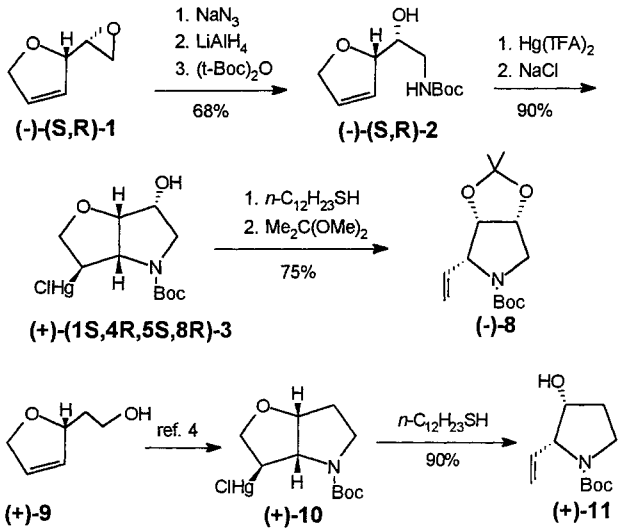


Scheme 2

The procedure is outlined in Scheme 2. The dihydrofuran-epoxide (2*S*,1′*S*)-**1** was subjected, in succession, to epoxide ring opening with sodium azide, lithium aluminum hydride reduction, and protection with *t*-butyl dicarbonate, to yield the Boc-protected amino alcohol (*S*,*S*)-**2**. Highly stereoselective cyclization of the latter was achieved by reaction with mercury(II) trifluoroacetate to give, after NaCl-chloridation, the bicyclic chloro-mercury derivative (*S*,*R*,*S*,*S*)-**3** as a single product. This, deoxymercurated with dodecane-1-thiol, and protected as the dibenzyl ether, gave the α-vinylpyrrolidine (*R*,*S*,*S*)-**4**. Cleavage of the *t*-Boc group with trifluoroacetic acid in dichloromethane,[8] followed by acylation with but-3-enoyl chloride furnished the amide **5**. This, subjected to the action of a ruthenium carbene complex, bis(tricyclohexylphosphane)benzylideneruthenium dichloride,[9] in benzene at reflux cyclized to the unsaturated lactam **6**.

Lithium aluminum hydride reduction of the carbonyl group followed by hydrogenation gave **7** as a solid, mp 137–138 °C, $[\alpha]_D^{23} = -5.8$ (*c* 0.885, MeOH).

The acetonide of 3,4-dihydroxy-2-vinylpyrrolidine (−)-**8** was prepared along lines similar to those described in Scheme 2, starting, however, from the epimeric dihydrofuran (*S,R*)-**1** via intermediates (*S,R*)-**2** and (*S,R,S,R*)-**3** (Scheme 3). The monohydroxylated pyrrolidine **11** was obtained by deoxymercuration with *n*-dodecanethiol of the corresponding, previously reported,[5] bicyclic mercury intermediate **10**, in turn obtained from dihydrofuran **9**.[3]



Scheme 3

The application of the ring closing metathesis procedure[9,10] to α-vinylpyrrolidines **4,8**, and **10** offers ample opportunities for the synthesis of indolizidines with hydroxy substituents at either ring moieties. Such developments are underway in our laboratory.

Melting points were obtained with a Büchi apparatus and are uncorrected. Yields are for isolated compounds. Unless specified otherwise, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ as solvent. Chemical shifts are in ppm downfield of TMS; signal multiplicities were established by DEPT experiments. Signal assignments were supported by 2D H–C NMR experiments. Due to the slow (in the NMR time scale) rotation of N–C(O) bonds, amides and urethanes may give rise to broad or split signals in the NMR spectra taken at the spectrometer temperature (21 °C). Where this is the case the signals of both conformers are reported below separated by a dash. Electron impact mass spectra were obtained with a VG 7070 instrument at 70 eV. For optical rotations a Jasco polarimeter was used. Preparative flash chromatographic experiments were performed using ICN Silica Adsorbienten 3263 60 A. For TLC precoated glass plates were used (Stratochrom SIF_{254}, 0.25 mm thick). Solvents and reagents were obtained as follows: THF was distilled from benzophenone ketyl, MeCN, CH_2Cl_2, benzene, and DMF were distilled from CaH_2. Satisfactory microanalyses obtained (C ±0.25, H ±0.10, N ±0.07).

(2*S*,1′*S*)-(−)-2-(2′-Azido-1′-hydroxyethyl)-2,5-dihydrofuran:
Sodium dihydrogen phosphate monohydrate (12.3 g) and, in sequence, epoxide (*S,S*)-**1** (1.97 g, 17.6 mmol) were added to a soln of NaN_3 (5.87 g, 87.3 mmol) in 60 mL of MeOH:H_2O (5:1, vv). The reaction mixture was left at r.t. for 60 h, the disappearance of the epoxide being monitored by TLC. The solids were filtered off, CH_2Cl_2 (50 mL) was added and the phases separated. The aq layer was washed twice with 20 mL of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated at reduced pressure. The residue was purified by flash chromatography to furnish the title compound. Yield: 2.1 g (77%); oil, $[\alpha]_D^{27.8}$: −85.7 (*c* 1.16, $CHCl_3$).

^{1}H NMR: δ = 6.05 (m, 1 H, H3), 5.78 (m, 1 H, H4), 4.77–4.70 (m, 1 H, H2), 4.74–4.60 (m, 2 H, H5), 3.80–3.72 (m, 1 H, C*H*OH), 3.43–3.32 (m, 2 H, CH_2N_3), 2.86 (d, *J* = 5.0 Hz, 1 H, OH). Irradiation at δ 4.67 changed the m at 6.05 in to a dd (*J*'s = 6.3 and 2.0 Hz).

^{13}C NMR: δ = 129.01 (d, C3), 125.63 (d, C4), 86.78 (d, C2), 75.65 (t, C5), 72.44 (d, CHOH), 53.39 (t, CH_2N_3).

(2*S*,1′*S*)-(−)-*N*-*tert*-Butoxycarbonyl-2-(2′-amino-1′-hydroxyethyl)-2,5-dihydrofuran [(*S,S*)-2]:
A solution of the above azide (2.1 g, 13.8 mmol) in THF (138 mL) was added dropwise under N_2 to an $LiAlH_4$ suspension (0.531 g, 14 mmol, in 86 mL THF). The mixture was first stirred at r.t. for 1 h, then heated at reflux. After 2 h, the excess hydride was quenched at −10 °C with, in sequence, H_2O (1 mL), 15% NaOH (2 mL), H_2O (2 mL), and stirred at r.t. for 15 min. For amine protection, a solution of $(Boc)_2O$ (3.6 g, 16.6 mmol, in THF 8 mL) was added, stirring being continued overnight at r.t. The solid was filtered off and washed with CH_2Cl_2 (2 × 20 mL). The residue after solvent evaporation was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). After solvent evaporation the crude product was subjected to flash chromatography (EtOAc:petroleum ether, 1:1) to give (89%, overall 69% from **1**) the title compound as an oil. Yield: 2.8 g; $[\alpha]_D^{25.8}$: −94.5 (*c* 1.31, $CHCl_3$).

^{1}H NMR (200 MHz): δ = 6.00 (m, 1 H, H3), 5.85 (m, 1 H, H4), 5.35 (br s, 1 H, NH), 4.81–4.59 (m, 3 H, H2+H5), 3.71–3.61 (m, 1 H, C*H*OH), 3.43–3.29 (m, 2 H, OH+C*H*NH), 3.23–3.11 (m, 1 H, C*H*NH), 1.45 (s, 9 H, CMe_3).

^{13}C NMR: δ = 156.41 (s, C=O), 128.36 (d, C3), 126.09 (d, C4), 87.38 (d, C2), 79.21 (s, *C*Me$_3$), 75.41 (t, C5), 72.67 (d, CHOH), 43.09 (t, CH_2N), 28.22 (q, C*Me*$_3$).

(1*S*,4*R*,5*S*,8*S*)-(+)-*N*-*tert*-Butoxycarbonyl-4-(mercuriochloro)-8-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane [(1*S*,4*R*,5*S*,8*S*)-3]:
The Boc-protected amino alcohol **2** (2.65 g, 11.6 mmol) was added at 0 °C under N_2 to a soln of $Hg(CF_3CO_2)_2$ (5.56 g, 12.7 mmol) in THF (200 mL). The mixture was first stirred at 0 °C for 30 min then at r.t. until the starting material was not detectable on TLC (AcOEt:pet. ether, 7:3). To the mixture cooled at −5 °C, brine (5 mL) was added and, after 30 min at r.t., the phases were separated. The organic phase was washed with H_2O:brine 1:1 (5 mL) and dried ($MgSO_4$). After solvent evaporation, the solid residue was dissolved in CH_2Cl_2, filtered on a silica gel plug, and crystallized (EtOAc) to give the title compound as white solid. Yield: 4.14 g (77%); mp 178–180 °C (dec.); $[\alpha]_D^{27.0}$: +62.7 (*c* 0.69, MeOH). Most protons and all the carbons give rise to split NMR signals of about equal intensity.

^{1}H NMR (CD_3OD): δ = 4.80 (m, 1 H, H5), 4.32/4.24 (m's, 1 H, overall, H1), 4.16–3.88 (m, 3 H overall, H3+H8), 3.58 and 3.36 (m's, 1 H each, H7), 2.59/2.45 (m's, 1 H overall, H4), 1.53/1.47 (s's, 9 H overall, CMe_3).

^{13}C NMR (CD_3OD): δ = 156.35/155.81 (s's, C=O), 88.92/88.18 (d's, C1), 81.84/81.36 (s's, *C*Me$_3$), 74.32/73.50 (d's, C8), 73.66/73.35 (t's, C3), 66.09/65.78 (d's, C5), 54.67/53.44 (t's, C7), 51.71/51.31 (d's, C4), 29.10/28.77 (q's, CMe_3).

(2*R*,3*S*,4*S*)-(+)-*N*-*tert*-Butoxycarbonyl-2-vinyl-3,4-dihydroxypyrrolidine:
To the above chloro-mercury derivative (3.4 g, 7.33 mmol) dissolved in degassed MeOH (73 mL) dodecane-1-thiol (1.82 g, 8.8 mmol) was added at r.t. under N_2. The mixture was protected from light, stirred for 4 h, filtered through paper, and the solid washed with MeOH. After solvent evaporation, the crude material was flash chromatographed (EtOAc:pet. ether, 1:1) to give, after crystallization from

benzene, a white solid. Yield: 1.12 g (67%), mp 66–68°C, $[\alpha]_D^{25.4}$: +13.7 (*c* 1.11, $CHCl_3$).

^{1}H NMR (most signals br): δ = 5.87–5.70 (m, 1H, C*H*=CH_2), 5.30–5.10 (m, 2H, CH=CH_2), 4.47 (m, 1H, H2), 4.20 (m, 1H, H4), 4.10 (m, 1H, H3), 3.74 (dd, *J* = 11.5 and 5.8 Hz, 1H, H5), 3.40 (m, 1H, H5), 2.92 and 2.60 (s's, 1H each, OH's), 1.42 (s, 9H, CMe_3).

^{13}C NMR (signals br or split): δ = 155.2 (s, C=O), 134.1/133.9 (d's, *C*H=CH_2), 117.3 (t, CH=*C*H_2), 80.3 (s, *C*Me_3), 77.1 and 73.4 (d's, C4 and C5 interchangeable), 61.8/61.0 (d's, C2), 50.3 (t, C5), 28.39 (q, C*Me*$_3$).

(2*R*,3*S*,4*S*)-(+)-*N*-*tert*-Butoxycarbonyl-2-vinyl-3,4-dibenzyloxypyrrolidine [(*R*,*S*,*S*)-4]:

For protection as dibenzyl ether, the above diol (0.423 g, 1.85 mmol) dissolved in DMF (4.3 mL) was added under N_2 at −10°C to a suspension of NaH in THF (4.3 mL) (0.193 g, 4.8 mmol, washed with hexane). The temperature was allowed to rise up to r.t. under stirring; benzyl bromide (0.60 mL, 5 mmol) was then added dropwise. After 5 h the reaction was quenched with H_2O (0.1 mL) at 0°C and the resulting mixture poured on to EtOAc: benzene 1:1 (50 mL). The organic solution was washed with brine: H_2O 1:1 (10 mL) and dried ($MgSO_4$). The residue after solvent evaporation was flash chromatographed (EtOAc:pet. ether , 1:5.5) to give the title compound as an undistillable oil. Yield: 0.733 g (96%); $[\alpha]_D^{27.0}$: +65.6 (*c* 0.862, $CHCl_3$).

^{1}H NMR: δ = 7.35 (m, 10H, 2Ph's), 5.83 (m, 1H, C*H*=CH_2), 5.25–5.10 (m, 2H, CH=CH_2), 4.67–4.40 (m, 5H overall, H2+2PhCH_2's), 4.12–4.00 (m, 2H, H3+H4), 3.64 and 3.46–3.31 (m's, 2H, H5), 1.42 (s, 9H, CMe_3).

^{13}C NMR (signals br or split): δ = 154.5 (s, C=O); aromatic C's: 138.0/137.7 (s), 128.39 (d, 2C), 127.72 (d, 3C), 127.58 (d). 134.3/133.8 (d, *C*H=CH_2), 116.5 (t, CH=*C*H_2), 83.3/82.9 (d, C3), 79.6 (s, *C*Me_3), 79.6/79.0 (d, C4), 72.28 and 71.96 (t, 2PhCH_2), 60.6/59.8 (d, C2), 48.7/48.2 (t, C5), 28.36 (q, C*Me*$_3$).

(2*R*,3*S*,4*S*)-(+)-*N*-(Vinylacetyl)-2-vinyl-3,4-dibenzyloxypyrrolidine (5):

To the dibenzyloxypyrrolidine (*R*,*S*,*S*)-**4** (0.438 g, 1.07 mmol) dissolved in CH_2Cl_2 (1 mL), TFA (1 mL) was added at r.t. and stirred for 30 min. The residue, after solvent and TFA evaporation at reduced pressure, was dissolved in THF:MeOH 5:1 (3 mL) and $NaHCO_3$ (0.084 g) was added. The suspension was stirred for 15 min, diluted with CH_2Cl_2 (5 mL), and filtered. Evaporation of the solvent left a light brown oil (R_f 0.22, CH_2Cl_2:MeOH, 20:1). To this crude material, dissolved in CH_2Cl_2 (3 mL) containing Et_3N (0.226 mL, 1.6 mmol) and cooled at 0°C, vinylacetyl chloride (0.136 g, 1.3 mmol) was added. The mixture was stirred at r.t. for 4 h and evaporated under reduced pressure. The residue was flash chromatographed (EtOAc:pet. ether 1:3) to give **12** as a colorless oil. Yield: 0.363 g (90%); bp 230°C/0.1 mbar (Kugelrohr); $[\alpha]_D^{26.6}$: +60.7 (*c* 0.789, $CHCl_3$). The presence of two conformers in about 2:1 ratio is inferred from the NMR spectra; the first value of each couple of values given below pertain to the major conformer.

^{1}H NMR: δ = 7.3 (m, 10H, 2Ph), 6.00–5.75 (m, 2H, 2 C*H*=CH_2), 5.33–5.02 (m, 4H, 2 CH=CH_2), 4.47/4.87 (m, 1H overall, CH_2), 4.72–4.51 (m, 4H, 2 PhCH_2), 4.22–3.98 (m, 2H, H3+H4), 3.80–3.71 (m, 1H, H5), 3.61/3.38 (m, 1H overall, H5), 3.05 (m, 2H, CH_2C=O).

^{13}C NMR: δ = 170.6/169.7 (s's, C=O); aromatic carbons: 137.6/137.7, 137.4/137.3 (s), 128.4 (2C), 127.8, 127.7, 127.6, 127.5 (d); 133.9/131.4 and 132.3/130.8 (d, 2 *C*H=CH_2), 117.6/118.1 and 117.2/117.0 (t, 2 CH=*C*H_2), 83.4/82.1 (d, C3), 78.3/79.5 (d, C4), 72.5/72.3 and 72.0/72.3 (t, 2 PhCH_2), 60.7/58.9 (d, C2), 47.9/49.1 (t, C5), 38.6/39.4 (t, *C*H_2C=O).

(1*S*,2*S*,8a*R*)-(+)-1,2-Dibenzyloxy-1,2,3,5,6,8a-hexahydro-5-oxoindolizine [(+)-6]:

A 100-mL, oven-dried, three-necked, round-bottomed flask, equipped with a reflux condenser and an Ar inlet, was charged with bis-(tricyclohexylphosphane)benzylideneruthenium dichloride (0.05 g, 0.061 mmol) and degassed anhyd benzene (50 mL). The diene **5** (0.542 g, 1.44 mmol) was added under Ar into the purple solution. The mixture was slowly brought to reflux, the color changed to orange-brown and, after 2 h, to green, indicating the RCM catalyst was spent. The residue after solvent evaporation was supported on silica gel and purified by flash chromatography (MeOH:EtOAc, 1:10) to give **6** as an oil. Yield: 0.403 g (80%); bp 230°C/0.1 mbar (Kugelrohr); $[\alpha]_D^{26}$: +15.7 (*c* 0.356, $CHCl_3$).

^{1}H NMR: δ = 7.30 (m, 10H, 2 Ph), 5.96–5.78 (m, 2H, H7+H8), 4.68–4.43 (m, 4H, 2 PhCH_2), 4.39 (m, 1H, H8a), 4.09–4.00 (m, 2H, H1+H2), 3.94 and 3.52–3.44 (m, 2H overall, H3), 3.00–2.92 (m, 2H, H6). Irradiation at δ = 2.95 changed the 5.96–5.78 m in to a dd at 5.90 (*J*'s = 10.0 and 2.4 Hz), and a dd at 5.83 (*J*'s = 10.0 and 1.8 Hz).

^{13}C NMR: δ = 166.94 (s, C=O); aromatic carbons: 137.54 and 137.33 (s), 128.51, 128.46, 127.94, 127.6 (d); 124.45 (d, C8), 121.42 (d, C7), 80.69 and 77.50 (d, C1 and C2, interchangeable), 71.58 and 71.31 (t, 2 PhCH_2), 60.99 (d, C8a), 49.18 (t, C3), 32.65 (t, C6).

In the chromatographic purification a minor product was obtained (0.037 g, 8%) whose NMR spectra suggest it to be *N*-but-2-enoyl-2-vinyl-3,4-dibenzoxypyrrolidine (the olefinic region of the ^{13}C spectrum shows three doublets, δ = 139.85, 133.95, 121.50, a triplet at 117.05, in addition to methyl quartet a δ = 15.41) a species which may have reasonably arisen from the starting material by hydrogen migration resulting in the double bond moving into conjugation with the carbonyl.

(1*S*,2*S*,8a*R*)-(+)-1,2-Dibenzyloxy-1,2,3,5,6,8a-hexahydroindolizine:

The above unsaturated lactam **6** (0.397 g, 1.13 mmol) dissolved in THF (5 mL) was added under N_2 to a suspension of $LiAlH_4$ in THF (0.088 g, 2.3 mmol, in 10 mL) and heated at reflux for 5 h. Excess hydride was decomposed at 0°C with 5% aq NH_4Cl (0.2 mL), the solid was filtered, and washed with EtOAc (20 mL). The organic phase was dried ($MgSO_4$), and, after solvent evaporation, the crude material was adsorbed on silica gel and column chromatographed (h 5 cm, Ø 2.5 cm, eluent CH_2Cl_2: MeOH, 20:1) to obtain the product as an oil. Yield: 0.230 g (60%); $[\alpha]_D^{25}$: +41.6 (*c* 0.44, $CHCl_3$).

^{1}H NMR: δ = 7.3 (m, 10H, 2 Ph), 5.90–5.75 (m, 2H, H7+H8), 4.56 (2H, AB q, $\delta\nu$ = 25 Hz, *J* = 12.4 Hz, $PhCH_2$), 4.52 (2H, AB q, $\delta\nu$ = 16 Hz, *J* = 11.8 Hz, $PhCH_2$), 4.08 (ddd, *J* = 6.6, 4.4, and 1.8 Hz, 1H, H2), 3.95 (dd, *J* = 5.1 and 1.8 Hz, 1H, H1), 3.35 (m, 2H overall, H8a+H3), 3.02 (ddd, *J* = 11.5, 5.9, and 3.5 Hz, 1H, H5), 2.75–2.62 (m, 2H, H5+H3), 2.43–2.28 and 2.13–2.00 (m, 2H overall, H6).

^{13}C NMR: Aromatic C's at δ = 138.10 and 137.86 (s), 128.30, 128.24, 127.62 (3C), 127.55 (d); 126.78 (d, C8), 123.92 (d, C7), 83.61 and 82.14 (d, C1 and C2 interchangeable), 71.50 and 71.41 (t, 2 PhCH_2), 62.11 (d, C8a), 56.99 (t, C3), 47.72 (t, C5), 23.66 (t, C6).

(1*S*,2*S*,8a*R*)-(−)-1,2-dihydroxyindolizidine (7):

To a solution of the above hexahydroindolizine (0.20 g, 0.596 mmol, in 10 mL MeOH) was added concd HCl (10 drops) and the mixture hydrogenated at 3.3 bar (0.06 g of 10% Pd on carbon). TLC monitoring indicated the reaction was complete in 8 h. NaOH soln (1.5 mL, 3 M) was added followed by filtration on Celite and flash chromatography (CH_2Cl_2:MeOH: 15% aq NH_3, 82:16:2). The title compound **7** was obtained as a white solid. Yield: 86 mg (91%); mp 137–138°C (benzene); $[\alpha]_D^{26.6}$: −5.8° (*c* 0.885, MeOH).[11]

^{1}H NMR: δ = 4.34–4.00 (br s superimposed to m, 3H overall, 2OH+H2), 3.86 (m, 1H, H1), 3.47 (m, 1H, H3), 3.07 (m, 1H, H5), 2.22–2.14 (m, 1H, H8a), 2.10–1.96 (m, 2H, H3+H5), 1.90–1.80 (m, 1H), 1.75–1.42 (m, 4H), 1.38–1.20 (m, 1H). Irradiation at δ = 4.2 changed the m's at 3.47 and 2.0 into d's (*J* = 10.4 Hz). Irradiation at δ = 2.0 changed the m's at 4.2 and 3.4 in to d's (*J* = 7.0 Hz).

^{13}C NMR: δ = 80.49 (d, C1), 77.58 (d, C2), 66.79 (d, C8a), 61.55 (t, C3), 53.36 (t, C5), 24.81, 24.39, 23.77 (t, C6, C7 and C8 interchangeable).

HRMS (Calcd. for $C_8H_{15}O_2N$: *m*/*z* = 157.11028 (M^+). Found: 157.11034.

MS: m/z = 157 (13), 97 (100), 84 (34), 69 (31), 56 (13), 42 (14), 41 (16).

(2*S*,1′*R*)-(−)-2-(2′-Azido-1′-hydroxyethyl)-2,5-dihydrofuran:
Prepared from epoxide (*S*,*R*)-**1** (2.3 g, 20.5 mmol) as described above for its epimer to give the product as an oil. Yield: 2.67 g (84%); $[\alpha]_D^{25}$: −118.9 (*c* 1.07, $CHCl_3$).

^{1}H NMR: δ = 6.02–5.95 (m, 1 H, H3), 5.86–5.80 (m, 1 H, H4), 4.78–4.70 (m, 1 H, H2), 4.67–4.54 (m, 2 H, H5), 3.76–3.66 (m, 1 H, C*H*OH), 3.42–3.28 (m, 2 H, CH_2N), 3.02 (br s, 1 H, OH).

^{13}C NMR: δ = 128.52 (d, C3), 125.70 (d, C4), 86.98 (d, C2), 75.64 (t, C5), 73.01 (d, CHOH), 53.23 (t, CH_2N).

(2*S*,1′*R*)-(−)-*N*-*tert*-Butoxycarbonyl-2-(2′-amino-1′-hydroxyethyl)-2,5-dihydrofuran, [(*S*,*R*)-2]:
The azido alcohol (1.56 g, 10 mmol) was reduced with $LiAlH_4$ and the amino function protected as described above for the epimer (*S*,*S*)-**2**. The product was a white solid. Yield: 1.87 g (81%); mp 70–71 °C (benzene); $[\alpha]_D^{23}$: −69.1 (*c* 1.03, $CHCl_3$).

^{1}H NMR: δ = 6.06–5.97 (m, 1 H, H3), 5.97–5.88 (m, 1 H, H4), 5.06 (br s, 1 H, NH), 4.83–4.74 (m, 1 H, H2), 4.72–4.58 (m, 2 H, H5), 3.78–3.62 (m, 1 H, C*H*OH), 3.52–3.38 (m, 1 H, CHN), 3.23 (br s, 1 H, OH), 3.19–3.04 (m, 1 H, CHN), 1.45 (s, 9 H, CMe_3).

^{13}C NMR: δ = 157.03 (s, C=O), 128.00 (d, C3), 126.38 (d, C4), 87.42 (d, C2), 79.51 (s, *C*Me$_3$), 75.54 (t, C5), 73.69 (d, CHOH), 43.08 (t, CH_2N), 28.25 (q, C*Me*$_3$).

(1*S*,4*R*,5*S*,8*R*)-(+)-*N*-*tert*-Butoxycarbonyl-4-mercuriochloro-8-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane [(1*S*,4*R*,5*S*,8*R*)-3]:
Obtained from (*S*,*R*)-**2** (1.3 g, 5.68 mmol) by reaction with $Hg(CF_3CO_2)_2$ according to the procedure described for the preparation of the epimer, to give a white solid. Yield: 2.4 g (90%); (i-PrOH); mp 190–195 °C (dec.); $[\alpha]_D^{21}$: +65.9 (*c* 0.52, CH_3OH).

^{1}H NMR (CD_3OD): δ = 4.70/4.63 (m, 1 H overall, H5), 4.40/4.31 (m, 1 H overall, H1), 4.27–3.90 (m, 3 H overall, H3+H8), 3.81–3.66 and 3.18–3.02 (m, 1 H each, H7), 2.56/2.47 (m, 1 H overall, H4), 1.53/1.48 (s, 9 H overall, CMe_3).

^{13}C NMR (CD_3OD): δ = 155.63/154.35 (s, C=O), 83.38/82.89 (d, C1), 82.38/81.78 (s, *C*Me$_3$), 75.17/74.47 (t, C3), 71.80/71.30 (d, C8), 66.70/66.60 (d, C5), 53.02/51.14 (t, C7), 52.47/51.82 (d, C4), 29.34/29.02 (q, C*Me*$_3$).

(2*R*,3*S*,4*R*)-(−)-*N*-*tert*-Butoxycarbonyl-3,4-di-*O*-isopropylidene-2-vinylpyrrolidine, [(−)-8]:
To (1*S*,4*R*,5*S*,8*R*)-**3** (2.4 g, 5.17 mmol), dissolved in MeOH (120 mL), dodecane-1-thiol (1.28 g, 6.2 mmol) was slowly added at r.t. and stirred until the starting material disappeared (about 4 h; TLC monitoring, EtOAc:pet. ether, 3:2). After filtration through Celite, washing (CH_2Cl_2, 20 mL), and solvent evaporation, the residue was dissolved in benzene (62 mL), treated with 2,2-dimethoxypropane (3.2 mL) and cat. PTSA, and brought to reflux. After 3 h (TLC monitoring, Et_2O:pet. ether, 1:5) $NaHCO_3$ was added and, after solvent evaporation and flash chromatography (pet. ether:ether 7:3) the title compound was obtained as a white solid. Yield: 1.04 g (75%); mp 70–71 °C (*n*-hexane); $[\alpha]_D^{22}$: −38.7 (*c* 0.534, $CHCl_3$).

^{1}H NMR: δ = 5.82 (ddd, J = 16.9, 10.2, and 6.6 Hz, 1 H, C*H*=CH_2), 5.27–5.10 (m, 2 H, CH=C*H*$_2$), 4.79–4.70 (m, 2 H, H3+H4), 4.37–4.27 (m, 1 H, H2), 3.77 (m, 1 H, H5), 3.46 (dd, J = 12.6 and 2.5 Hz, H5), 1.51 (s, 3 H, Me), 1.42 (s, 9 H, CMe_3), 1.33 (s, 3 H, Me). Irradiation at δ = 4.74 changed the m's at 4.33, 3.77, and 3.46 in to d's with J of, respectively, 6.65, 12.6, and 12.6 Hz. Irradiation at δ = 4.3 changed the ddd at 5.82 in to a dd, J = 16.9 and 10.2 Hz.

^{13}C NMR: δ = 154.00 (s, C=O), 134.48 (d, C*H*=CH_2), 115.20 (t, CH=C*H*$_2$), 112.35 (s, *C*Me$_2$), 80.85 (d, C3), 79.43 (s, *C*Me$_3$), 77.55 (d, C4), 62.24 (d, C2), 50.28 (t, C5), 27.98 (q, C*Me*$_3$), 26.01 and 24.80 (q, 2 Me).

(2*R*,3*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-hydroxy-2-vinylpyrrolidine (11):
The mercury derivative **10**[4] (3.40 g, 758 mmol) dissolved in MeOH:acetone (9:1, 150 mL) was treated with dodecane-1-thiol (2 g, 9.86 mmol). The oily product was purified by flash chromatography and distilled (Kugelrohr) to give the product. Yield: 1.4 g (87%); bp 135 °C/0.5 mbar; $[\alpha]_D^{23}$: +7.20 (*c* 2.9 $CHCl_3$).

^{1}H NMR: δ = 5.89–5.74 (m, 1 H, C*H*=CH_2), 5.38–5.14 (m, 2 H, CH=C*H*$_2$), 4.40–4.22 (m, 2 H, H2+H3), 3.54–3.35 (m, 2 H, H5), 2.55 (br s, 1 H, OH), 2.12–1.97 and 1.92–1.77 (m, 2 H overall, H4), 1.42 (s, 9 H, CMe_3).

^{13}C NMR (at 45 °C): δ = 154.60 (s, C=O), 134.30 (d, *C*H=CH_2), 117.20 (t, CH=*C*H$_2$), 79.42 (s, *C*Me$_3$), 72.14 (d, C3), 62.55 (d, C2), 43.40 (t, C5), 31.24 (t, C4), 28.33 (q, C*Me*$_3$).

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