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An expedient stereoselective synthesis of polysubstituted piperidin-2-ones

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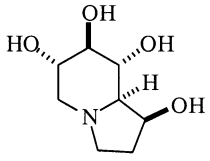
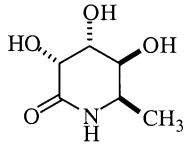
Abstract—A versatile approach to the synthesis of various chiral substituted azido compounds is described. The utility and flexibility of this methodology has been demonstrated by the stereoselective synthesis of optically active polysubstituted piperidin-2-ones which are promising precursors for the synthesis of several indolizidine and piperidine alkaloids. © 2002 Published by Elsevier Science Ltd.

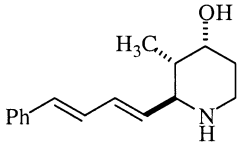
Many sugar-like alkaloids (azasugars) such as polyhydroxylated piperidines and pyrrolidines have been isolated from plants and microorganisms and received a great deal of attention since some of these compounds have been shown to possess potent inhibitory activity against various glycosidases and others exhibit antibiotic, antiviral or anticancer activity.[1] Some lactams have also been shown to be effective glycosidases inhibitors[2,3] and have proven to be effective intermediates for the synthesis of indolizidine, piperidine and pyrrolidine alkaloids.[4]



Castanospermine
Antiviral, anticancer



Glycosidase inhibitor



(+)-Dienomycine
Antibiotic activity

Our interest was to develop a facile synthesis of new optically active substituted δ-lactams via various functionalized azido compounds, starting from readily available polyhydroxylated enoates and dienoates.[5] With that aim, the azido function had to be introduced with good regio- and stereoselectivity in various positions on the polyols before achieving the chemoselective transformation of those azides in a stereoselective and efficient way, to the corresponding substituted piperidin-2-ones, which are precursors for polyhydroxylated indolizidines and piperidines.

Our approach to these compounds started from the octadienedioate **1** readily available from D-mannitol according to a previously reported method.[5] It has been shown[5] that the bulky *tert*-butyldimethylsilyl protecting group on the central diol leads to a high facial selectivity in the reactions on the C=C double bonds of this class of compounds. The key step was the introduction of the azido function that would allow us to obtain the lactam derivatives. Three ways were investigated to prepare the necessary 4-azidodienedioate: treatment of the monosilylated compound **1** under Mitsunobu conditions (TPP, DEAD, HN_3) gave, with a moderate yield (56%) an inseparable mixture of azide **5a** and another compound we tentatively assign structure **5b** (**5a/5b** varying from 50:50 to 80:20). A similar mixture was obtained when the tosylate group of **2** was displaced by sodium azide in dimethylformamide as outlined in Scheme 1. Mitsunobu

Keywords: stereoselective synthesis; piperidin-2-ones; indolizidine .
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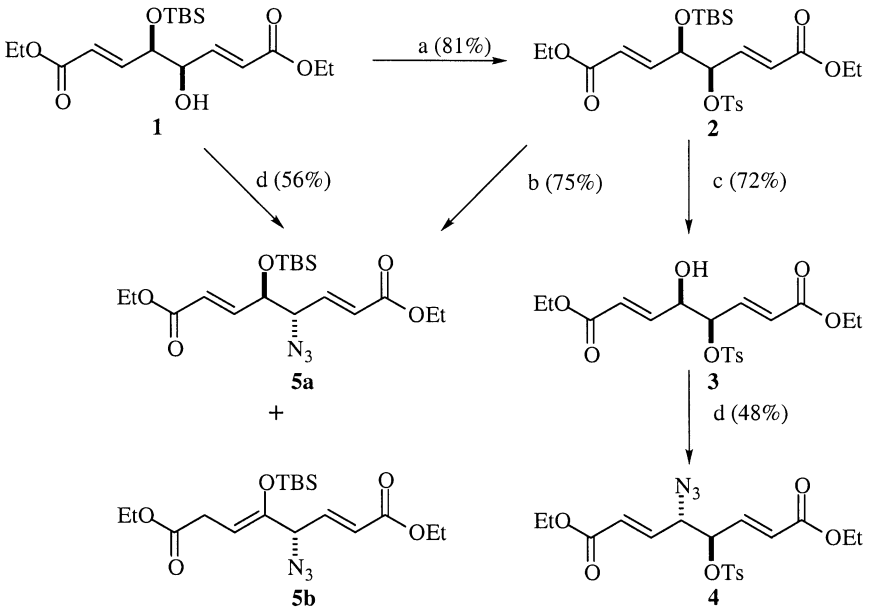


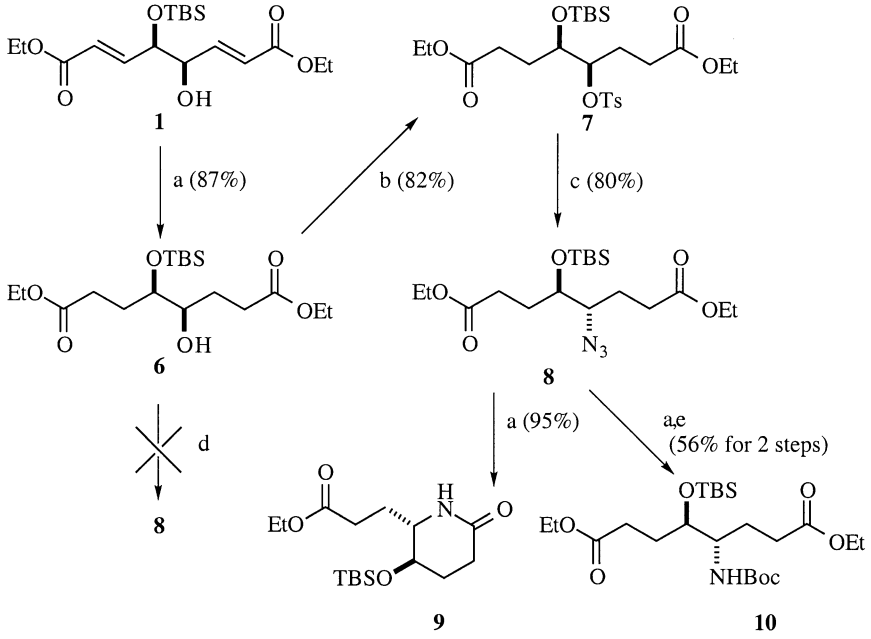
Scheme 1. (a) TsCl, Pyr/$CHCl_3$, (b) NaN_3, DMF, (c) HF, CH_3CN, (d) HN_3, TPP, DEAD, THF.

displacement of the hydroxyl group of compound **3** was successful however.

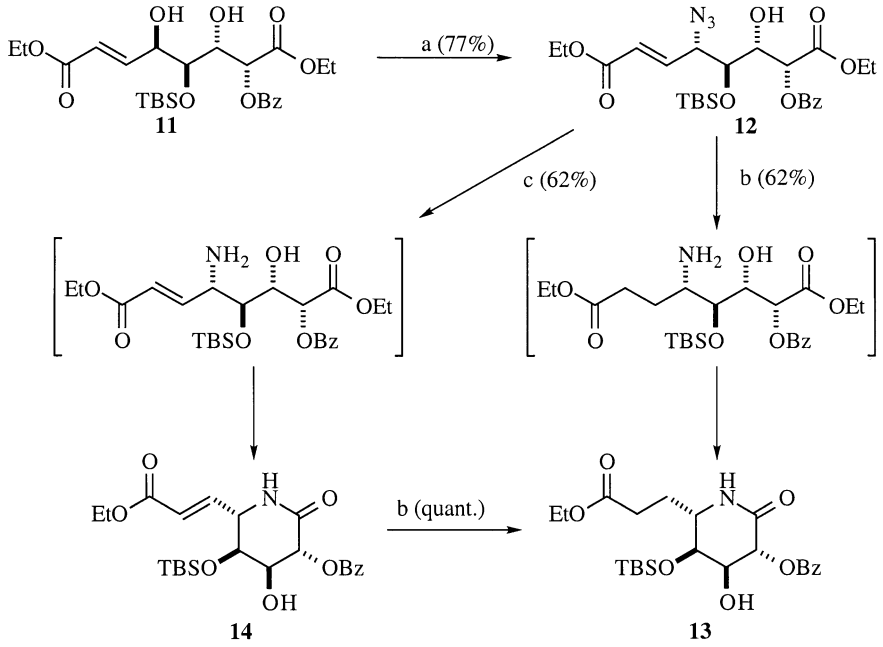
Catalytic hydrogenation of the mixture of **5a** and **5b** in order to obtain lactams directly through a reductive cyclization led to a complex mixture that was not further investigated.

An alternative pathway to functionalize the 5-position of compound **1** was thus devised. After catalytic hydrogenation of **1**, all attempts to introduce the azido group on the saturated compound **6**, using Mitsunobu technology, failed. Substitution of the tosyl group of **7** was successful and azide **8** was formed in good yield. Compound **8** was easily converted into the desired monohydroxylated chiral δ-lactam **9** by catalytic hydrogenation. The intermediate amine could be isolated as its Boc-derivative **10** by protection of the crude product immediately after hydrogenation of the azide **8** (Scheme 2).

In order to synthesize a series of chiral polyhydroxylated δ-lactams we studied the synthesis of the azide synthon **12** starting from the allylic alcohol **11** prepared according to a previously reported method.[5] Selective Mitsunobu inversion using TPP, DEAD, HN_3 at the allylic hydroxyl of **11**, afforded the desired azide **12** with no isomerisation. Catalytic hydrogenation of compound **12** in ethanol in the presence of Pd/C led to the corresponding amine which underwent spontaneous cyclization to give a sole product



Scheme 2. (a) H_2, 10% Pd/C (b) TsOTs, CH_2Cl_2, Pyr, (c) NaN_3, DMF, (d) HN_3, TPP, DEAD, THF, (e) $(Boc)_2O$, CH_2Cl_2.



Scheme 3. (a) HN_3, TPP, DEAD, THF, (b) H_2, 10% Pd/C, (c) TPP, THF/H_2O, reflux.

in 62% yield that appeared to be the δ-lactam **13**, according to the presence in the ^{13}C NMR spectrum of the signal corresponding to an amide carbonyl at 172 ppm. However, the formation of the corresponding γ-lactam could not be excluded. To confirm and prove the formation of the lactam **13**, selective reduction of the azide function on **12** should allow us to obtain only the δ-lactam **14** with a *trans* unsaturated side-chain (Scheme 3). The azide **12** was reacted with triphenylphosphine in refluxing THF in the presence of water (Staudinger reaction). This afforded directly the expected δ-lactam **14** in 62% yield. Catalytic hydrogenation of lactam **14** with H_2 in the presence of Pd/C led quantitatively to the lactam **13**, proving its structure. The IR bands appearing at 1669, 1683, 1691 cm^{-1}, respectively for δ-lactams **9**, **13** and **14** were attributed to the amido carbonyl which characterized the six-membered ring and were consistent with literature data.[1b] The structures of novel compounds **2**–**14** were all characterized and confirmed on the basis of spectral data and where possible, elemental analysis.

We have demonstrated an efficient synthesis of enantiopure diversely functionalized azide synthons, using stereo- and chemoselective reactions, which offers excellent opportunities for the synthesis of various optically active polysubstituted δ-lactams. This approach allows for the stereoselective introduction of variable substituents on the piperidin-2-one ring. As such this methodology represents a highly attractive and facile procedure for the preparation of indolizidine and piperidine alkaloids which is currently under investigation in our laboratory.

1. Experimental

1.1. General procedures

Melting points were determined on an Electrothermal Melting Point apparatus IA6304 and are uncorrected. Infrared spectra (neat product) were recorded on a Perkin–Elmer SPECTRUM 1000 FTIR spectrometer. Optical rotations were recorded on an Optical Activity AA 1000 polarimeter using a 0.5 dm cell at 20°C. Concentrations are given in g/100 mL. NMR spectra were recorded on a Brüker ARX400 spectrometer (^1H: 400 MHz, ^{13}C 100 Hz 100 MHz) in $CDCl_3$ using Me_4Si as an internal reference for ^1H and the solvent peak at δ 77.1 ppm for ^{13}C. Chemical shifts are expressed in parts per million downfield. Analytical thin layer chromatography were performed on precoated Merck plates (silica gel 60) with fluorescence indicator (254 nm). Elemental analyses were performed by the Microanalytical Laboratory, operated by the analytical department at Instituto Superior Técnico (Portugal).

1.1.1. Diethyl (4*R*,5*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-5-(toluene-4-sulfonyloxy)-octa-2(*E*),6(*E*)-dienedioate 2. To 500 mg (1.34 mmol) of **1** in 5 mL of chloroform was added 384 mg (1.5 equiv.) of tosyl chloride in 3 mL of chloroform and 216 μL of pyridine (2 equiv.) at 0°C. The mixture was stirred at rt for 72 h. The solvent was evaporated, the crude product was dissolved in toluene, filtered and concentrated under reduced pressure. The resulting syrup (900 mg) was purified by flash chromatography (Hex/AcOEt 4:1) to give 570 mg (81%) of **2** as a colorless syrup which crystallized after standing below 4°C for several days. Mp 49–52°C; $[\alpha]_D^{20}=+6.7$ (*c* 0.60, $CHCl_3$); IR (cm^{-1}, ν): 1723.48 (C=O), 1663.12 (C=C), 1597.93 (arom.); ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J*=8.0 Hz, arom.); 7.34 (d, 2H, arom.); 6.80 (dd, 1H, *J*=15.6, 5.0 Hz, H-6); 6.67 (dd, 1H, *J*=15.8, 5.0 Hz, H-3); 6.03 (dd, 1H, *J*=15.6, 1.5 Hz, H-7); 5.86 (d, 1H, *J*=15.8, 1.7 Hz, H-2); 4.96 (ddd, 1H, *J*=1.5, 5.0, 5.0 Hz, H-5); 4.51 (dt, 1H, *J*=1.7, 5.0, 5.0 Hz, H-4); 4.26–4.09 (m, 4H, 2× OCH_2CH_3); 2.04 (s, 3H, CH_3, Ts); 1.32–1.23 (m, 6H, 2× OCH_2CH_3); 0.88 (s, 9H, *t*Bu); 0.05 (s, 3H, CH_3, TBDMS); 0.03 (s, 3H, CH_3, TBDMS); ^{13}C NMR: 165.77, 165.14

(C═O); 145.47 (quat. Ts); 143.58 (C-6); 138.79 (C-3); 133.29 (quat Ts); 130.18, 130.03 (Ts); 124.88 (C-2); 123.89 (C-7); 80.31 (C-4); 72.15 (C-5); 60.75, 60.67 (2× OCH_2CH_3); 25.74 (*t*Bu); 21.72 (CH_3, Ts); 18.13 (quat. *t*Bu); 14.26, 14.19 (2×OCH_2CH_3); −4.86, −5.04 ($SiCH_3$).

Anal. calcd for $C_{25}H_{36}O_8SSi$: C 57.01; H 7.27. Found: C 56.99; H 7.21.

1.1.2. Diethyl (4*R*,5*R*)-4-hydroxy-5-(toluene-4-sulfonyloxy)-octa-2(*E*),6(*E*)-dienedioate 3. To a stirred solution of **2** (250 mg, 0.475 mmol) in acetonitrile (10 mL) was added 337 μL of 40% aqueous HF (16 equiv.). The mixture was stirred for 40 h at rt then quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3×10 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification of the crude product by preparative TLC (Hex/AcOEt 7:3) yielded 150 mg (72%) of **3** as a colorless oil. $[\alpha]_D^{20}$= +25.2 (*c* 0.53, $CHCl_3$); IR (cm^{-1}, ν): 3474.54 (OH), 1722.71, 1712.29 (C═O), 1663.12 (C═C), 1597.93 (arom.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J*= 8.0 Hz, arom. Ts); 7.27 (d, 2H, *J*=7.8 Hz, arom. Ts); 6.75–6.65 (m, 2H, H-3, H-6); 6.05 (d, 1H, *J*=15.6 Hz, H-7); 5.89 (d, 1H, *J*=15.7 Hz, H-2); 5.04 (dd, 1H, *J*=5.1, 5.1 Hz, H-5); 4.46 (bm, 1H, H-4); 4.15–4.04 (m, 4H, 2×OCH_2CH_3); 3.76 (bs, 1H, OH); 2.37 (s, 3H, CH_3 Ts); 1.21 (2 partially overlapped t, 6H, 2×OCH_2CH_3); ^{13}C NMR: 165.8, 165.1 (C═O); 145.4 (quat. Ts); 143.2 (C-6); 139.1 (C-3); 132.8 (quat. Ts); 129.9, 127.9 (arom. Ts); 125.2 (C-7); 123.7 (C-2); 81.0 (C-5); 71.3 (C-4); 60.8, 60.6 (OCH_2CH_3); 21.6 (CH_3 Ts); 14.0 (OCH_2CH_3).

1.1.3. Diethyl (4*S*,5*R*)-4-azido-5-(toluene-4-sulfonyloxy)-octa-2(*E*),6(*E*)-dienedioate 4. To 200 mg (0.485 mmol) of **3** dissolved in 5 mL of dry THF was added triphenylphosphine (254 mg, 2 equiv.) and 647 μL of a 1.5 M solution of hydrazoic acid in benzene (2 equiv.). The mixture was stirred for 15 min then DEAD (169 μL in 1 mL of THF, 2 equiv.) was added dropwise for 5 min. After 10 min the solvent was evaporated and the crude product was purified by flash chromatography (Hex/EtOAc 4:1) to yield **4** (101 mg, 48%) as a yellow syrup. $[\alpha]_D^{20}$=+1.4 (*c* 0.74, $CHCl_3$); IR (cm^{-1}, ν): 2112.64 (N_3), 1722.71, 1712.29 (C═O), 1663.12 (C═C), 1597.74 (arom.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J*=8.0 Hz, arom Ts); 7.36 (d, 2H, *J*=7.9 Hz, arom Ts); 6.70–6.60 (m, 2H, H-3, H-6); 6.08 (d, 1H, *J*=15.5 Hz, H-7); 5.98 (d, 1H, *J*= 16.7 Hz, H-2); 5.11 (m, 1H, *J*=4.6 Hz, H-5); 4.40 (m, 1H, *J*=4.6 Hz, H-4); 4.25–4.12 (m, 4H, 2×OCH_2CH_3); 2.45 (s, 3H, CH_3, Ts); 1.33–1.25 (m, 6H, 2×OCH_2CH_3); ^{13}C NMR: 164.76, 164.67 (C═O); 145.58 (quat. Ts); 137.69, 137.52 (C-3, C-6); 132.98 (quat. Ts); 129.97, 127.94 (arom. Ts); 126.60, 126.36 (C-2, C-7); 79.44 (C-5); 64.39 (C-4); 60.95, 60.89 (OCH_2CH_3); 21.61 (CH_3 Ts); 14.06 (OCH_2CH_3).

The product was too unstable to obtain a good microanalysis.

1.1.4. Diethyl (4*S*,5*R*)-4-azido-5-(*tert*-butyl-dimethyl-silanyloxy)-octa-2(*E*),6(*E*)-dienedioate 5. To 31 mg (0.059 mmol) of **2** in 1 mL of DMF was added 11 mg (2.7 equiv.) of NaN_3 with stirring under argon. The solution became orange-red and was stirred for 1 h (TLC Hex/AcOEt 4:1). The solvent was evaporated and the crude product was purified by preparative TLC to yield 15 mg (75%) of a 80:20 mixture of **5a** and **5b**. **5a**: IR (cm^{-1}, ν) 2109.94 (N_3), 1726.18 (C═O), 1658.10 (C═C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (dd, 1H, *J*=4.8, 15.6 Hz, H-6); 6.75 (dd, 1H, *J*=6.28, 15.6 Hz, H-3); 4.37 (m, 1H, H-5); 4.20–4.07 (m, 5H, 2×OCH_2CH_3, H-4); 1.25 (2t, superposed, 6H, 2×OCH_2CH_3); 0.88 (s, 9H, *t*Bu); 0.06 (s, 3H, $SiCH_3$); 0.01 (s, 3H, $SiCH_3$). **5b**: $[\alpha]_D^{20}$=+79.8 (*c* 1.08, $CHCl_3$); IR (cm^{-1}, ν): 2112.45 (N_3), 1727.33 (C═O), 1657.52 (C═C); ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.94 (dd, 1H, *J*=15.6, 3.2 Hz, H-3); 6.21 (dd, 1H, *J*=15.6, 2.4 Hz, H-2); 5.05 (dd, 1H, *J*=7.2, 6.8 Hz, H-6); 4.97 (dd, 1H, *J*=3.2, 2.4 Hz, H-4); 4.21 (q, 2H, CH_2, Et); 4.14 (q, 2H, CH_2, Et); 3.12 (m, 2H, AB part of an ABX system, H-7,7′); 1.35–1.23 (m, 6H, CH_3, Et); 0.94 (s, 9H, Si*t*Bu); 0.12 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR: 170.89, 165.39 (C═O); 146.67 (C-3); 136.96 (C-5); 122.52 (C-2); 109.30 (C-6); 75.22 (C-4); 60.75, 60.57 (OCH_2CH_3); 31.86 (C-7); 25.58 (Si*t*Bu); 18.07 (quat. *t*Bu), 14.13 (OCH_2CH_3); −5.06, −5.34 ($Si(CH_3)_2$). Anal. calcd for $C_{18}H_{31}N_3O_5Si$: C 54.38; H 7.86; N 10.57. Found: C 54.20; H 7.72; N 10.11.

1.1.5. Diethyl (4*R*,5*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-5-hydroxy-octanedioate 6. 138 mg (0.37 mmol) of **1** were shaken for 0.5 h under pressure of hydrogen (10 psi) in the presence of 20 mg (5% mol of Pd) of 10% Pd/C. When TLC (Hex/AcOEt 4:1) monitoring showed total disappearing of starting material and formation of a single compound (invisible by UV), the mixture was filtered and solvent evaporated. Flash chromatography of the crude product gave **6** (122 mg, 87%) as a clear oil. $[\alpha]_D^{20}$=+7.3 (*c* 0.55, $CHCl_3$); IR (cm^{-1}, ν): 3527.76 (OH); 1779.02, 1722.90 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (m, 4H, 2×OCH_2CH_3); 3.59 (m, 1H, H-4); 3.44 (m, 1H, H-5); 2.52–2.39 (m, 2H, H-2, H-2′); 2.38–2.30 (m, 2H, H-7, H-7′); 2.27 (d, 1H, *J*=7.2 Hz, OH); 2.00–1.85 (m, 1H, H-3); 1.82–1.63 (m, 3H, H-3, H6, H-6′); 1.23 (m, 6H, 2× OCH_2CH_3); 0.89 (s, 9H, *t*Bu); 0.08 (s, 3H, $SiCH_3$); 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR: 173.79, 173.35 (C═O); 73.98 (C-4); 72.18 (C-5); 60.31 (CH_2, Et); 30.86, 29.62 (C-2, C-7); 28.77, 28.46 (C-3, C-6); 25.81 (*t*Bu); 18.02 (quat. *t*Bu); 14.15 (CH_3, Et); −4.37, −4.67 ($SiCH_3$). Anal. calcd for $C_{18}H_{36}O_6Si$: C 57.41; H 9.64. Found: C 57.38; H 9.59.

1.1.6. Diethyl (4*R*,5*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-5-(toluene-4-sulfonyloxy)-octanedioate 7. To 0.721 g (1.92 mmol) of **6** dissolved in 20 mL of dry CH_2Cl_2 was added 0.31 mL of pyridine followed by 1.289 g (2 equiv.) of TsOTs. The mixture was stirred for 2 h at rt then 7 mL of 1N aqueous HCl was added. The organic phase was separated, washed with saturated $NaHCO_3$, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent Hex/EtOAc 6:1) to yield 0.966 g (95%) of **7** as a colorless syrup. $[\alpha]_D^{20}$=+34.5 (*c* 0.84, $CHCl_3$); IR (cm^{-1}, ν): 1732.54 (C═O), 1598.32 (arom.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J*=8.0 Hz, arom. *ortho*); 7.35 (d, 2H *J*=8.0 Hz, arom. *meta*); 4.47 (ddd, 1H, *J*=10.3, 3.9, 2.7 Hz, H-4); 4.18–4.00 (m, 4H, 2×OCH_2CH_3); 3.80 (ddd, 1H, *J*=9.4, 3.9, 1.9 Hz, H-5); 2.47–2.03 (m, 8H with 1s (2.47), CH_3 (Ts), H-2,2′,7,7′,3); 1.95–1.59 (m, 3H, H-3′,6,6′); 1.30–1.20 (m, 6H, 2×OCH_2CH_3); 0.86 (s, 9H,

Si*t*Bu); 0.06 (s 3H, $SiCH_3$); 0.01 (s 3H, $SiCH_3$). Irradiation at 4.47 ppm showed *inter alias* the signal of H-5 at 3.80 ppm as a dd (J=9.4, 1.9 Hz). Irradiation at 3.80 ppm showed *inter alias* the signal of H-4 at 4.47 ppm as a dd (J=10.3, 2.2 Hz). ^{13}C NMR: 173.34, 172.71 (C=O); 145.10 (Ts quat.); 134.01 (Ts quat.); 130.03 (arom. *ortho*); 128.08 (arom. *meta*); 82.62 (C-4); 71.21 (C-5); 60.41 (2× OCH_2CH_3); 30.67, 29.98 (C-2, C-7); 25.64 (Si*t*Bu); 21.55 (C-3, C-6); 17.74 (quat. Si*t*Bu); 14.14, 14.08 (2×OCH_2CH_3); −4.65, −5.22 ($SiCH_3$). Anal. calcd for $C_{25}H_{42}O_8SSi$: C 56.57; H 7.98; S 6.04. Found: C 56.37; H 8.07; S 6.21.

1.1.7. Diethyl (4*S*,5*R*)-4-azido-5-(*tert*-butyl-dimethyl-silsanyloxy)-octanedioate 8. To 0.205 g (0.39 mmol) of **7** dissolved in 6 mL of dry DMF and kept under argon was added 31 mg (1.2 equiv.) of NaN_3. The mixture was warmed to 80°C and stirred for 5 h (followed by TLC, hex/AcOEt 4:1). It was then cooled to rt and diluted with 50 mL of CH_2Cl_2, washed with water and dried over sodium sulfate. Evaporation of the solvent and purification by flash column chromatography (eluent Hex/AcOEt 1:6) yielded **8** (0.137 g, 88%) as a colorless oil. $[\alpha]_D^{20}$=−15.6 (*c* 0.36, $CHCl_3$); IR (cm^{-1}, ν): 2101.63 (N_3), 1735.36 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17–4.10 (m, 4H, 2×OCH_2CH_3); 3.82 (m, 1H, J=3.5 Hz, H-5); 3.48 (dt, 1H, J=3.20, 10.56 Hz, H-4); 2.59–2.28 (m, 4H, H-2,2′,7,7′); 1.90–1.57 (m, 4H, H-3,3′,6,6′); 1.28–1.23 (m, 6H, 2× OCH_2CH_3); 0.91 (s, 9H, Si*t*Bu); 0.10 (s, 3H, $SiCH_3$); 0.07 (s, 3H, $SiCH_3$). ^{13}C NMR: 173.65, 173.10 (C=O); 74.00 (C-5); 66.50 (C-4); 60.59, 60.44 (2×OCH_2CH_3); 31.15, 29.80, (C-2, C-7); 26.97 (C-3); 25.75 (Si*t*Bu); 25.63 (C-6); 17.93 (quat. Si*t*Bu); 14.14 (2×OCH_2CH_3); −4.39, −4.97 ($SiCH_3$). Anal. calcd for $C_{18}H_{35}N_3O_5Si$: C 53.84; H 8.78; N 10.46. Found: C 54.23; H 8.72; N 10.56.

1.1.8. (5*R*,6*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-6-(2-ethoxycarbonylethyl)-piperidin-2-one 9. The azide **8** (0.336 g, 0.84 mmol) was dissolved in 10 mL of absolute ethanol and shook for 3.5 h under a pressure of 50 psi of H_2 in the presence of 75 mg of 10% Pd/C. The catalyst was filtered off and washed several time with ethanol and AcOEt. The solvent was evaporated and the remaining syrup was allowed to stand overnight at room temperature. Purification of the resulting crude solid product (0.205 g, 95%) by medium pressure column chromatography (AcOEt) yielded analytically pure **9** (78%) as a white solid. Mp 79–80°C; $[\alpha]_D^{20}$=−31.5 (*c* 0.55, $CHCl_3$); IR (cm^{-1}, ν): 3188.26, 3079.78 (NH), 1726.29 (CO_2Et), 1669.51, (N–C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (bs, 1H, NH); 4.12 (q, 2H, OCH_2CH_3); 3.71 (m, 1H, H-5); 3.25 (m, 1H, H-6); 2.52 (ddd, 1H, J=6.8, 7.2, 18.0 Hz, H-8); 2.39 (m, 2H, J=16.4 Hz, H-3,3′); 2.27 (ddd, 1H, J=6.4, 6.8, 18.0 Hz, H-8′); 1.92 (m, 2H, H-4, H-7); 1.82–1.66 (m, 2H, H-4′, H7′); 1.24 (t, 3H, OCH_2CH_3); 0.86 (s, 9H, *t*Bu); 0.06 (s, 6H, $SiCH_3$); ^{13}C NMR: 173.13, 172.01 (C=O); 68.08 (C-5); 60.59 (OCH_2CH_3); 58.82 (C-6); 30.27 (C-3); 29.15 (C-4); 27.63 (C-8); 27.00 (C-7); 25.59 (Si*t*Bu); 17.82 (quat. Si*t*Bu); 14.08 (OCH_2CH_3); −4.59 ($SiCH_3$), −5.01 ($SiCH_3$). Anal. calcd for $C_{16}H_{31}NO_4Si$: C 58.32; H 9.48; N 4.25. Found: C 58.14; H 9.47; N 4.14.

1.1.9. Diethyl (4*S*,5*R*)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyl-dimethyl-silanyloxy)-octanedioate 10. The azide **8** (0.270 g, 0.67 mmol) was hydrogenated as described earlier. Evaporation of the solvent yielded 0.243 g of a syrup that was dissolved in 6 mL of dry DCM under argon. 0.166 g (1.1 equiv.) of $(Boc)_2O$ and 0.206 mL of Et_3N were added at room temperature and the mixture was stirred overnight. The reaction was quenched with HCl 1N (10 mL) and the organic phase was decanted. The aqueous phase was extracted with 3×12 mL of DCM and the combined organic extract were dried over sodium sulfate. Evaporation of the solvent yielded 0.333 g of crude product that was purified by medium pressure column chromatography (Hex/AcOEt 1:7 then 1:1) to give 0.184 g (57% from **8**) of **10** as a colorless syrup. $[\alpha]_D^{20}$=−14.0 (*c* 2.0, $CHCl_3$); IR (cm^{-1}, ν): 3380.73 (NH), 1735.16 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (bd, 1H, J=9.28 Hz, NH); 4.15–4.08 (m, 4H, 2×OCH_2CH_3); 3.73 (bs, 1H, H-5); 3.53 (bs, 1H, H-4); 2.36 (m, 4H, H-2,2′,7,7′); 1.92–1.51 (m, 4H, H-3,3′,6,6′); 1.41 (s, 9H, *t*Bu (Boc)); 1.24 (m, 6H, 2×OCH_2CH_3); 0.88 (s, 9H, Si*t*Bu); 0.07 (s, 3H, $SiCH_3$); 0.05 (s, 3H, $SiCH_3$). ^{13}C NMR: 173.89, 173.55 (C-1, C-8); 155.70 (C=O, Boc); 79.23 (*t*Bu quat); 73.68 (C-5); 60.43 (2×OCH_2CH_3); 53.66 (C-4); 31.03, 30.11, (C-7, C-2); 28.75 (C-6*); 28.30 (*t*Bu, Boc) 25.81 (Si*t*Bu); 23.68 (C-3*); 17.98 (quat. Si*t*Bu); 14.11 (2×OCH_2CH_3); −4.56, −4.76 ($SiCH_3$). Anal. calcd for $C_{23}H_{45}NO_7Si$: C 58.07; H 9.53; N 2.94. Found: C 58.24; H 9.56; N 3.02.

1.1.10. Diethyl (4*R*,5*S*,6*S*,7*R*)-4-azido-7-benzoyloxy-5-(*tert*-butyl-dimethyl-silanyloxy)-6-hydroxy-oct-2-enedioate 12. To 151 mg (0.3 mmol) of diol **11**[5] in 5 mL of anhydrous THF was added triphenylphosphine (0.123 g, 1.5 equiv.) and 0.63 mL of a 1.12 M solution of hydrazoic acid in benzene. DEAD (123 mg in 1 mL of THF) was then added dropwise in 5 min. The mixture was stirred for 15 min then concentrated under reduced pressure to give 495 mg of a residue. Purification by flash chromatography (Hex/AcOEt 7:3) gave **12** (92 mg, 77%) as a viscous oil. $[\alpha]_D^{20}$=−9.9 (*c* 0.83, $CHCl_3$); IR (ν, cm^{-1}): 3431.58 (OH), 2102.38 (N_3), 1727.72 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 2H, J=7.6 Hz, arom. *ortho*); 7.62 (t, 1H, J=7.2, 7.6 Hz, arom. *para*); 7.48 (t, 2H, J=7.6 Hz, arom. *meta*); 6.98 (dd, 1H, J=7.2, 15.6 Hz, H-3); 6.12 (d, 1H, J=15.6 Hz, H-2); 5.37 (s, 1H, H-7); 4.61 (d, 1H, J= 7.6 Hz, H-4); 4.32–4.20 (m, 4H, 2×OCH_2CH_3); 4.08–3.95 (m, 2H, H-5, H-6); 2.64 (d, 1H, J=8.4 Hz, HO-6); 1.35–1.20 (m, 6H, 2×OCH_2CH_3); 0.87 (s, 9H, *t*Bu); 0.11 (s, 3H, $SiCH_3$); −0.10 (s, 3H, $SiCH_3$); ^{13}C NMR: 168.6, 165.7 (C=O); 140.3 (C-3); 133.7, 129.9, 129.1, 128.7 (arom.); 125.4 (C-2); 74.0, 72.6, 72.0 (C-5,C-6,C-7); 65.2 (C-4); 62.2, 60.9 (OCH_2CH_3); 25.9, 18.2 (*t*Bu); 14.2, 14.1 (OCH_2CH_3); −3.7, −5.3 ($SiCH_3$).

The product was too unstable to obtain good microanalysis.

1.1.11. (3*R*,4*S*,5*S*,6*S*)-3-Benzoyloxy-5-(*tert*-butyl-dimethyl-silylanyloxy)-6-(2-ethoxycarbonylethyl)-4-hydroxy-piperidin-2-one 13. The azide **12** (220 mg, 0.4 mmol) was dissolved in 15 mL of ethanol and submitted to a 20 psi pressure of hydrogen in the presence of 10% Pd/C catalyst (22 mg) for 20 min. Then 60 mg more of catalyst was added and the pressure was raised to 45 psi for 6 h. The catalyst was filtered and the solvent evaporated. The crude was

purified by preparative TLC (Hex/EtOAc 7:3) to yield 119 mg (62%) of lactam **13** as a viscous oil. $[\alpha]_D^{20}=+24.7$ (*c* 1.0, $CHCl_3$); IR (ν, cm^{-1}): 1727 (C=O), 1683 (N–C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 2H, *J*=7.2 Hz, arom. *ortho*); 7.58 (t, 1H, *J*=7.2 Hz, arom. *para*); 7.45 (t, 2H, arom. *meta*); 6.62 (bs, 1H exchangeable with D_2O, NH); 5.54 (d, 1H, $J_{2,3}$=8.4 Hz, H-3); 4.22 (dd, 1H, *J*=2.0, 8.8 Hz, H-4); 4.13 (q, 2H, OCH_2CH_3); 4.07 (bs, 1H, H-5); 3.48 (bm, 1H, H-6); 2.51–2.40 (m, 3H, H-8,8′ HO-4 exchangeable with D_2O); 1.96 (m, 1H, H-7); 1.85 (m, 1H, H-7′); 1.25 (t, 3H, OCH_2CH_3); 0.93 (s, 9H, *t*Bu); 0.16 (s, 3H, $SiCH_3$); 0.14 (s, 3H, $SiCH_3$); ^{13}C NMR: 172.55, 167.41, 166.67 (C=O); 133.43, 130.17, 129.54 (quat.), 128.44 (arom.); 73.03, 72.32, 69.20 (C-3, C-4, C-5); 60.96 (OCH_2CH_3); 56.20 (C-6); 30.65, 29.69 (C-7, C-8); 25.76 (*t*Bu); 18.08 (quat. *t*Bu); 14.25 (OCH_2CH_3); −4.59, −4.69 ($SiCH_3$). Anal. calcd for $C_{23}H_{35}NO_7Si$: C 59.33; H 7.58; N 3.01. Found: C 59.47; H 7.59; N 3.03.

1.1.12. (3*R*,4*S*,5*S*,6*S*)-3-Benzoyloxy-5-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-ethoxycarbonyl-vinyl)-4-hydroxy-piperidin-2-one 14. Azide **12** (0.433 g, 0.8 mmol) in 5 mL of dry THF was refluxed in the presence of triphenylphosphine (0.234 g, 1.1 equiv.) and 150 μL of H_2O. Reaction was followed by TLC (Hex/AcOEt 3:7). After 2 h the solvent was evaporated and the crude product purified by preparative TLC (Hex/AcOEt 3:7) to yield **14** (0.234 g, 62%) as a slightly yellow viscous oil. $[\alpha]_D^{20}=+4.4$ (*c* 0.41, $CHCl_3$); IR (ν, cm^{-1}): 1719.97, 1691, 47; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, 2H, *J*=8.0 Hz, arom. *ortho*); 7.58 (t, 1H, *J*=7.2 Hz, arom. *para*); 7.45 (t, 2H, arom. *meta*); 6.92 (dd, 1H, *J*=16.0, 4.4 Hz, H-7); 6.62 (bs, 1H, NH); 6.14 (d, 1H, *J*=16.0 Hz, H-8); 5.65 (d, 1H, *J*=8.8 Hz, H-3); 4.25–4.13 (m, 4H, 2×OCH_2CH_3, H-5, H-6); 4.12 (d, 1H, *J*=8.8 Hz, H-4); 2.57 (bs, 1H, OH-4); 1.31 (t, 3H, 2×OCH_2CH_3); 0.94 (s, 9H, *t*Bu); 0.18 (s, 3H, $SiCH_3$); 0.15 (s 3H, $SiCH_3$); ^{13}C NMR: 167.62, 166.56, 165.40 (C=O); 143.95 (C-7), 133.42 (arom. *ortho*); 130.09 (arom. *para*); 129.25 (arom. quat.), 128.36 (arom. *meta*); 124.17 (C-8); 72.27, 71.87, 68.83 (C-3, C-4, C-5); 60.90 (OCH_2CH_3); 58.01 (C-6); 25.64 (*t*Bu); 18.01 (quat. *t*Bu); 14.15 (OCH_2CH_3); −4.68, −4.88 ($SiCH_3$). Anal. calcd for $C_{23}H_{33}NO_7Si$: C 59.59; H 7.17; N 3.02. Found: C 59.50; H 7.18; N 2.97.

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