An expeditious stereoselective synthesis of natural (−)-Cassine *via* cascade HWE [3 + 2]-cycloaddition process†

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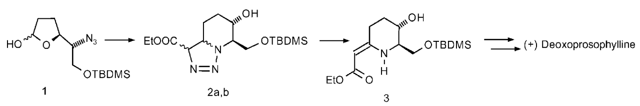
L-Rhamnose is transformed to (−)-Cassine *via* a remarkable four step one pot reaction. The Horner–Wadsworth–Emmons [3 + 2]-1,3-dipolar cycloaddition reaction cascade is the pivotal step in this reaction sequence and makes the synthesis highly efficient.

Introduction

Domino, also called tandem or cascade, reaction processes enable the facile synthesis of complex molecules with different stereogenic centers.[1a–g] This type of reaction is also applicable to the synthesis of piperidine derivatives.[5,6a] In recent years highly substituted piperidines[2] and piperidine alkaloids,[3] especially polyhydroxylated piperidine derivatives (iminosugars), have been the subject of intensive investigations because of their ability to act as glycosidase inhibitors.[4]

In our continuing studies of chiral, non-racemic piperidine derivatives we showed that the tandem Wittig [3 + 2]-cycloaddition process is a general strategy for building up azasugars and piperidine alkaloids with multiple stereogenic centers starting from γ-(sugar)lactol derivatives based on a ring-enlargement reaction.[5,6a] Lactol **1** is an example for this strategy, which was reacted with (ethoxycarbonlymethylene)triphenylphosphorane to the diastereomeric triazolines **2a,b**, which were submitted to a Rh(II)-mediated extrusion of nitrogen to furnish the vinylogous urethane **3**. This material could be easily transformed to (+)-deoxoprosophylline[6a] (Scheme 1).



Scheme 1

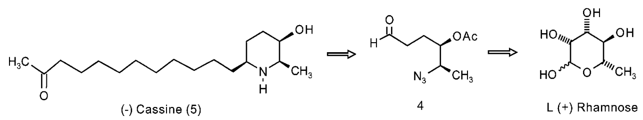
Results and discussion

Surprisingly we found, meanwhile, that the transformation of lactols to piperidine derivatives (*e.g.* **1** to **3**) can be accomplished as a one-pot reaction which makes this process highly attractive and broadens the scope of such a procedure in synthetic organic chemistry.

We envisaged that a 4-hydroxy-5-azidoaldehyde derivative in which the OH-functionality is blocked by a protecting group, therefore preventing lactolisation, should also react according to our tandem Wittig [3 + 2]-cycloaddition methodology.

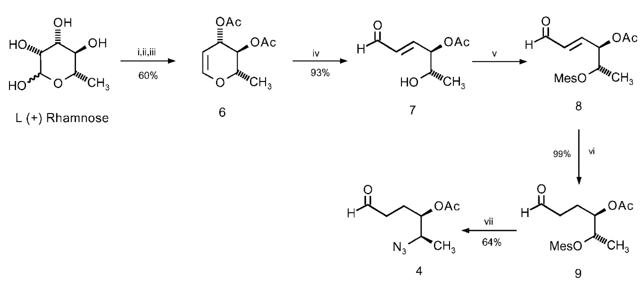
To prove our concept we devised a new route to (−)-Cassine (**5**), an alkaloid which was isolated from the leaves of *Cassia excelsa.* Its structure[7] and absolute configuration was established in 1966.[8] It is reported that (−)-Cassine shows antimicrobial activity against *Staphylococcus aureus*.[9] A series of elegant synthetic routes to (−)-Cassine has been published. All of them are multistep reaction sequences starting from difficult, available enantio-pure or -enriched substrates.[10]

The key intermediate in our reaction sequence is the azidoaldehyde **4** as shown in the retrosynthetic plan (Scheme 2).



Scheme 2

Towards this end, L-(+)-rhamnose, a cheap starting material, was transformed to diacetylrhamnal (**6**) in a three step, one-pot process, modified and optimised according to Laatsch[11] in acceptable yields (60%). The following modified Perlin-oxidation provided the α,β-unsaturated aldehyde **7** in 90% yield (Scheme 3).[12] Both compounds were prepared on a 100 g scale.



Scheme 3 (i) $HClO_4$, Ac_2O, 2 h; (ii) PBr_3, H_2O, 15 °C, 2 h; (iii) Zn/Cu, AcOH/NaOAc, −10 °C, 6 h; (iv) $HgSO_4/H_2O$, acetone; (v) $MeSO_2Cl$/Et_3N, CH_2Cl_2, −20 °C → 20 °C; (vi) Lindlar/H_2, EtOAc; (vii) NaN_3, DMSO, 60 °C, 12 h.

The mesylation of the OH-function, according to standard procedure, proved to be uneventful and mesylate **8** was isolated in moderate yield. It turned out that the chemoselective catalytic hydrogenation of the double bond without reduction of the aldehyde functionality is only successful after careful recrystallisation

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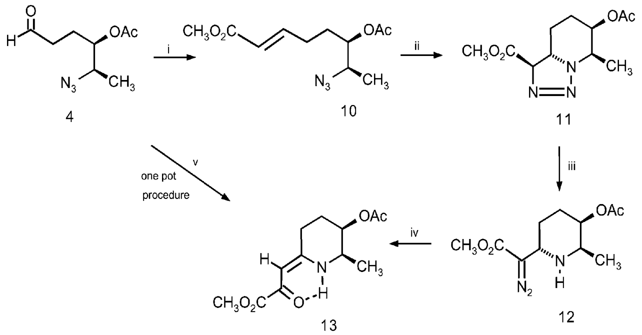
† Dedicated to Professor Dr Fritz Eiden on the occasion of his 80th birthday.

and purification of the mesylate **8**. Contrary to the literature data,[13] the double bond could only be hydrogenated with a Lindlar catalyst without reducing the aldehyde function.

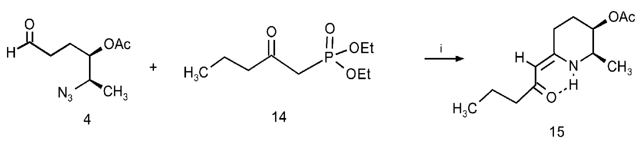
On the basis of our previous work[5,6a] we tested the reactivity of the azide **4** with (methoxycarbonylmethylene)triphenylphosphorane in a Wittig-reaction and found a rapid olefination within 10 min which can be monitored by TLC and NMR spectroscopy. The crystalline ester **10** can be isolated and characterised on preparative scale. In solution a slow 1,3-dipolar cycloaddition of the azide functionality to the double bond of the α,β-unsaturated ester moiety at room temperature was observed. After 41 h, and monitoring the reaction by ^{1}H- and ^{13}C-NMR spectroscopy, a complete conversion of **10** to triazoline **11** was found. The following isomerisation to the diazoester **12** in an equilibrium mixture with **11** (**11** : **12** = 1 : 1) was completed after 45 days. This isomerisation process could be accelerated and brought to completion with a Hunig base or triethylamine (Scheme 4, (v)).



Scheme 4 (i) $CDCl_3$, $MeO_2CCHP(Ph)_3$, 10 min; (ii) 41 h; (iii) 45 days, **11** : **12** = 1 : 1; (iv) $Rh_2(OAc)_4$; (v) (a) CH_2Cl_2, $MeO_2CCHP(Ph)_3$, 2 days, r. t., (b) NEt_3, (5%), 8 h, (c) $Rh_2(OAc)_4$, r. t., 84% yield.

This four step reaction sequence was scaled up and streamlined as a one pot reaction process by reacting azidoaldehyde **4** with (methoxycarbonylmethylene) triphenylphosphorane in methylene chloride for 2 days. After addition of triethylamine the reaction mixture turned yellow and TLC showed a complete conversion to the diazoester **12** after 8 h. When rhodium acetate (dimer) was added (0.132%) an evolution of N_2 started immediately and a spot to spot reaction was observed. After 12 h the vinylogous urethane **13** was isolated by column chromatography in 84% yield (Scheme 4).

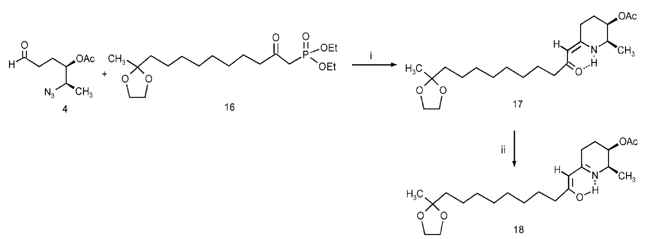
With this reaction in hand it was envisioned that an attempt should be made to introduce the complete side chain of Cassine *via* a HWE-reaction and concomitant cycloaddition. As a model reaction ketophosphonate **14** was reacted with azidoaldehyde **4** following the procedure of HWE–Masamune.[14] After addition of rhodium acetate not unexpectedly the vinylogous amide **15** was isolated in 71% yield (Scheme 5).



Scheme 5 (i) (a) CH_3CN, **9**, DIPEA, 2 days, r. t., (b) $Rh_2(OAc)_4$, 12 h., r. t., 71% yield.

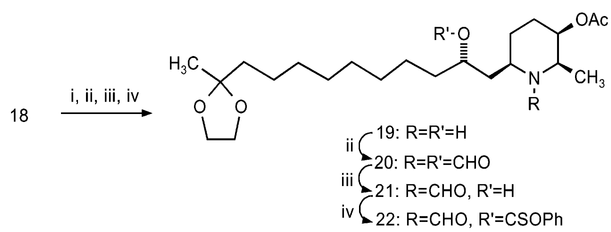
Overall, the two successful model reactions described in Schemes 4 and 5, set the precedent necessary to apply our idea of coupling the appropriate side chain of Cassine to azidoaldehyde **4**.

To this end, **4**, ketophosphonate **16** and DIPEA were dissolved in acetonitrile and stirred until a slight yellow colour appeared. Monitoring by TLC showed complete consumption of **4** and **16**. After addition of rhodium acetate the vinylogous amide **17** was isolated as an oil in 74% yield. Interestingly, upon standing this oil crystallized to colourless needles which turned out to be the tautomeric compound **18** (Scheme 6).



Scheme 6 (i) (a) CH_3CN, **16**, DIPEA, 3 days, r. t., (b) $Rh_2(OAc)_4$, 12 h, r. t., 74% yield; (ii) Crystallisation.

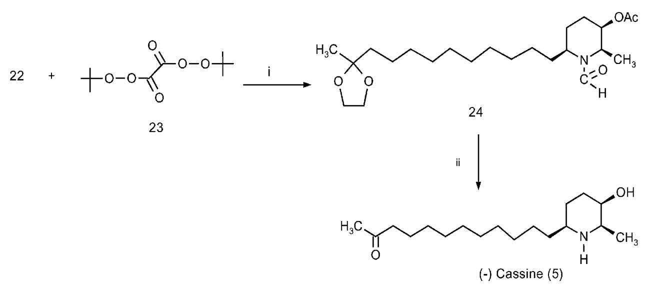
As a result of the formation of the planar enamide functionality, we anticipated that the reduction of both double bonds of **17** or **18**, respectively, over $Pd/C/H_2$ should result in a high diastereoselective hydrogenation from the less shielded α-side.[10b] Indeed the all-*cis* configurated piperidine derivate **19** was isolated in 77% together with 17% of ketone which was separated by column chromatography. The Barton–McCombie deoxygenation was attempted to complete the synthesis. We envisioned that the introduction of the phenylthioformiate group to the hydroxyl functionality should be accomplished with high regioselective control because the attack on the piperidine nitrogen is blocked by steric hindrance.[5a] However various attempts failed and complex mixtures of products were isolated. Therefore formylation of both functional groups with pivaloylformyl anhydride[15] to compound **20** was accomplished in 89% yield. In methanolic ammonia a clean and quantitative deprotection to the alcohol **21** occurred, which was treated with phenylthiochloroformiate in methylene chloride and triethylamine to furnish the thiocarbonate **22** (Scheme 7).



Scheme 7 (i) $Pd/H_2/C$, EtOAc, 74% **19**; (ii) Pivaloylformyl anhydride, CH_2Cl_2, 89% **20**; (iii) MeOH/25% aq. NH_3, 97% **21**; (iv) PhOCSCl, Et_3N, DMAP, CH_2Cl_2, 91% **22**.

We expected the deoxygenation of compound **22** to be straightforward according to the classical Barton–McCombie conditions[16] (Bu_3SnH, AIBN, boiling toluene) but all attempts to provide the fully protected Cassine derivative **24** failed. We reasoned that the harsh reaction conditions and the formamide functionality in the vicinity of the secondary radical might prevent a high selectivity of the reaction.

A similar problem occurred in the synthesis of (*R*)-homobaclofen[17] which was ultimately solved with di-*tert*-butyl peroxyoxalate[18] (**23**) as a radical initiator. Indeed, when **22** was treated with **23** and tributyltin hydride with rigorous absence of oxygen in acetone at room temperature, **24** was isolated in 83% (Scheme 8). Acid hydrolysis of **24** completed the synthesis and provided (−)-Cassine (**5**) in 79% yield (mp. 58 °C, $[\alpha]_D^{20} = -6.5$, ($c = 0.6$, $CHCl_3$)).[19]



Scheme 8 (i) Bu_3SnH, r. t., acetone, 83%; (ii) 2 M H_2SO_4/CH_3OH, rfl. 79%.

In conclusion we have developed a protocol for the preparation of trisubstituted, all-*cis* configurated piperidine derivatives, which employs a cascade reaction as a key step. The synthesis of other bioactive trisubstituted piperidine alkaloids are under current investigation.

Experimental

General details

Reagent grade solvents and reagents were purchased. All reactions with organometallic reagents were carried out under a N_2 atmosphere. THF was freshly distilled from sodium, CH_2Cl_2 from CaH_2. TLC chromatography was performed on glass plates coated with Merck SiO_2 60 F254. The modified Barton–McCombie reaction was done under rigorous exclusion of oxygen. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at $\lambda = 589$ nm and are given 10^{-1} deg cm^2 g^{-1}.

(4*R*,5*R*)-4-Acetoxy-5-azido-hexanal (4). To a solution of mesylate **9** (22.5 g, 89 mmol) in DMSO (200 ml) sodium azide (17.4 g, 267 mmol; 3 equiv.) was added and stirred overnight at 60 °C. After cooling to room temperature, water was added (1000 ml) and the mixture was extracted with five portions (5 × 100 ml) of diethyl ether. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The resulting residue was subjected to column chromatography (silica gel) with EtOAc/petroleum ether 1 : 9). Yield: 11.4 g (64%) of a colourless liquid. R_f: 0.62 (EtOAc/petroleum ether 8 : 2). IR (film): ν (cm^{-1}) = 2995 (w, CH), 2121 (m, N=N=N), 1769 (s, C=O). ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, $^3J_{6,5}$ = 6.8 Hz, 3H, 6-H), 1.82–1.96 (m, 2H, 3-H), 2.04 (s, 3H, O_2CCH_3), 2.39–2.47 (m, 2H, 2-H), 3.37–3.48 (m, 1H, 5-H), 4.83 (m, 1H, 4-H), 9.69 (t, $^3J_{1,2}$ = 1.0 Hz, 1H, 1-H). ^{13}C NMR ($CDCl_3$): δ = 15.7 (C_6), 21.0 (O_2CCH_3), 23.9 (C_3), 40.0 (C_2), 59.2 (C_5), 75.2 (C_4), 170.8 (C=O), 201.1 (C_1). $[\alpha]_D^{20}$ = −3.3 (c = 1.3, $CHCl_3$). $C_8H_{13}N_3O_3$ (199.21) requires C, 48.23; H, 6.58; N, 21.09% found C, 48.27; H, 6.65; N, 20.42%.

Diethyl (2-oxo-pentyl)-phosphonate (14). To a solution of diethyl methylphosphonate (2.60 g, 17.2 mmol) in THF (10 ml) was added a solution of methyllithium in diethyl ether (10.8 ml, 17.2 mmol, 1.6 M) at −78 °C under nitrogen. After 30 min a solution of ethyl butyrate (1.2 ml, 8.6 mmol) in THF (10 ml) was added dropwise. The mixture was stirred at −78 °C for 45 min, quenched with NH_4Cl solution and extracted with CH_2Cl_2 (three times). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated. The residue was distilled: bp. 92 °C/0.06 mbar. Yield: 59%. IR: ν (cm^{-1}) = 2967, 2935, 2910, 2877 (s, CH), 1715 (s, C=O), 1256, 1024 (s, OCH_2). ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, $^3J_{6,5}$ = 7.32 Hz, 3H, 6-H), 1.31 (t, J = 7.04 Hz, 6H, CH_3CH_2O), 1.58 (sext, $^3J_{5,6} = {}^3J_{5,4}$ = 7.32 Hz, 2H, 5-H), 2.57 (t, $^3J_{4,5}$ = 7.32 Hz, 2H, 4-H), 3.04 (d, $^2J_{3,P}$ = 22.76 Hz, 2H, CH_2P), 4.11 (t, $^3J_{CH2,CH3}$ = 7.04 Hz, 4H, CH_3CH_2O). ^{13}C NMR ($CDCl_3$): δ = 13.7 (C_6), 16.5 (CH_3CH_2O), 17.1 (C_5), 42.0 (d, J = 126 Hz, C_3), 46.1 (C_4), 62.5 (CH_2O), 202.2 (C=O).

(*Z*)-(2*R*,3*R*)-2-Methyl-6-(2′-oxo-pentylidene)-3-piperidinyl-acetate (15). To a suspension of lithium chloride (42 mg, 1.00 mmol) in CH_3CN (12 ml) was added phosphonate **14** (222 mg, 1.00 mmol), DIPEA (129 mg, 1.00 mmol) and after 1 min azidoaldehyde **4** (199 mg, 1.00 mmol). The turbid solution became clear after 20 min. Stirring was continued for 12 h and the solution turned yellow (diazoketone). After two days rhodium(II) acetate (2 mg, 4.52 µmol) was added and the solution turned colourless with the evolution of nitrogen. After stirring overnight, CH_2Cl_2 (30 ml) was added and the mixture was extracted with water (30 ml). The organic phase was separated, dried (Na_2SO_4) and filtered. After evaporation of the solvent, the oily residue was purified by column chromatography with diethyl ether. Yield: 169 mg (71%). R_f: 0.42 (diethyl ether). IR (film): ν (cm^{-1}) = 3450 (s, NH), 2980, 2940, 2860 (s, CH), 1730 (C=O) 1600, 1560, 1230. ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.89 (t, 1.24, $^3J_{5',4'}$ = 7.32 Hz, 3H, 5′-H), 1.18 (d, $^3J_{2,Me}$ = 6.80 Hz, 3H, 2-Me), 1.57 (tt, $^3J_{4',5'}$ = 7.32 Hz, $^3J_{4',3'}$ = 7.36 Hz, 2H, 4′-H), 1.86 (m, 1H, 4-H_{ax}), 1.95 (m, 1H, 4-H_{eq}), 2.05 (s, 3H, O_2CCH_3), 2.17 (t, $^3J_{3',4'}$ = 7.36 Hz, 2H, 3′-H), 2.25 (m, 1H, 5-H), 2.50 (m, 1H, 5-H), 3.56 (qd, $^3J_{2,Me}$ = 6.80 Hz, $^3J_{2,3}$ = 3.04 Hz, 1H, 2-H), 4.89 (m, 1H, 1′-H), 5.09 (m, 1H, 3-H), 10.94 (br., 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 13.8 ($C_{5'}$), 17.4 (2-CH_3), 19.4 ($C_{4'}$), 20.9 (O_2CCH_3), 23.5 (C_5), 24.1 (C_4), 43.9 ($C_{3'}$), 49.3 (C_2), 68.4 (C_3), 92.9 (C_1), 162.2 (C_6), 170.4 (O_2CCH_3), 197.9 ($C_{2'}$). $[\alpha]_D^{20}$ = −3.6 (c = 1.14, $CHCl_3$).

Ethyl 9-(2-methyl-(1,3-dioxolan-2-yl))-nonanoate

To a solution of ethyl 10-oxo-decanecarboxylate (5 g) in $CHCl_3$ (20 ml) was added ethylene glycol (1.05 g, 0.016 mol; 1.1 equiv.) and *p*-toluenesulfonic acid (5 mg, 29 µmol). The solution was refluxed overnight. After cooling, the mixture was washed with sat. $NaHCO_3$ solution and the organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. Distillation provided a colourless oil. Yield: 3.47 g (86%), b. p. 110–114 °C/0.06 mbar. ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, ^3J = 7.3 Hz, 3H, CH_3CH_2), 1.29–1.39 (m, 10H, 4-H, 5-H, 6-H, 7-H, 8-H), 1.32 (s, 3H, 2′-CH_3), 1.61–1.65 (m, 4H, 3-H, 9-H), 2.29 (t, $^3J_{2,3}$ = 7.6 Hz, 2H, 2-H), 3.94 (m, 4H, 4′-H, 5′-H), 4.13 (q, ^3J = 7.3 Hz, 2H, CH_3CH_2). ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_2CH_3), 23.6 (2′-CH_3), 23.7, 24.0, 24.9, 29.1, 29.3, 33.9, 39.2, 43.7 (C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9), 60.1 (CH_2CH_3), 64.5 ($C_{4'}$, $C_{5'}$), 110.1 ($C_{2'}$), 173.8 (C_1).

Diethyl [10′-(2′-methyl-1,3-dioxolan-2-yl)-2′-oxo-decyl]-phosphonate (16)

To a stirred solution of methane diethylphosphonate (1.48 g, 9.74 mmol) in abs. THF (20 ml) was added 1.6 M butyllithium (6.09 ml, 9.74 mmol) at −78 °C. The mixture was stirred for 15 min then ethyl 9-(2-methyl-[1,3]-dioxolan-2-yl)-nonanoate (1.33 g, 4.87 mmol) dissolved in abs. THF (10 ml) was added. This mixture was stirred for a further 30 min. A solution of saturated aqueous NH_4Cl (100 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with brine (25 ml), dried (Na_2SO_4) and the solvent was evaporated. Purification by column chromatography (CH_2Cl_2/MeOH 19 : 1) provided **16** as a colourless oil. Yield 1.25 g (68%). R_f: 0.72 (CH_2Cl_2/MeOH 19 : 1). ^{1}H-NMR ($CDCl_3$): δ 1.18–1.31 (m, 19H, 2 × OCH_2CH_3, 2′-CH_3, 5-H, 6-H, 7-H, 8-H, 9-H), 1.50–1.56 (m, 4H, 4-H, 10-H), 2.54 (t, $^3J_{3,4}$ = 7.3 Hz, 2H, 3-H), 3.01 (d, $^2J_{1,P}$ = 22.7 Hz, 2H, 1-H), 3.85 (m, 4H, 4′-H, 5′-H), 4.05 (m, 4H, 2 × OCH_2CH_3). ^{13}C-NMR ($CDCl_3$): δ 16.2 (2′-CH_3), 23.3, 24.0, 28.9, 29.0, 29.2, 29.3, 29.7 (C_4, C_5, C_6, C_7, C_8, C_9, C_{10}), 23.7 (2 × OCH_2CH_3), 42.3 (d, $^1J_{1,P}$ = 126 Hz, C_1), 44.0 (C_3), 62.42, 2.49 (2 × OCH_2CH_3), 64.5 ($C_{4'}$, $C_{5'}$), 110.1 ($C_{2'}$), 202.1/202.2 (C_2). $C_{18}H_{35}O_6P$ (378,45)

(2*R*,3*R*)-2-Methyl-6-[10′-(2′-methyl-1,3-dioxolan-2-yl)-2′-oxo-decyliden]-piperidin-3-yl acetate (17)

(2*R*,3*R*)-2-Methyl-6-[2′-hydroxy-10′-(2′-methyl-1,3-dioxolan-2-yl)-dec-1′-en-yl]-2,3,4,5-tetrahydro-pyridin-3-yl-acetate (18). To a degassed suspension of lithium chloride (56 mg, 1.32 mmol) in abs. acetonitrile (15 ml) was added phosphonate **16** (500 mg, 1.32 mmol), DIPEA (171 mg, 1.32 mmol) and after 1 min azidoaldehyde **4** (263 mg, 1.32 mmol). After 12 h of stirring the resulting colourless solution turned yellow (diazoketone). After 3 days rhodium(II) acetate (2 mg, 4.52 µmol) was added. Under evolution of nitrogen the mixture turned colourless. Stirring was continued overnight then the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (50 ml) and extracted with H_2O (50 ml). The organic phase was dried (Na_2SO_4) and evaporated. Column chromatography provided **17** as a colourless oil. After some hours at 8 °C the oil crystallized as the tautomeric compound **18**. Yield: 386 mg (74%). Mp. 43 °C. R_f: 0.36 (diethyl ether). IR (KBr) ν (cm^{-1}) = 3450 (s, OH, NH), 2950, 2860 (s, CH), 1600 (s, C=C). ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, $^3J_{2,Me}$ = 6.32 Hz, 3H, 2-Me), 1.10–1.44 (m, 13H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 2″-CH_3), 1.55–1.66 (m, 4H, 4′-H, 10′-H), 1.81 (m, 1H, 4-H), 1.99–2.07 (m, 1H, 4-H), 2.11 (s, 3H, O_2CCH_3), 2.25 (t, $^3J_{3',4'}$ = 6.84 Hz, 2H, 3′-H), 2.34 (m, 1H, 5′-H), 2.56 (m, 1H, 5′-H), 3.65 (m, 1H, 2-H), 3.94 (m, 4H, 4″-H, 5″-H), 4.93 (br., 1H, 1′-H), 5.15 (m, 1H, 3-H), 10.89 (br., 1H, OH). ^{13}C NMR ($CDCl_3$): δ = 17.4 (2-CH_3), 20.9 (2″-CH_3), 23.7 (O_2CCH_3), 24.1, 26.1, 29.4, 29.5, 29.6, 29.8 (C_4, C_5, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{8'}$, $C_{9'}$), 39.2 ($C_{10'}$), 42.0 ($C_{3'}$), 49.5 (C_2), 64.6 ($C_{4''}$,$C_{5''}$), 68.3 (C_3), 110.2 ($C_{2''}$), 170.4 (O_2CCH_3). $[\alpha]_D^{20}$ = −35.7 (c = 1.135, $CHCl_3$). $C_{22}H_{37}NO_5$ (395.54) requires C, 66.81; H, 9.43; N, 3.54%, found C, 66.72; H, 9.67; N, 3.79%

(2*R*,3*R*,6*R*)-2-Methyl-[2′-hydroxy-10′-(2′-methyl-1,3-dioxolan-2-yl)-decyl]-piperidin-3-yl-acetate (19). Compound **18** (135 mg, 341 µmol) was dissolved in ethyl acetate (15 ml) and Pd/C 10% (50 mg) was added. The mixture was hydrogenated (50 bar) for 2 days with stirring at room temperature. After filtration, the solvent was removed under vacuum and the oil was purified by column chromatography. CH_2Cl_2/MeOH 9 : 1). Yield: 105 mg (77%) colourless oil. R_f: 0.21 (CH_2Cl_2/MeOH 9 : 1). IR (film): ν (cm^{-1}) = 3600–3100 (s, OH), 2940, 2860 (s, CH), 1730 (s, C=O), 1430, 1360, 1220. ^{1}H NMR ($CDCl_3$): δ = 1.06 (d, $^3J_{2,Me}$ = 6.8 Hz, 3H, 2-Me), 1.22–1.52 (m, 19H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H, 2″-CH_3), 1.53–1.66 (m, 4H, 5-H, 1′-H), 1.71 (m, 1H, 4-H), 2.03 (m, 1H, 4-H), 2.12 (s, 3H, O_2CCH_3), 2.92 (m, 2H, 2-H, 6-H), 3.83 (m, 1H, 2′-H), 3.93 (m, 4H, 4″-H, 5″-H), 4.84 (m, 1H, 3-H). ^{13}C NMR ($CDCl_3$): δ = 18.3 (2-CH_3), 21.1 (O_2CCH_3), 23.7 (2″-CH_3), 24.1, 25.4, 27.5, 29.1, 29.5, 29.7, 29.9, 38.1, 39.2, 42.4 (C_4, C_5, $C_{1'}$, $C_{3'}$,$C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{7'}$, $C_{8'}$, $C_{9'}$, $C_{10'}$), 53.5, 58.1 (C_2, C_6), 64.6 ($C_{4''}$,$C_{5''}$), 69.7 (C_3), 73.0 ($C_{2'}$) 110.2 ($C_{2''}$), 170.4 (O_2CCH_3). $[\alpha]_D^{20}$ = −15.6 (c = 2.3, $CHCl_3$). MH^+ $C_{22}H_{42}NO_5$ requires 400.30575, found MH^+ 400.30535.

(2*R*,3*R*,6*R*)-*N*-Formyl-2-methyl-6-[2′-formyloxy-10′-(2′-methyl-[1,3]-dioxolan-2-yl)-decyl]-3-piperidinyl-acetate (20). To a solution of **19** (98 mg, 245 µmol) in CH_2Cl_2 (30 ml) pivaloylformyl anhydride (67 mg, 515 µmol; 2.1 equiv.) was added with stirring. After 20 min the solvent was removed under vacuum, and the residue was purified by column chromatography (CH_2Cl_2/MeOH 19 : 1). Yield: 99 mg (89%) colourless oil. R_f: 0.46 (CH_2Cl_2/MeOH 19 : 1). IR (film): ν (cm^{-1}) = 2920, 2860 (s, CH), 1740, 1650 (2 × s, C=O), 1420, 1360, 1200. ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, $^3J_{2,Me}$ = 6.56 Hz, 3H, 2-Me), 1.11–1.35 (m, 15H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 2″-CH_3), 1.44–1.89 (m, 10H, 4-H, 5-H, 1′-H, 3′-H, 10′-H), 1.99/2.00 (2 × s, 3H, O_2CCH_3), 3.54/3.99 (2 × m, 1H, 6-H), 3.86 (m, 4H, 4″-H, 5″-H), 4.42/4.71 (2 × m, 1H, 2-H), 4.71 (m, 1H, 3-H), 4.93 (m, 1H, 2′-H), 7.98/8.05 (2 × s, 2H, CHO). ^{13}C-NMR ($CDCl_3$): δ = 16.3 (CH_3), 18.7 (CH_3), 22.8 (CH_2), 22.9(CH_2) 23.0 (CH_3), 23.9 (CH_3), 24.0 (CH_2), 25.0, 25.2, 26.1, 26.2, 29.3, 29.4, 29.5, 34.1, 34.6, 38.5, 39.2, 40.0 (12 × CH_2), 43.3/44.9 (C_2) 49.9/51.4 (C_6), 64.8 ($C_{4''}$,$C_{5''}$), 70.4/71.4 (C_3), 71.5/71.6 ($C_{2'}$) 110.1 ($C_{2''}$), 160.7/161.0 (CHO) 162.2/162.5 (CHO), 169.8/170.1 (O_2CCH_3). $[\alpha]_D^{20}$ = +33.9 (c = 2.0, $CHCl_3$). MS (70 eV, CI): m/z (%) = 456.7 (100) [M + H$^+$], 396.6 (23) [M$^+$ – $C_2H_5O_2$], 227.2 (56).

(2*R*,3*R*,6*R*)-*N*-Formyl-2-methyl-6-[2′-hydroxy-10′-(2′-methyl-[1,3]-dioxolan-2-yl)-decyl]-3-piperidinyl-acetate (21). To a solution of compound **20** (88 mg, 193 µmol) in methanol (15 ml) was added NH_4OH solution (25%, 2 drops) with stirring. The reaction was monitored by TLC. After 5 h the solvent was removed under vacuum. The crude oil is pure enough for the next reaction step. Yield: 79 mg (97%). R_f: 0.15 (CH_2Cl_2/MeOH 19 : 1). IR (film): ν (cm^{-1}) = 3660–3140 (s, OH), 2915, 2860 (2 × s, CH), 1720, 1650 (2 × s, C=O), 1200. ^{1}H NMR ($CDCl_3$): δ = 1.15–1.42 (m, 18H, 2-CH_3, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 2″-CH_3), 1.45–1.91 (m, 10H, 4-H, 5-H, 1′-H, 3′-H, 10′-H), 1.98/2.10 (2 × s, 3H, O_2CCH_3), 3.49 (m, 1H, 2′-H), 3.86 (m, 4H, 4″-H, 5″-H), 3.86/4.02 (2 × m, 1H, 2-H), 4.45/4.74 (2 × m, 1H, 2-H), 4.71 (m, 1H, 3-H), 7.96/8.06 (2 × s, 1H, CHO). ^{13}C-NMR ($CDCl_3$): δ = 16.3 (CH_3), 18.7 (CH_3), 22.8 (CH_2), 22.9 (CH_3) 23.7 (CH_2), 24.0 (CH_3), 25.5, 25.7, 26.2, 26.7, 27.1, 29.5, 29.5, 29.5, 29.6, 29.7, 29.8, 29.8, 37.8, 38.3, 39.2, 43.0, 43.3 (17 × CH_2), 44.8/44.8 (C_2), 50.2/51.6 (C_6), 64.6/64.9 ($C_{4''}$,$C_{5''}$), 69.3/70.0 ($C_{2'}$), 70.7/71.4 (C_3), 110.2 ($C_{2''}$), 162.5/163.0 (CHO), 170.1 (O_2CCH_3). $[\alpha]_D^{20}$ = +17.8 (c = 0.5, $CHCl_3$). $C_{23}H_{41}NO_6$ (427.59). MS (70 eV, CI): m/z (%) = 428.4

(100) [M + H+], 410.3 (16) [$M^+ - H_2O$], 368.3 (16) [$M^+ - C_2H_4O_2$], 340.4 (12) [$M^+ - C_2H_4O_2 - CO$], 227.2 (62).

(2*R*,3*R*,6*R*)-*N*-Formyl-2-methyl-6-[10′-(2′-methyl-[1,3]-dioxolan-2-yl)-2′-phenoxythiocarbonyloxy-decyl]-3-piperidinyl-acetate (22). To a solution of compound **21** (50 mg, 121 μmol) in CH_2Cl_2 (15 ml) phenylchlorothioformiate (23 mg, 133 μmol; 1.1 equiv.), DMAP (16 mg, 133 μmol; 1.1 equiv.) and triethylamine (24 mg, 242 μmol; 2 equiv.) were added with stirring. The reaction was monitored by TLC. After 2 days at room temp. the mixture was extracted with 1 M HCl, washed with H_2O (10 ml) and the organic phase was dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (Et_2O). Yield: 62 mg (91%). R_f: 0.22 (Et_2O). IR (film): ν (cm^{-1}) = 2940, 2860 (s, CH), 1735, 1665 (2 × s, C=O), 1200. ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, $^3J_{2,Me}$ = 7.08 Hz, 3H, 2-Me), 1.27–1.39 (m, 15H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 2″-CH_3), 1.61–2.04 (m, 10H, 4-H, 5-H, 1′-H, 3′-H, 10′-H), 2.06/2.07 (2 × s, 3H, O_2CCH_3), 3.77/4.09 (2 × m, 1H, 6-H), 3.93 (m, 4H, 4″-H, 5″-H), 4.66/4.83 (2 × m, 1H, 2-H), 4.83 (m, 1H, 3-H), 5.44 (m, 1H, 2′-H), 7.11 (m, 2H, Ar–H), 7.29 (m, 1H, Ar–H), 7.42 (m, 2H, Ar–H), 8.08/8.11 (2 × s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ = 14.7/16.8 (CH_3), 20.8/23.7 (CH_3), 21.0, 24.0, 24.0, 25.0, 25.0, 26.8, 27.0, 29.3, 29.4, 29.5, 29.5, 29.8, 29.8, 33.5, 34.1, 38.2, 39.2, 39.7 (18 × CH_2), 43.2/44.9 (C_2), 50.2/51.4 (C_6), 64.6 ($C_{4''}$,$C_{5''}$), 70.4/71.5 (C_3), 83.1/83.4 ($C_{2'}$), 110.1/110.2 ($C_{2''}$), 121.9/122.0 (Ar–C), 126.4/126.7 (Ar–C), 129.5/129.6 (Ar–C), 153.3/153.4 (Ar–C), 162.2/162.4 (CHO), 169.8/170.1 (O_2CCH_3), 194.8/194.9 (OCSO). $[\alpha]_D^{20}$ = −8.1 (*c* = 1.6, $CHCl_3$). $C_{30}H_{47}NO_7S$ (563.76). MS (70 eV, CI): *m*/*z* (%) = 410.3 (78) [$M^+ - C_7H_6O_2S$], 350.3 (54) [$M^+ - C_7H_6O_2S - C_2H_4O_2$], 243.2 (100), 154.2 (13) [$C_7H_6O_2S$].

(2*R*,3*R*,6*S*)-*N*-Formyl-2-methyl-6-[10′-(2′-methyl-[1,3]-dioxolan-2-yl)-decyl]-3-piperidinyl-acetate (23). To a solution of compound **22** (40 mg, 71 μmol) in oxygen free acetone was added tributyltin hydride (207 mg, 710 μmol; 10 equiv.) under N_2 atmosphere. Di-*t*-butylperoxyoxalate (4 mg, 14 μmol; 0.2 equiv.) was added in three portions over 12 h with stirring. The reaction progress was monitored by TLC. After 30 h the solvent was removed under vacuum and the residue was purified by column chromatography (Et_2O). Yield: 24 mg (83%). R_f: 0.19 (Et_2O). IR (film): ν (cm^{-1}) = 2940, 2860 (s, CH), 1740, 1660 (2 × s, C=O), 1230. ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, $^3J_{2,Me}$ = 6.84 Hz, 3H, 2-Me), 1.17–1.88 (m, 27H, 4-H, 5-H, 1′-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H, 8′-H, 9′-H, 10′-H, 2″-CH_3), 1.99/2.00 (2 × s, 3H, O_2CCH_3), 3.42/3.99 (2 × m, 1H, 6-H), 3.88 (m, 4H, 4″-H, 5″-H), 4.33/4.72 (2 × m, 1H, 2-H), 4.72 (m, 1H, 3-H), 7.97/8.00 (2 × s, 2H, CHO). ^{13}C NMR ($CDCl_3$): δ = 14.5/16.8 (CH_3), 20.8 (CH_3), 29.8 (CH_3), 23.7, 24.1, 26.2, 26.8, 26.9, 27.2, 27.7, 29.4, 29.4, 29.5, 29.6, 29.9, 30.3, 34.4, 35.2, 39.2 (16 × CH_2), 44.9/46.9 (C_2), 51.6/53.7 (C_6), 64.6 ($C_{4''}$,$C_{5''}$), 70.8/71.8 (C_3), 162.4/162.6 (CHO), 169.9/170.2 (O_2CCH_3). $[\alpha]_D^{20}$ = +7.9 (*c* = 1.1, $CHCl_3$). $C_{23}H_{41}NO_5$ (411.59), MS (70 eV, CI): *m*/*z* (%) = 428.3 (6) [$M + CH_5^+$], 411.4 (3) [M^+], 383.1 (2) [$M^+ - CO$], 351.4 (26) [$M^+ - C_2H_4O_2$], 323.4 (22) [$M^+ - C_2H_4O_2 - CO$] 291.1 (100).

(2*S*,5*R*,6*R*)-12-(5-Hydroxy-6-methyl-piperidin-2-yl)-dodecan-2-one, (−)-Cassine (5). Compound **23** (24 mg, 59 μmol) was dissolved in a mixture of methanol (4 ml) and 2 M H_2SO_4 (1 ml) and refluxed for 4 h. The solvent was removed under vacuum and the residue dissolved in sat. $NaHCO_3$ solution. The aqueous phase was extracted (three times) with CH_2Cl_2 (15 ml), and the combined organic phases were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (CH_2Cl_2/MeOH/NH_4OH 25% 88 : 10 : 2). Yield: 14 mg (47 μmol; 79%). mp: 58 °C; ref.: 57–58 °C.[19] R_f : 0.25 (CH_2Cl_2/MeOH/NH_4OH 25% 88 : 10 : 2). IR (KBr): ν (cm^{-1}) = 3700–3050 (s, NH, OH), 2900, 2840 (s, CH), 1675 (s, C=O). ^{1}H NMR ($CDCl_3$): δ = 1.04 (d, $^3J_{CH3,6'}$ = 6.56 Hz, 3H, 6′-CH_3), 1.17–1.25 (m, 16H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H), 1.27 (m, 1H, 3′-H), 1.39 (m, 1H, 3′-H), 1.42 (m, 1H, 4′-H_{ax}), 1.49 (m, 2H, 4-H), 1.83 (m, 1H, 4′-H_{eq}), 2.06 (s, 3H, 1-H), 2.34 (t, $^3J_{3,4}$ = 7.56 Hz, 2H, 3-H), 2.47 (m, 1H, 2′-H), 2.70 (m, 1H, 6′-H), 3.48 (m, 1H, 5′-H). ^{13}C NMR ($CDCl_3$): δ = 18.6 (6′-CH_3), 23.9, 25.8, 26.0, 29.2 (4 × CH_2), 29.3 (C_1), 29.4, 29.4, 29.5, 29.5, 29.7, 32.0, 36.9 (7 × CH_2), 43.8 (C_3), 55.8 ($C_{2'}$), 57.3 ($C_{6'}$), 68.0 ($C_{5'}$), 209.4 (C_2). $[\alpha]_D^{20}$ = −6.5 (*c* = 0.6, $CHCl_3$). MS (70 eV, CI): calc. 298.27406 for [$C_{18}H_{36}NO_2$]$^+$, found 298.27416.

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