



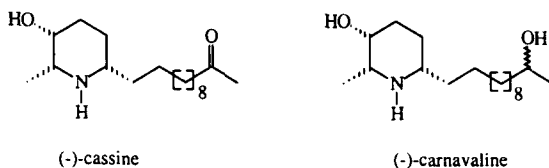
Total synthesis of the piperidinol alkaloid (–)-(2*R*,3*R*,6*S*)-cassine

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Abstract: A highly efficient, flexible and diastereoselective route to all-cis-2,6-disubstituted 3-piperidinols has been accomplished. The key component of the synthesis is a chiral β -hydroxyester, which was obtained by lipase catalyzed kinetic resolution. Based on this starting material, diastereoselective alkylation of its dianion, Curtius rearrangement to a 2-oxazolidinone, Grignard reaction to introduce the side-chain and conversion of the aliphatic 2-oxazolidinone into a 3-piperidinol by imine cyclization lead to the exemplary total synthesis of naturally occurring (–)-(2*R*,3*R*,6*S*)-cassine. © 1997 Elsevier Science Ltd. All rights reserved.

All cis-2,6-disubstituted 3-piperidinols such as cassine or its C-11' reduced analogue carnauvaline display interesting naturally occurring structures with three centres of asymmetry in the piperidine ring.¹ After discovery and structure elucidation of different 3-piperidinol alkaloids much effort has been directed towards efficient, stereoselective syntheses of this class of compounds owing to the variety of their biological activities and the difficulty in isolating these compounds in pure form from their natural sources.²

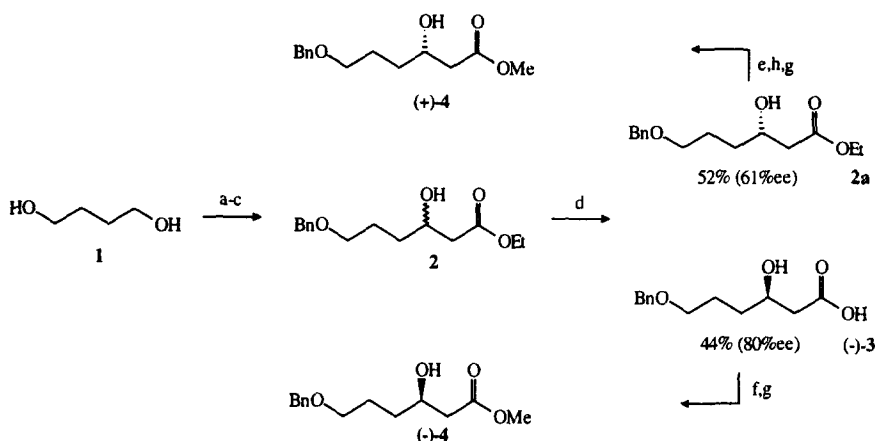


Most of the recently published syntheses of these or analogous compounds refer to racemic materials or suffer from difficult access to the starting material (multistep reaction sequences, low yielding steps etc.) and deviation in the physical data between the synthesized compounds and the natural products.³ We now wish to present a simple route to enantiomerically pure all-cis-configured 3-piperidinol alkaloids. To exemplify, the synthesis of (–)-(2*R*,3*R*,6*S*)-cassine was carried out showing the efficiency of the newly introduced access to all-cis-piperidinol alkaloids.

Synthesis

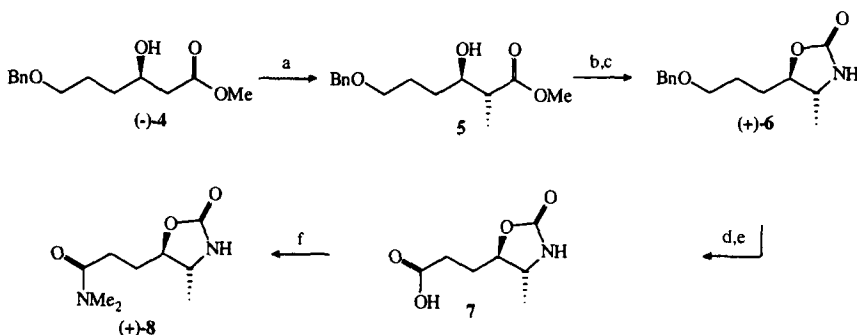
As starting material the homochiral (3*R*)-hydroxyester (–)-**4** was used. This compound is easily accessible via monobenylation of versatile 1,4-butanediol by variation of a known procedure,⁴ oxidation of the monobenzylated alcohol and coupling of the resulting aldehyde to ethyl bromoacetate in a Reformatsky reaction.⁵ Kinetic resolution of the racemic β -hydroxyethyl ester **2** by porcine pancreas lipase (PPL) catalyzed saponification in a phosphate-buffer (pH 7/RT) yielded e.g. 44% of the corresponding (3*R*)-hydroxyacid (–)-**3** (80% ee)⁶ and 52% of remaining (3*S*)-hydroxyethyl ester (61% ee) **2a**. Treatment of (–)-**3** with (1*R*,2*S*)-ephedrine gave a salt, which was crystallized to obtain enantiomerically pure (–)-**3** after liberation of the free hydroxyacid by mineral acid. The other enantiomer was also obtained in optically active form after hydrolysis of the remaining enantiomerically enriched hydroxyethyl-ester **2a** and treatment of the resulting acid in the same manner as described for the (3*R*)-enantiomer [in this case (1*S*,2*R*)-ephedrine was used] (Scheme 1).⁷

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(a) KOtBu, BnCl, 90→130°C, 85%; (b) (COCl)₂, NEt₃, DMSO, DCM, -78°C→rt, 88%; (c) Zn/Cu, BrCH₂COOEt, THF/ Et₂O, reflux, 89%; (d) PPL, phosphate-buffer, rt; (e) NaOH, EtOH, 0°C, 100%; (f) (1*R*,2*S*)-ephedrine, EtOAc then H₂SO₄, Et₂O; (g) CH₂N₂, Et₂O, 100%; (h) (1*S*,2*R*)-ephedrine, EtOAc then H₂SO₄.

Scheme 1.

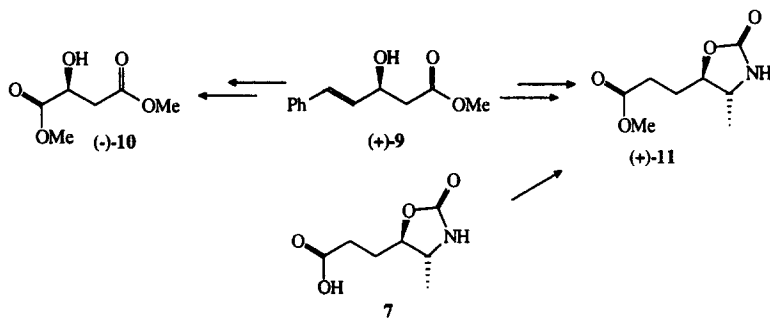


(a) LDA, CH₃I, THF, -78°C→rt; (b) N₂H₄, DMAP_{cat}, MeOH; (c) NaNO₂, 6*N* HCl, MeOH, 0°C→rt, 66%; (d) 10% Pd/ C_{cat}, 3.5bar H₂, MeOH, rt, quant.; (e) Jones-oxidat. (f) CDI, DCM, 0°C→rt, then NHMe₂, 0°C→rt, 77%.

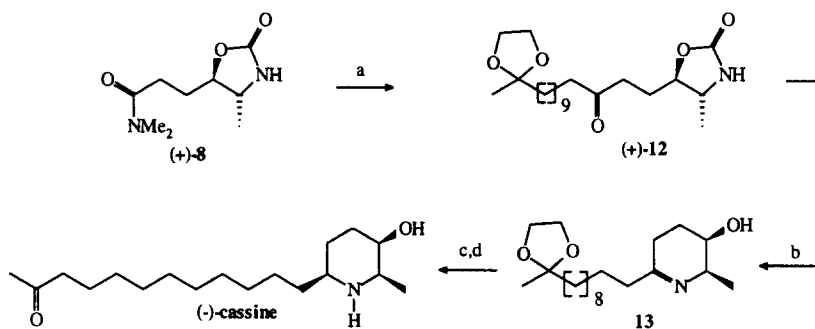
Scheme 2.

Hydroxyacid **(-)-3** was esterified by reaction with diazomethane and the second stereogenic centre was introduced by diastereoselective anti alkylation of the dianion of hydroxyester **(-)-4** with methyl iodide.^{8,9} The ratio of anti:syn-products was determined by analysis of the ¹H-nmr-spectrum as 9:1. The crude reaction product was treated with hydrazine hydrate in methanol to give the hydrazide, which after evaporation of the volatile components was rearranged in a Curtius reaction to 2-oxazolidinone **(+)-6**.¹⁰ Pure **(+)-(4*R*,5*R*)-6** was obtained by chromatography on SiO₂ in 66% yield from the hydroxyester **(-)-(4*R*)-4**. Deprotection of **(+)-6**, Jones oxidation¹¹ to the corresponding acid **7** and generation of its dimethylamide **(+)-8** proceeded in 77% over three steps (Scheme 2).

To confirm the absolute configuration of **7**, the acid was chemically correlated to compound **(+)-9**, which itself was correlated to malic acid dimethyl ester **(-)-(2*S*)-10** in the course of another synthesis.¹² The link between acid **7** and styrylhydroxy ester **(+)-9** was methyl ester **(+)-11**, of which a sample was available from a former work.¹³ This compound was also accessible by esterification of



Scheme 3.



a: Grignard reagent from 12-bromo-2-dodecanon-ethylenacetal, THF, HMPA, reflux, 51%; b: Ba(OH)₂, dioxane, reflux; c: 10% Pd/C, H₂, MeOH, 73% from (+)-12; d: 2N H₂SO₄, MeOH, reflux, 98%.

Scheme 4.

the acid **7**. Comparison of the specific rotation and the other spectra available proved both compounds to be identical (Scheme 3).

To establish the aliphatic side-chain the dimethylamide (+)-**8** was treated with the Grignard reagent from 12-bromo-2-dodecanon-ethylenacetal to give ketone (+)-**12** (Scheme 4).¹⁴

Ketone (+)-**12** contains all functionality necessary for the generation of the piperidine ring. Barium hydroxide mediated hydrolysis of the 2-oxazolidinone-heterocycle produced *in situ* the acyclic imine precursor, which condensed spontaneously under the reaction conditions to imine **13**. This compound was stereospecifically hydrogenated without further purification to the corresponding all-cis-configured piperidine. Not even a trace of the C-2 epimer could be detected. Acid hydrolysis of the acetal function at C-11' completed the total synthesis of the piperidinol alkaloid (-)-(2*R*,3*R*,6*S*)-cassine.

Comparison of natural and synthesized (-)-cassines

Comparison of the published spectral data and of the melting point as well as the sense of the specific rotation of natural (-)-cassine^{1a} and the synthesized compound indicates that both compounds are identical (Table 1).

On the one hand the high melting point of our (-)-cassine exhibits its excellent purity compared to the other isolated or synthesized compounds.

On the other hand the small value and the deviation of the specific rotation (up to 50%) of the

Table 1. Comparison of natural and synthesized (–)-cassines

	Natural (–)-cassine isolated by Highet <i>et al.</i> ^{1a}	Synthetic (–)-cassine by Momose <i>et al.</i> ^{1d}	Synthesized (–)-cassine
Melting Point [°C]	57–58°C	55–57°C	59–60°C
Specific Rotation $[\alpha]_D^T$	$[\alpha]_D^{25} = -0.6$ (c=8.0 in EtOH)	$[\alpha]_D^{26} = -0.7$ (c=0.59 in EtOH)	$[\alpha]_D^{20} = -1.07$ (c=8.43 in EtOH)

different (–)-cassines is obvious. Because of the small value of the specific rotation the influence of experimental errors becomes appreciable in terms of proportional deviations. We found that measurement in chloroform furnishes a value about ten times higher than in ethanol ($[\alpha]_D^{20} = -10.4$, c=2.27 in CHCl_3), which leads to a minimization of the influence of experimental inaccuracy.

Results

Based on the optically active hydroxyester (–)-(*R*)-**4** the naturally occurring piperidinolalkaloid (–)-cassine was synthesized in a 10 step sequence with superior purity and an excellent overall yield of 19%. All reactions can be easily carried out on the multigram-scale and so gram-quantities of optically active all-cis-piperidinols are accessible. Since both enantiomers of the starting material are available, it is also possible to synthesize the unnatural enantiomer of (–)-cassine, which emphasizes the synthetic utility of the presented reaction sequence. Further studies to elaborate the depicted concept in order to accomplish the synthesis of other naturally occurring 3-piperidinols are currently in progress.

Experimental section

Melting points were determined in a Tottoli apparatus and are not corrected. ¹H-nmr and ¹³C-nmr spectra were recorded with 200 respectively 50 MHz on a Bruker WP 200 SY spectrometer with tetramethylsilane as internal reference. ¹³C-nmr spectra were measured as APT spectra. IR-spectra were recorded with a Perkin–Elmer electrophotometer 580 or a fourier transformation spectrometer 1710. Mass spectra were recorded with a Finnigan MAT 312 instrument (low resolution) and a VG Autospec (high resolution). Microanalyses were carried out on a Heraeus CHN-Rapid. Column chromatographies were performed on silica gel from J. T. Baker (0.05–0.2mm). Standard acidic workup: The reaction mixture was cooled with ice and an adequate amount of 0.5N H₂SO₄ was added. The aqueous layer was extracted several times with DCM or Et₂O, depending on the solubility of the product, the combined organic layers were washed with water and brine and dried over MgSO₄ and the solvent was evaporated *in vacuo*.

(±)-6-Benzoyloxy-3-hydroxy-hexanoic acid ethylester **2**

24.7g Zn and 2.47g copper(II)acetate monohydrate were stirred in 40ml glacial acetic acid for 30min at rt. The liquid phase was decanted and the remaining residue was washed five times with dry THF and then covered with 20ml of a 2:1 mixture of Et₂O/THF. A mixture of 32.1g (180mmol) 4-benzyloxybutanal and 26ml (234mmol) ethyl-bromoacetate in 150ml of 2:1 Et₂O/THF was added to this heterogenous system that the reaction mixture slightly boiled (15–20min). After the addition the solution was refluxed for 1h and then quenched by a standard acidic work up with Et₂O as solvent. Column chromatography on silica gel gave 42.5g (89%) of **2** as a colourless oil. ¹H-nmr (CDCl₃): δ=1.27 (t, J=7.25Hz; ethyl-CH₃), 1.45–1.66 (m; 5-CH₂), 1.68–1.91 (m; 4-CH₂), 2.41 (dd, J=17Hz, J=8Hz; 1 H; 2-CH₂), 2.51 (dd, J=17Hz, J=4.5Hz; 1 H; 2-CH₂), 3.32 (s; OH), 3.52 (t, J=6Hz; 6-OCH₂), 3.97–4.09 (m; 3-CHO), 4.16 (q, J=7.25Hz, ethyl-CH₂), 4.51 (s; benzyl-CH₂), 7.23–7.4 (m; ar-H) ppm. ¹³C-nmr (CDCl₃): δ=14.17 (↓; ethyl-CH₃), 25.91, 33.63 (↑; 4+5-CH₂), 41.54 (↑; 2-CH₂), 60.60 (↑; ethyl-CH₂), 67.83 (↓; 3-CHO), 70.17 (↑; 6-OCH₂), 72.94 (↑; benzyl-CH₂), 127.58, 127.65,

128.37, (↓; ar-C), 139.31 (↑; ar-C), 172.31 (↑; 1-C)ppm. IR (cap.film): 3446, 3031, 2981, 2937, 2860, 1733, 1496, 1455, 1372, 1099, 1029, 739, 699 cm^{-1} . MS (rt): $m/e=266$ (M^+), 160, 157, 142, 117, 114, 111, 107, 99, 91. HR-MS: calc.: 266.1518; found: 266.1511.

(-)-6-Benzoyloxy-3-hydroxy-hexanoic acid methylester (-)-4

79.8g (300mmol) **2** and 1g PPL were suspended in 200ml 1M phosphate-buffer (pH 7)¹⁵ and were vigorously stirred at rt. The progress of the reaction was followed by TLC and after 3 and 14 days 1g PPL was added. The hydrolysis stopped at ~45% conversion (even after 64 days no further hydrolysis was observed). The reaction mixture was acidified to pH 2–3 under ice cooling and extracted with Et₂O for 4h. Three times extraction of the organic layer with NaHCO₃ sat. separated the carboxylate from the unreacted ester. The combined aqueous layers were acidified (pH 2–3) with 6N H₂SO₄ and five times extracted with Et₂O. The organic layer was dried over MgSO₄ and evaporated. This process afforded 30.6g (43%; 82% ee) **(-)-3**.

For further enantiomeric enrichment the hydroxyacid was converted to its corresponding ephedrinium salt (with 22.4g (1R,2S)-ephedrine) and crystallized two times from ethylacetate, which afforded 41.6g (34%) ephedrinium-salt, $[\alpha]_D^{20}=-28.9$ ($c=1.055$ in CHCl₃).

73.4g of the salt were suspended in water and acidified under ice-cooling by 6N H₂SO₄. Five times extraction with Et₂O and reduction of the solution to 200ml by evaporation of the solvent afforded the hydroxyacid. The solution of the acid was cooled with ice and esterified with diazomethane.¹⁶ Column filtration yielded 43.9g of hydroxymethyl ester **(-)-4**. ¹H-nmr (CDCl₃): $\delta=1.49-1.66+1.66-1.84$ (2 m; 4+5-CH₂), 2.43 (dd, $J=16\text{Hz}$, $J=8\text{Hz}$, 1H; 2-CH₂), 2.52 (dd, $J=16\text{Hz}$, $J=4\text{Hz}$, 1H; 2-CH₂), 3.31 (d, $J=4\text{Hz}$; OH), 3.52 (t, $J=6\text{Hz}$; 6-OCH₂), 3.71 (s; OCH₃), 3.97–4.11 (m; 3-CHO), 4.51 (s; benzyl-CH₂), 7.23–7.39 (m; ar-H)ppm. ¹³C-nmr (CDCl₃): $\delta=25.90, 33.67$ (↑; 4+5-CH₂), 41.48 (↑; 2-CH₂), 51.62 (↓; OCH₃), 67.78 (↓; 3-CHO), 70.15 (↑; 6-OCH₂), 72.89 (↑; benzyl-CH₂), 127.56, 127.64, 128.35 (↓; ar-C), 138.31 (↑; ar-C), 173.06 (↑; 1-C)ppm. IR (CHCl₃): 2962, 1724, 1608, 1440, 1276, 1172, 1096, 908 cm^{-1} . MS (rt): $m/e=252$ (M^+), 234, 160, 146, 128, 107, 91. HR-MS: calc.: 252.1361; found: 252.1360. $[\alpha]_D^{20}=-10.4$ ($c=1.58$ in CHCl₃) ee>99%.

(+)-(4R,5R)-5-(3'-Benzoyloxypropyl)-4-methyl-2-oxazolidinone (+)-6

(-)-4 was dilithiated under Ar-atmosphere by adding a solution of 22.82g (90.44mmol) **(-)-4** in 25ml dry THF dropwise to a solution of 225mmol LDA in 130ml THF at -78°C that the temperature is maintained below -65°C . For completion of the dilithiation the solution was warmed to -35°C over a period of 2h and then cooled to -78°C again. The reaction mixture was treated with 28.2ml 5eq CH₃I and allowed to warm to ambient temperature in 14h. Standard acidic work-up afforded 24.2g of an orange oil, which was dissolved in 50ml MeOH, mixed with 20ml hydrazine hydrate (100% solution) and a catalytic amount of 300mg 4-DMAP was also added. The homogenous mixture was stirred at 80°C for 14h. After 4h the hydrazide began to crystallize from the solution. The volatile components were evaporated and the hydrazide was dried *in vacuo* at 50°C and then dissolved in 250ml MeOH and 90ml 6N HCl were added at 0°C . A solution of 16.6g (240mmol) NaNO₂ in 135ml water was added to maintain the temperature of the solution below 5°C . The reaction mixture was stirred overnight at ambient temperature, brought to pH 6 by adding 6N NaOH and evaporated. The remaining residue was extracted four times with DCM and the combined organic layers were washed with water, dried over MgSO₄ and the solvent was removed to yield 22.4g red oil, which was purified by column chromatography. This procedure afforded 14.95g (66% over three steps) colourless oily **(+)-6** free from syn epimer. ¹H-nmr (CDCl₃): $\delta=1.25$ (d, $J=6\text{Hz}$; 4-CH₃), 1.68–1.87 (m; 1'+2'-CH₂), 3.45–3.62 (m; 4-CH + 3'-CH₂), 4.07–4.16 (m; 5-CH), 4.50 (s; benzyl-CH₂), 5.89 (s; NH), 7.28–7.41 (m; ar-H)ppm. ¹³C-nmr (CDCl₃): $\delta=20.57$ (↓; 4-CH₃), 25.26, 31.02 (↑; 1'+2'-CH₂), 53.67 (↓; 4-CH), 69.48 (↑; 3'-CH₂), 72.94 (↑; benzyl-CH₂), 83.99 (↓; 5-CH), 127.65, 128.40 (↓; ar-C), 138.34 (↑; ar-C), 154.48 (↑; 2-C)ppm. IR: 3245, 2837, 1734, 1498, 1455, 1398, 1249, 1108, 1016, 736 cm^{-1} . MS (120°C): $m/e=249$ (M^+), 188, 143, 114, 107, 91. $[\alpha]_D^{20}=+40.2$ ($c=1.275$ in CHCl₃).

(+)-(4R,5R)-5-(2'-N,N-Dimethylcarbamoyl-ethyl)-4-methyl-2-oxazolidinone (+)-8

14.95g (59.96mmol) (+)-6 were dissolved in 250ml MeOH and hydrogenated with 500mg Pd/C (10%) and stirred under 3.5bar H₂ for 12h. The catalyst was filtered off and the solvent removed under reduced pressure. Column filtration on silica gel afforded 9.5g (100%) of the debenzylated alcohol as a colourless oil.

2.57g (16.1mmol) of the alcohol were dissolved at 0°C in 150ml acetone and cooled to 0°C. 16ml Jones reagent¹¹ were added in one portion and the reaction mixture was stirred for thirty minutes before excess Cr(VI) was reduced by 2ml i-PrOH. After evaporation of the volatile components the residue was extracted in a soxhlet apparatus with DCM. The crude carboxylic acid was dissolved in 150ml dry DCM and treated with 2.87g (17.7mmol) CDI at 0°C. After stirring for 1h at ambient temperature the solution was cooled to 0°C and 3ml N,N-dimethylamine were added. The resulting mixture was stirred at rt for 30min and evaporated to dryness. Excess imidazole was distilled off in a Kugelrohr and the remaining dimethylamide purified by column chromatography to yield 2.53g (78%) (+)-8 as white crystals. ¹H-nmr (CDCl₃): δ=1.30 (d, J=6.25Hz; 4-CH₃), 1.90 (ddt, J=14Hz, J=9.5Hz, J=7Hz, 1H; 1'-CH₂), 2.15 (ddt, J=14Hz, J=7Hz, J=3.5Hz, 1H; 1'-CH₂), 2.52 (t, J=7Hz; 2'-CH₂), 2.96 (s; amide-CH₃), 3.61 (quint, J=6.25Hz; 4-CH), 4.21 (ddd, J=9.5Hz, J=6.25Hz, J=3.25Hz; 5-CH), 6.14 (s; NH)ppm. ¹³C-nmr (CDCl₃): δ=20.28 (↓; 4-CH₃), 28.47, 29.44 (↑; 1'+2'-CH₂), 35.46, 37.13 (↓; amide-CH₃), 53.91 (↓; 4-CH), 83.33 (↓; 5-CH), 159.33 (↑; 2-C), 171.67 (↑; 3'-C)ppm. IR (KBr): 3252, 1773, 1742, 1626, 1396, 1251, 1090, 956, 693 cm⁻¹. MS (140°C): m/e=200 (M⁺), 185, 112, 100, 70. Analysis: calc.: C: 53.98 H: 8.06 N: 13.99; found: C: 53.64 H: 7.89 N: 13.82. Melting point: 110°C. [α]_D²⁰=+98.7 (c=1.04 in CH₃OH).

(+)-(4R,5R)-5-(2'-Methoxycarbonyl-ethyl)-4-methyl-oxazolidinone (+)-11

A small amount of the crude carboxylic acid **7** was dissolved in DCM and esterified with diazomethane. After evaporation of the solvent and column filtration on silica gel the enantiomerically pure methylester (+)-11 was obtained as a colourless solid. ¹H-nmr (CDCl₃): δ=1.29 (d, J=6Hz; CH₃), 2.02 (m; 1'-CH₂), 2.53 (m; 2'-CH₂), 3.6 (dq, J=6Hz, J=1Hz; 4-CH), 3.7 (s; OCH₃), 4.16 (ddd, J=8Hz, J=6Hz, J=4.5Hz; 5-CH), 6.48 (s; NH)ppm. ¹³C-nmr (CDCl₃): δ=20.09 (↓; 4-CH₃), 28.93, 29.19 (↑; 1'+2'-CH₂), 51.5 (↓; OCH₃), 53.38 (↓; 4-CH), 82.67 (↓; 5-CH), 159.0 (↑; 2-C), 172.85 (↑; COOCH₃)ppm. IR (CHCl₃): 2980, 1750, 1440, 1380, 1200, 1050, 960, 880 cm⁻¹. MS (rt): 187 (M⁺), 149, 119, 117, 96, 70. Melting point: 43°C. [α]_D²⁰=+86.8 (c=1.095 in CH₃OH).

(+)-(4R,5R)-4-Methyl-5-[3'-oxo-13'-(2-methyl-1,3-dioxolan-2-yl)]-tridecyl-2-oxazolidinone (+)-12

Under an Ar atmosphere 729mg (30mmol) Mg shavings were treated with 5ml of a solution of 9.21g (30mmol) 12-bromo-2-dodecanon-ethylenacetal in 30ml dry THF and heated to reflux. After addition of 2 drops of 1,2-dibromoethane the reaction started and the remaining solution was added dropwise within 30min and refluxed for another 2h. Then 1g (5mmol) (+)-8 in 50ml dry THF and 5ml HMPA was added in 2h and then the reaction mixture refluxed for another 2.5h. After standard acidic work-up the product was purified by column chromatography to afford 974mg (51%) white, waxy crystals of (+)-12. ¹H-nmr (CDCl₃): δ=1.27 (s; 6'-11'-CH₂), 1.29 (d, J=6.25Hz; 4-CH₃), 1.32 (s; 15'-CH₃), 1.52-1.65 (m; 5'+12'-CH₂), 1.78-1.90 (m, 1H; 1'-CH₂), 1.98-2.09 (m, 1H; 1'-CH₂), 2.42 (t, J=7.5Hz; 2'-CH₂), 2.64 (t, J=7Hz; 4'-CH₂), 3.58 (quint., J=6.25Hz; 4-CH), 3.89-3.99 (m; O(CH₂)₂O), 4.11 (ddd, J=9.75Hz, J=6.25Hz, J=3.5Hz; 5-CH), 5.88 (s; NH)ppm. ¹³C-nmr (CDCl₃): δ=20.31 (↓; CH₃), 23.65 (↓; 15'-CH₃), 23.79, 24.04, 27.76, 29.15, 29.29, 29.36, 29.42, 29.49, 29.80 (↑; 1',5'-12'-CH₂), 37.58, 39.18, 42.94 (↑; 2', 4', 13'-CH₂), 53.77 (↓; 4-CH), 64.53 (↑; O(CH₂)₂O), 83.10 (↓; 5-CH), 110.79 (↑; 14'-C), 159.01 (↑; 2-C), 209.85 (↑; 3'-C)ppm. IR (CHCl₃): 2984, 2920, 1756, 1712, 1380, 1236, 1056 cm⁻¹. MS (150°C): m/e=383 (M⁺), 368, 338, 294, 255, 228, 156, 87. Analysis: calc.: C: 65.77 H: 9.72 N: 3.65; found: 65.60 H: 9.74 N: 3.79. Melting point: 55°C. [α]_D²⁰=+45.2 (c=1.00 in CH₃OH).

(-)-(2R,3R,6S)-Cassine

938mg (2.45mmol) (+)-**12** were dissolved in 90ml dioxane and treated with a solution of 2.34g (7.43mmol) Ba(OH)₂ x 8H₂O in 60ml water and refluxed for 12h. The precipitated Ba(CO₃)₂ was filtered off. The filtrate was evaporated to half of its volume and three times extracted with DCM. The combined organic layers were dried over MgSO₄ and the solvent removed. The remaining crude imine was dissolved in 20ml methanol and 10mg Pd/C (10%) were added. The imine was hydrogenated under a H₂-atmosphere for 4h. After filtration of the reaction mixture from the catalyst, removing of the solvent and column chromatography the resulting 11'-acetal protected cassine (609mg) was submitted to acid hydrolysis. 482mg (1.41mmol) of the acetal were dissolved in a mixture of 13ml MeOH and 4.5ml 2N H₂SO₄ and refluxed for 45min. After removing the methanol the residue was treated with 2N NaOH and the basic aqueous layer was extracted three times with DCM. Drying over MgSO₄ and column chromatography yielded 411mg (98%) of (-)-cassine. ¹H-nmr (CDCl₃): δ=1.09 (d, J=6.25Hz; CH₃), 1.26 (s; 1'-8'-CH₂), 1.37-1.63 (m; 5-CH₂, 9'-CH₂, 4-CH_{2ax}), 1.89 (dm, J=14Hz; 4-CH_{2eq}), 2.14 (s; 12'-CH₃), 2.42 (t, J=7.5Hz; 10'-CH₂), 2.48-2.63 (mb, 6-CHN_{ax}), 2.75 (dq, J=1.75, 6.25Hz; 2-CH_{axN}), 3.55 (s; 3-CH_{eqO})ppm. ¹³C-nmr (CDCl₃): δ=18.77 (l; CH₃), 23.81 (l; CH₂), 25.82, 26.14 (l; 5-CH₂, CH₂), 29.14, 29.37, 29.42, 29.50, 29.53, 29.79 (l; 6xCH₂), 29.29 (l; 12'-CH₃), 32.18 (l; 4-CH₂), 37.08 (l; 1'-CH₂), 43.72 (l; 10'-CH₂), 55.64 (l; 6-CHN), 57.06 (l; 2-CHN), 67.78 (l; 3-CHO), 209.23 (l; 11'-CHO)ppm. IR (KBr): 3158, 2970, 2917, 2850, 1704, 1467, 1372, 1272, 1235, 1210, 1165, 1074, 1005, 990, 859, 834, 786 cm⁻¹. MS (220°C): m/e=297 (M⁺), 282, 240, 238, 212, 179, 167, 135, 115, 114, 96, 87, 70. Analysis: calc.: C: 72.67 H: 11.86 N: 4.71; found: C: 72.44 H: 11.88 N: 5.20. Melting Point: 59-60°C. [α]_D²⁰=-1.07 (c=8.43 in EtOH), [α]_D²⁰=-10.4 (c=2.27 in CHCl₃).

References

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