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A New Access to Enantiopure β-Hydroxylated Piperidines from *N*-Boc-2-Acyloxazolidines. Application to the Synthesis of (–)-Desoxoprosopinine and (+)-Pseudoconhydrine

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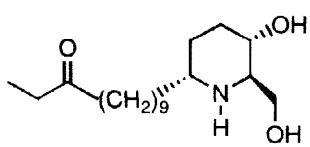
Abstract: The synthesis of (–)-desoxoprosopinine and (+)-pseudoconhydrine were achieved from a common oxazolidine precursor. The three stereocenters present in (–)-desoxoprosopinine as well as the two stereocenters of (+)-pseudoconhydrine were created in highly stereoselective ways. The stereoselectivity observed during the reduction of the ketone moiety in the starting oxazolidine was dependent on the occurrence of a chelated intermediate. The others stereocenters arose from stereoselective reductions or alkylations of intermediate iminium ions.

Piperidine heterocycles susbstituted at the β-position of the heterocycle by a hydroxyl group are commonly found in nature and some of them display important biological activities. For example, (+)-prosopinine **1** is an alkaloid isolated among seven others from *Prosopis africana*.[1] This plant is used in indigenous medicine and this is in accordance with the antibiotical and anesthetical properties of **1**. In the animal kingdom, quinolizidines alkaloids clavepictine A (**2a**) and B (**2b**) were recently isolated from the tunicate *Clavelina picta*[2] and these compounds exhibit significant cytotoxic activity as they were found to inhibit the growth of human solid tumor cell lines.



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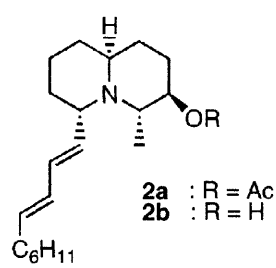
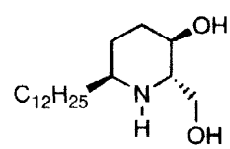


2a : R = Ac
2b : R = H



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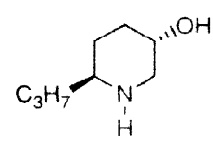

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In this article, we wish to report a new access to the diastereoselective and enantioselective construction to this kind of compounds and this was applied to the synthesis of (-)-desoxoprosopinine **3**,[3] and (+)-pseudoconhydrine **4**,[4] an alkaloid present in hemlock tree *Conium maculatum*.

It is worth noting that the structures of **3** and **4** differ in particular by the absolute configuration of the hydroxyl-bearing stereogenic center (C-3), and by its relative configuration with respect to the alkyl side chain at C-6. The methodology we wish to present hereafter is specially well suited for the control of the configuration of this stereogenic center and is based on the diastereoselective reduction of 2-acyl-*N*-Boc oxazolidines.[5] This strategy is depicted in the following scheme:

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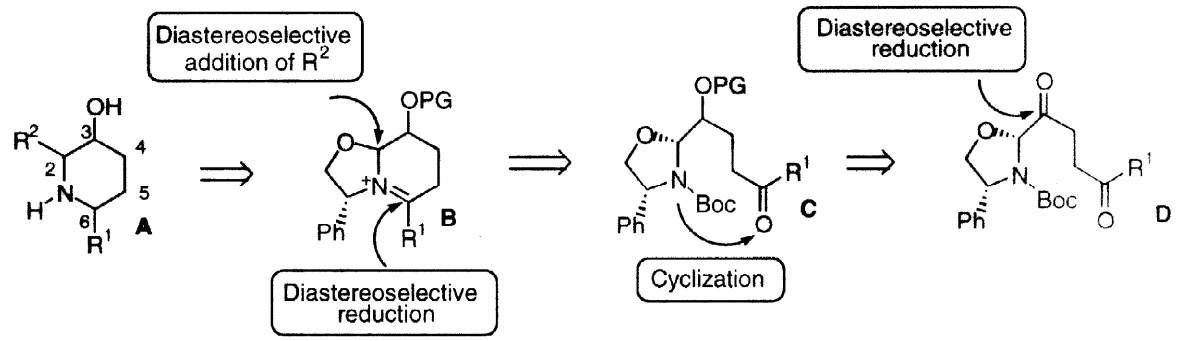
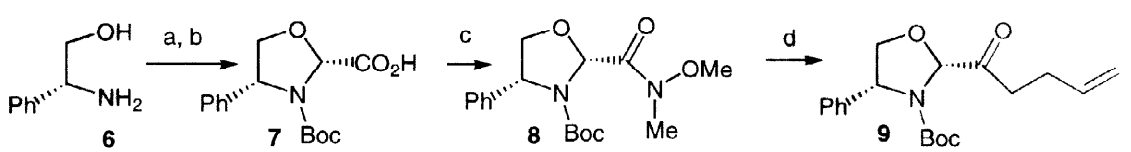


Scheme 1. General strategy for the synthesis of piperidine cores **A**

The trisubstituted piperidine core of general structure **A** would arise from bicyclic iminium ion **B**. The stereogenic centers located at C-2 and C-6 in **A** result respectively from (i) a reduction of the iminium moiety of **B** and (ii) an opening of the oxazolidine ring followed by a nucleophilic addition onto the new iminium moiety thus generated. The latter operation is not to be performed in the case of the synthesis of (+)-pseudoconhydrine which is devoid of stereocenter at C-6. Iminium ion **B** could in turn be produced from oxazolidine **C**, in which *N*-Boc deprotection followed by intramolecular condensation affords the desired iminium ion. Intermediate **C** would result from the reductive alkylation of the starting material, namely 2-acyloxazolidine **D**.

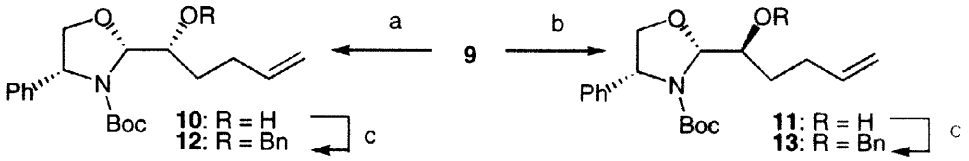
I. SYNTHESIS AND REDUCTION OF *N*-BOC-2-ACYLOXAZOLIDINES

The *N*-Boc 2-acyloxazolidine **9** required as substrate was prepared from Weinreb amide **8** (Scheme 2). This amide was prepared using a three-step sequence starting from (*R*)-phenylglycinol **6**. Condensation of this amino alcohol with ethyl glyoxylate followed by treatment with $(Boc)_2O$ and saponification furnished acid **7**. The synthesis of **8** from **7** was achieved via the mixed anhydride method.[6] The amide obtained in this way was used without further purification in the next step. Treatment of **8** with 4-butenylmagnesium bromide gave ketone **9**:



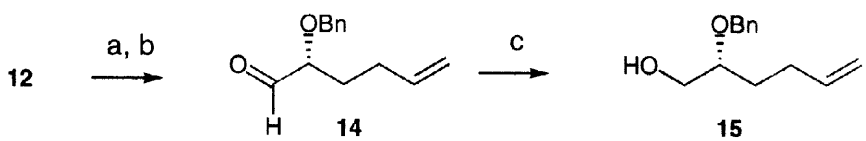
Scheme 2. (a) $OHCCO_2Et$, toluene, reflux $-H_2O$, then $(Boc)_2O$; (b)LiOH, EtOH/THF/H_2O, rt; (c) *N*-methyl morpholine, *i*-$BuCO_2Cl$, -40°, then NH(OMe)Me.HCl, $(Et)_3N$, 78% overall yield; (d) 4-butenylmagnesium bromide, Et_2O, rt, quant.

As shown in Scheme 3, the reduction of ketone **9** with $NaBH_4$ in ethanol at -78° afforded alcohol **10** in a high diastereoisomeric ratio (de = 90% as determined by NMR on the crude mixture). Alternatively, when an analogous reduction was performed in the presence of $CeCl_3.7(H_2O)$, diastereoisomer **11** was produced (de = 70%) in this case. Alcohols **10** and **11** respectively were separated from their minor stereomers by flash chromatography and isolated with overall yield of 84 and 63% (two steps from amide **8**). These alcohols were then protected as their benzyl ethers :



Scheme 3. (a) $NaBH_4$, EtOH, -78°, 84%; (b) $NaBH_4$, $CeCl_3.7\ H_2O$, EtOH, 78°, 63%; (c) NaH, BnBr, $N(Bu)_4I$, DMF, rt, 93% (**12**) and 88% (**13**).

At this stage, the absolute configuration of the newly created stereocenter was determined by means of a chemical correlation with the known alcohol **15**.[7] For this purpose, *N*-Boc deprotection of **12** followed by hydrolysis gave aldehyde **14**, whose reduction afforded alcohol **15** in 70% overall yield (optical purity: 37%) thus establishing its absolute configuration as *R*. Partial epimerisation occured during this sequence, probably at the aldehydic stage.



Scheme 4. (a) CF_3COOH, 1,2-dichloroethane, rt; (b) THF, H_2O, rt; (c) $NaBH_4$, EtOH, 0°C, 70 % overall yield.

The origin of the diastereoselectivity observed during the reduction of 2-acyloxazolidine **9** can now be adressed. Under the chelating conditions favored by the presence of cerium cation, this reaction affords alcohol **11**, whereas its diastereoisomer **10** was the major product in the absence of such an additive. Figure 1 provides a possible explanation for these opposite stereochemical outcomes: the chelated structure **B** compels the nucleophile to add to the least hindered *Re* diastereoface, whereas a Felkin-Ahn model[8] **A** orientates the hydride attack onto the *Si* diastereoface. In this model, the *N*-Boc group is considered as both the bulkier and the more electronattracting group. A similar Felkin-Ahn model was previously proposed by Scolastico,[9] and Hoppe[10] for nucleophilic attacks onto *N*-tosyl-2-acyloxazolidines.

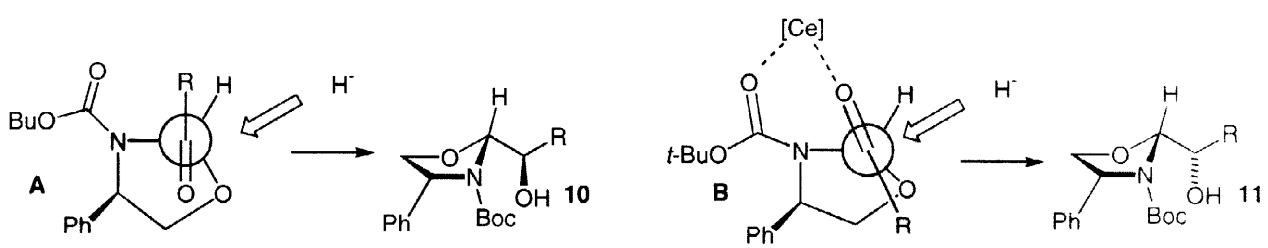
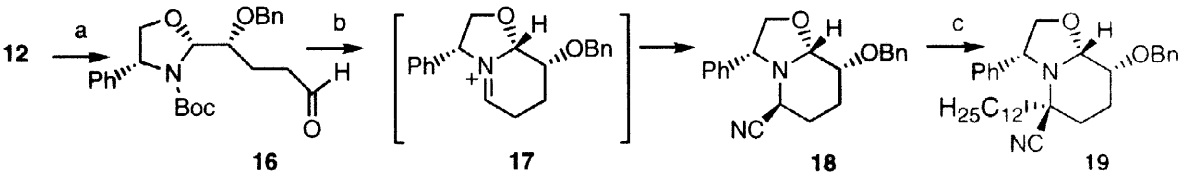


Figure 1. Chelated model and Felkin-Ahn models applied to the diastereoselective reduction of ketooxazolidine **9**, leading respectively to alcohols **10** and **11**.

Stereomeric compounds **12** and **13** present one of the stereocenters belonging to the target molecules and were used for the synthesis of (–)-desoxoprosopinine **3** and of (+)-pseudoconhydrine **4** respectively.

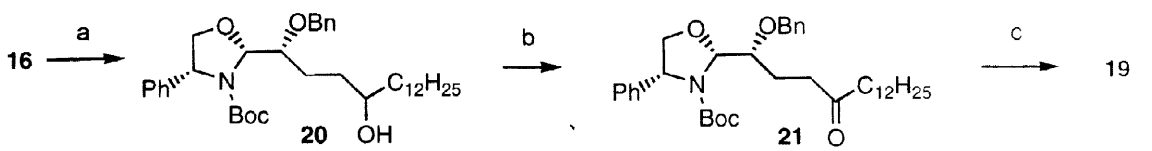
II. CONSTRUCTION OF THE PIPERIDINE CORES

A. Synthesis of (–)-desoxoprosopinine. Scheme 5 illustrates the synthesis of the piperidine intermediate **19**. The olefinic double bond in **12** was oxidatively cleaved and this operation yielded aldehyde **16**: this operation was achieved with a catalytic amount of OsO_4 in the presence of $NaIO_4$. In order to create the second stereogenic center (the R_1-bearing carbon in **A**, see Scheme **1**), two ways were experimented. The first way consisted in the direct cyclization of aldehyde **16**. Bicyclic compound **18** was obtained from an intramolecular condensation between this aldehyde and the amine moiety present in substrate **16**, once the *N*-Boc group removed. This reaction involves the formation of an intermediate iminium ion **17** which is trapped by a cyanide anion. This amino nitrile was treated with a base and alkylated with 1-bromododecane: this alkylation was totally stereoselective and afforded only stereoisomer **19** in agreement with similar results described by Husson et al.[11]



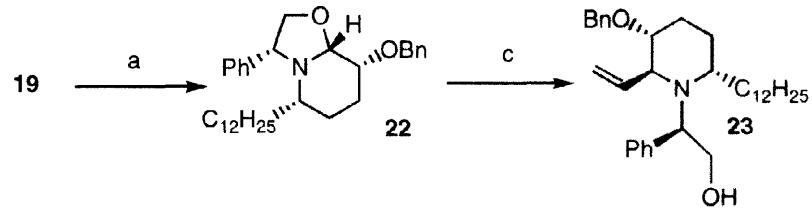
Scheme 5. (a) OsO_4 (cat.), $NaIO_4$, THF/water, rt, 78%; (b) CF_3COOH, 1,2-dichloroethane, rt, then aqueous KCN, 69%; (c) LDA, THF, -78°, then $C_{12}H_{25}Br$, 66%.

The above synthesis of the key intermediate **19** is a short two-step process. However it suffers from a serious drawback: the alkylation step was hardly reproducible with a good yield. In order to circumvent this difficulty, a new method was projected in which the introduction of the alkyl chain is introduced before the cyclization step. To this end, aldehyde **16** was reacted with dodecylmagnesium iodide and the resulting alcohol **20** was oxidized to afford ketone **21**. This ketone was treated with trifluoroacetic acid and potassium cyanide was added to the reaction mixture in order to produce compound **19**. This bicyclic compound was now produced as a 83:17 mixture of stereomers differing by their configuration on the cyano-bearing carbon but this fact is inconsequential for the completion of the synthesis (vide infra).



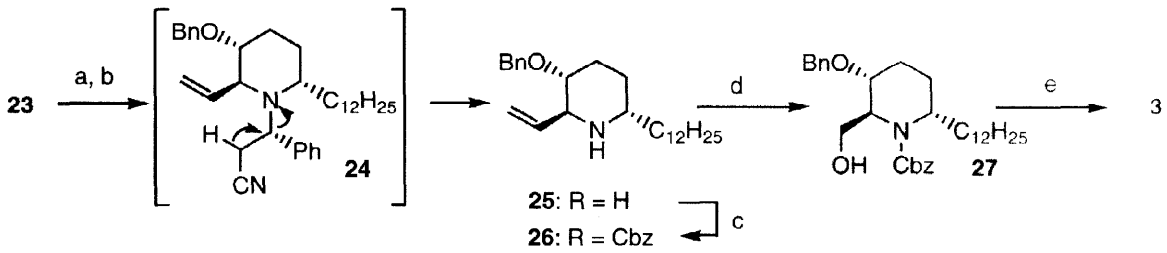
Scheme 6. (a) $C_{12}H_{25}MgI$, Et_2O, rt, 82%; (b) PDC, CH_2Cl_2, rt, 75%; (c) CF_3COOH, 1,2 dichloroethane, rt then aqueous KCN, 96%.

The second and the third stereogenic centers present in the target compound (see Scheme 6: C-2 and C-6 in structure **A**) were constructed as shown in Scheme 7. Diastereoselective reduction of the iminium ion generated from amino nitrile **19** following Husson's methodology[11] gave bicyclic oxazolidine **22** (de > 95%) possessing the correct stereochemistry present in the target molecule. The third stereogenic center present in (-)-desoxoprosopinine was then introduced by reacting compound **22** with vinylmagnesium bromide, in order to produce piperidine **23**:



Scheme 7. (a) $AgBF_4$, THF, -78°, then $Zn(BH_4)_2$, 78%; (b) vinylmagnesium bromide, THF, rt, 86%.

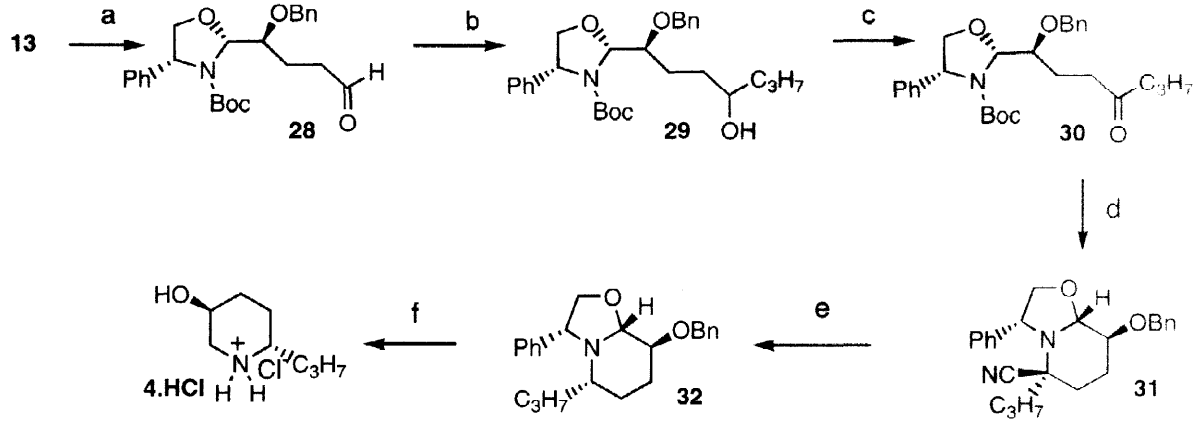
Transformation of **23** into (–)-desoxoprosopinine required further functional group transformations. First, the double bond had to be oxidatively cleaved in order to give the hydroxymethyl side chain present at C-2 in the target **3**. This operation was found to require the protection of the tertiary amine as a carbamate. An original chemoselective *N*-debenzylation (compatible with the presence of the ethylenic double bond) was thus devised. Reaction of alcohol **23** with thionyl chloride gave the corresponding chloride in quantitative yield. Treatment of this compound with an excess of KCN in DMSO gave nitrile **24** which underwent a β-elimination releasing the desired amine **25** in 86% overall yield. This amine was then protected as a *N*-Cbz group and the ethylenic appendage was cleaved by ozonolysis. In situ reduction of the produced aldehyde afforded the desired alcohol **27** with a good yield. Finally, hydrogenolysis of both the *N*-CBz group and the benzyl ether moiety gave (–)-desoxoprosopinine **3**:



Scheme 8. (a) $SOCl_2$, THF, rt (b) KCN, DMSO/THF (1/1), 86% overall yield; (c) CbzCl, DMAP, CH_2Cl_2, rt, 83%; d) O_3, CH_2Cl_2/MeOH, -78°, then $P(Ph)_3$, then $NaBH_4$, 82%; (e) H_2, $Pd(OH)_2$/C, EtOH/HCl (50/1), 88%.

B. Synthesis of (+)-pseudoconhydrine. A very similar route (Scheme 9) gave access to (+)-pseudoconhydrine **4**. In this case, the starting material was oxazolidine **13** which was transformed into aldehyde **28**. Reaction of this compound with propylmagnesium bromide followed by the oxidation of the resulting alcohol **29** gave ketone **30**. From this ketone, aminonitrile **31** was obtained as a unique stereoisomer, which was treated by $NaBH_4$, in order to effect the reductive decyanation, yielding stereoselectively compound **32**. In this case, the sequential treatment by $AgBF_4$ and $Zn(BH_4)_2$ which was

successfully used in the above synthesis on compound **19** was less satisfactory. The last set of transformations was then straightforward and involved only treatment of bicyclic compound **32** with hydrogen in the presence of Pearlman's catalyst. This procedure effected three operations: (i) reduction of the oxazolidine moiety, (ii) *N*-debenzylation and (iii) *O*-debenzylation, yielding target **4** as its hydrocloride in good yield:



Scheme 9. (a) OsO_4 (cat.), $NaIO_4$, THF/water, 80%; (b) PrMgBr, Et_2O, rt, 78%; (c) PDC, CH_2Cl_2, rt, 70%; (d) CF_3COOH, 1,2-dichloroethane, rt then aqueous KCN, 92%. (e) $NaBH_4$, EtOH, reflux, 80%; (f) H_2, $Pd(OH)_2/C$, EtOH/HCl (50/1), 85%.

During the above synthesis of (–)-desoxoprosopinine, the addition of the Grignard reagent onto the iminium ion derived from bicyclic oxazolidine **22** occurred in a totally steroselective way (see formation of compound **23** from **22** in Scheme 7). The configuration of the third stereogenic center which results from this addition can be explained by an axial attack onto conformation **A** of this iminium ion. This conformation **A** (see Figure 2) is assumed as the more reactive one on the basis of the pseudoaxial geometry of the benzyloxy substituent which orientates the nucleophile approach in the *anti* direction, following well-precedented examples.[8] This stereoelectronic factor overrides the allylic 1,2-strain which would be relieved in conformation **B**: such conformation has been advocated by Husson and Royer,[11] in order to explain the formation of *cis* adducts in the case of similar iminium ions with no substituent at the C-3 position.

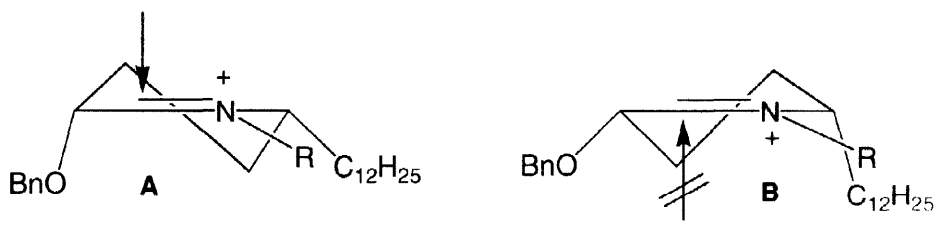


Figure 2. Reacting conformation **A** of compound **22**-derived iminium ion leading to *trans* adduct **23**.

In conclusion, the syntheses of (–)-desoxoprosopinine and of (+)-pseudoconhydrine were achieved starting from a common 2-acyloxazolidine precursor. This goal was reached owing to an efficient control during the creation of the stereogenic centers present in the targets. This strategy opens a new way for the enantioselective construction of polysubstituted piperidine alkaloids and highlights the usefulness of *N*-Boc-2-acyloxazolidines as starting substrates in asymmetric synthesis.

EXPERIMENTAL SECTION

General comments. ^1H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were respectively recorded on a Bruker ARX 250 spectrometer at 250 and 62.9 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin Elmer 141 instrument. All reactions were carried out under argon. Column chromatography was performed on silica gel 230-400 mesh by using various mixtures of diethyl ether (E) and petroleum ether (EP). TLC were run on Merck Kieselgel $60F_{254}$ plates. Melting points are uncorrected. THF and ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Mention of "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

(2R,4R)-2-(N-Methoxy-N-methyl)carbamoyl-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **8**

To a solution of acid **7**[5a] (7.5 g, 25.6 mmol) and *N*-methyl morpholine (2.7 g, 26.9 mmol) in THF (60 mL) cooled at -20° was added dropwise isobutyl chloroformate (3.7 g, 26.9 mmol). After stirring for 0.5 h, a suspension of (Me)(OMe)NH, HCl (2.74 g, 28 mmol) and triethylamine (4.1 mL, 29 mmol) in DMF (22 mL) was added. The mixture was allowed to reach 0°C and was stirred for 2h at this temperature. Water (100 mL) was then added followed by AcOEt (100 mL). The aqueous layer was extracted with AcOEt (2x100 mL). The combined organic layers were washed with 1N HCl (2x5 mL), a saturated solution of $NaHCO_3$ (2x5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil, dried under high vacuum, crystallized on standing: (8.4 g, 97%), mp 53-57°; Rf 0.72 (E/EP : 70/30); IR($CHCl_3$): 1675, 1685; ^{1}HNMR: 1.10 and 1.19 (two bs, 9H), 3.20 (bs, 3H), 3.74 (bs, 3H), 4.01-4.08 (bm, 1H), 4.31 (dd, J = 7 and 8.6, 1H), 4.68-4.75 (bm, 1H), 6.03 (bs, 1H), 7.14-7.60 (m, 3H), 7.64 (dd, J = 1.5 and 8.4, 2H); ^{13}CNMR: 27.0, 31.0, 60.3, 60.8, 74.5, 79.2, 82.5, 125.8, 126.5, 127.2, 138.5, 151.7, 167.7; Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 60.70; H, 7.19; N 8.33. Found: C, 60.85; H, 7.25; N,8.37.

(2R,4R)-2'-Pent-4'-enoyl-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **9**

To a suspension of magnesium (1.5 g, 61.8 mmol) covered with ether (3 mL) were added a few drops of 4-bromo-1-butene. After the reaction had started, the remaining halide (3.1 mL, 30.9 mmol) in ether (40 mL) was added dropwise in 0.75 h, and the resulting mixture was stirred for 1h at rt. This Grignard reagent was then cooled to 0°C and a solution of Weinreb amide **8** (6 g, 17.85 mmol) in ether (20 mL) was added dropwise. After an additional stirring of 0.5 h, the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl (20 mL). After usual work up, ketone **9** was obtained as a clear oil (6.3 g, quantitative). Rf 0.7 (E/EP: 50/50); $[\alpha]_D^{20}$: +26 (*c* 1.3, $CHCl_3$); IR (film): 1720; ^{1}H NMR: 1.06 (bs, 9H), 2.15-2.20 (m, 2H), 2.54-2.60 (m, 2H), 3.78 (dd, J = 8 and 8.9 Hz, 1H), 4.19 (dd, J = 7.1 and 8.9, 1H), 4.62 (bs, 1H), 4.75-4.88 (m, 2H), 5.28 (bs, 1H), 5.54-5.70 (m, 1H); 7.05-7.15 (m, 3H), 7.19-7.23 (m, 2H); ^{13}C NMR: 27, 28.1, 38, 60.9, 75.1, 81.4, 89.5, 115.4, 127.1, 127.7, 128.5, 136.8, 139.1, 153.4, 204.9.

(2R,4R,1'S)-2-(1'-Hydroxy-pent-4'-enyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **10**

To a solution of crude ketone **9** (6.2 g, 17.85 mmol) in ethanol (200 mL) cooled to -78° was added in one portion sodium borohydride (1.36 g, 35.7 mmol). After 0.5h, the reaction was hydrolized by addition of an

aqueous saturated solution of NH_4Cl and was allowed to reach rt. Ethanol was distilled off under reduced pressure and the residue was partitioned between water and ether. Usual work up gave an oil which was flash chromatographed (E/EP : 20/80) and yielded pure alcohol **10** as an oil (5.2 g, 84% overall yield from **8**). Rf 0.7 (E/EP: 50/50); $[\alpha]_D^{20}$: +19 (*c* 1.3, $CHCl_3$); IR (film): 3400, 2910, 1680, 1360; ^1H NMR: 1.20 (bs, 9H), 1.50-1.65 (m, 1H), 1.70-1.85 (m, 1H), 2.15-2.40 (m, 2H) 2.55 (bs, 1H), 3.70-3.80 (m, 1H), 3.92 (dd, J = 5.9 and 8.9, 1H), 4.19 (dd, J = 7 and 8.9, 1H), 4.82-4.98 (m, 3H), 5.05 (d, J = 3.2, 1H), 5.72-590 (m, 1H), 7.15-7.35 (m, 5H);^{13}C NMR: 28, 29.1, 32.7, 61, 73.4, 80.8, 82, 92.7, 114.6, 126.4, 127.7, 128.6, 138.7, 140.2, 157.7.

(2R,4R,1'R)-2-(1'-Hydroxy-pent-4'-enyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **11**

To a solution of crude ketone **9** (4.3 g, 14.5 mmol) in ethanol (190 mL) was added $CeCl_3(H_2O)_7$ (8.1 g, 21.7 mmol). After dissolution, the solution was cooled to -78° and sodium borohydride (1.2 g, 29.0 mmol) was added in one portion. After 0.5 h, the reaction was hydrolized by addition of an aqueous saturated solution of NH_4Cl and was allowed to reach rt. Ethanol was distilled off under reduced pressure and the residue was partitioned between water and ether. Usual work up gave an oil which was flash chromatographed (E/EP : 20/80) and yielded pure alcohol **11** as an oil (2.6 g, 63% overall yield from **9**). Rf 0.63 (E/EP: 50/50); $[\alpha]_D^{20}$: -26 (*c* 0.68, $CHCl_3$); IR (film): 3400, 2910, 1680, 1360; ^1H NMR: 1.29 (bs, 9H), 1.54-1.75 (m, 2H), 2.02-2.15 (m, 2H) 2.50 (bs, 1H), 3.82-3.98 (m, 1H), 4.01 (dd, J = 5.3 and 8.8, 1H), 4.23 (dd, J = 7.4 and 8.8, 1H), 4.80-5.05 (m, 3H) 5.04 (d, J = 3.5, 1H), 5.72-5.90 (m, 1H); 7.15-7.35 (m, 5H); ^{13}C NMR: 29.4, 30.2, 32.8, 61.8, 72.0, 74.3, 82.4, 93.9, 116.1, 127.7, 128.7, 129.7, 139.5, 141.6, 155.6.

(2R,4R,1'S)-2-(1'-Benzyloxy-pent-4'-enyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **12**

To a solution of alcohol **10** (0.51 g, 1.53 mmol) in dry DMF (10 mL), was added tetrabutylamonium iodide (1.12 g, 3 mmol), followed by benzyl bromide (0.36 mL, 3.07 mmol). The solution was cooled to 0°C, and sodium hydride (60%wt in mineral oil, 92 mg, 2.3 mmol) was added. After stirring for 2 h at rt, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL) and water (5 mL). Usual work up followed by flash chromatography (E/EP : 20/80) gave **12** as an oil (600 mg, 93 %). Rf 0.8 (E/EP: 50%); $[\alpha]_D^{20}$: -3 (*c* 0. 8, $CHCl_3$); IR (film): 2800, 1670, 1680, 1360, 1090; ^1H NMR: 1.30 (s, 9H), 1.54-1.70 (m, 2H), 1.95-2.18 (m, 2H), 3.82 (bs, 1H), 4.08 (dd, J = 6.8 and 8.7, 1H), 4.22 (t, J = 8.7, 1H), 4.52 (d, J = 11, 1H), 4.63 (d, J = 11.5, 1H), 4.83 (bs, 1H), 4.85-4.93 (m, 2H), 5.35 (d, J = 3.5, 1H), 5.60-5.80 (m, 1H), 7.15-7.32 (m, 10H); ^{13}C NMR: 28.2, 28.5, 29.6, 60.8, 72.7, 72.9, 79.9, 80.8, 90.7, 114.6, 126.8, 127.3, 127.4, 128.2, 128.3, 138.5, 138.6, 140.2, 154.7; Anal. Calcd for $C_{26}H_{33}NO_4$: C, 74.08; H, 7.41; N 3.32. Found: C, 74.00; H, 7.61; N, 3.35.

(2R, 4R, 1'R)-2-(1'-Benzyloxy-pent-4'-enyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **13**

Following the above procedure for the preparation of **12**, and starting with alcohol **11** (2.6 g, 7.5 mmol), compound **13** was obtained as an oil (2.8 g, 88%). Rf 0.79 (E/EP: 50%); $[\alpha]_D^{20}$: +10.4 (*c* 0. 87, $CHCl_3$); IR (film): 2800, 1670, 1680, 1360, 1090; ^1H NMR: 1.28 (s, 9H), 1.59-1.89 (m, 2H), 1.94-2.29 (m, 2H), 3.89 (bs, 1H), 4.01 (dd, J = 6.4 and 8.6, 1H), 4.20 (t, J = 8.6, 1H), 4.47 (d, J = 11.5, 1H), 4.59 (d, J = 11.5, 1H), 4.84 (bs, 1H), 4.83-5.01 (m, 2H), 5.14 (d, J = 6.6, 1H), 5.71-5.84 (m, 1H), 7.04-7.39 (m, 10H); ^{13}C NMR: 28.3, 29.9, 30.5, 61.1, 73.8, 77.9, 80.5, 92.4, 115.0, 127.1, 127.4, 127.6, 128.1, 128.3, 138.4, 136.5, 140.4, 154.3.

(2R)-2-Benzyloxy-hex-5-en-1-ol **15**

To a solution of **12** (580 mg, 1.37 mmol) in 1,2-dichloroethane (10 mL) and cooled at 0°C was added trifluoroacetic acid (2 ml). The solution was stirred for 1.5 h and concentrated under reduced pressure. The residue was taken up into THF (10 mL) and water (10 mL) and stirred overnight. After usual workup, the residue was dissolved into ethanol (10 mL) and sodium borohydride (90 mg, 2.36 mmol) was added portionwise at 0°C. After 1 h, the reaction medium was hydrolized by careful addition of an aqueous saturated solution of NH_4Cl (5 mL) followed by water (5 mL). The ethanol was distilled off under reduced pressure and the residue was dissolved in ether. Usual work up followed by flash chromatography gave **15** as an oil (220 mg, 78 %): Rf 0.34 (E/EP : 40/60); $[\alpha]_D^{20}$: -3.8 (*c* 1.3, $CHCl_3$); (ee = 36%); ^{1}H NMR: 1.35-1.65 (m, 2H), 1.95 (bq, J = 7.3, 1H), 2.15 (bs, 1H), 3.3-3.4 (m, 2H), 3.50-3.55 (m, 1H), 4.39 (AB, J = 11.6, 2H), 4.80 (d, J = 7, 1H), 4.85 (d, J = 15.5, 1H), 7.10-7.18 (m, 5H); ^{13}C NMR: 29.5, 30.0, 64.0, 71.5, 79.1, 114.8, 127.3, 128.4, 138.1, 138.4.

(2R,4R,1'R)-2-(1'-Benzyloxy-4'-oxo-butyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **16**

To a solution of **12** (1.4 g, 3.3 mmol) in THF (25 mL) and water (25 mL) was added OsO_4 (4%wt aqueous solution, 1.4 mL, 0.22 mmol) at rt. After 10 min, $NaIO_4$ (3.53 g, 16.5 mmol) was added portionwise into the black mixture and the suspension was stirred for 0.5 h. An aqueous solution of sodium thiosulfate (10%wt, 50 mL) was then added and the mixture was stirred for 10 min. Usual work up gave an oil that was subjected to flash chromatography (E/EP: 25/75). Aldehyde **16** was obtained as an oil (1.09 g, 78%). Rf 0.5 (E/EP : 30/70); $[\alpha]_D^{20}$: +4 (*c* 0.7, $CHCl_3$); IR (film): 2720, 1690, 1360, 1170, 1120; ^{1}HNMR: 1.32 (bs, 9H), 1.80-1.90 (m, 2H), 2.39 (td, J =1.3 and 7.1, 2H), 3.77 (td, J = 3.3 and 3.8, 1H), 4.10 (dd, J = 6 and 8.8, 1H), 4.20 (dd, J = 7.3 and 8.8, 1H), 4.47 (d, J = 11.5, 1H), 4.63 (d, J = 11.5, 1H), 4.93 (bs, 1H), 5.35 (d, J = 3.3, 1H), 7.14-7.30 (m, 10H), 9.55 (s, 1H); ^{13}C NMR: 21.9, 28, 39.7, 60.5, 72.4, 72.8, 79.1, 80.8, 90.2, 126.5, 127.2, 127.4, 127.7, 128.1, 128.2, 137.8, 139.9, 154.5, 202.2; Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.56; H, 7.34; N 3.29. Found: C, 70.65; H, 7.36; N, 3.31.

(3R,5S,8R,9R)-8-Benzyloxy -3-phenylhexahydrooxazol-[3, 2-a]-pyridine-5-carbonitrile **18**

To a solution of aldehyde **16** (0.8 g, 1.88 mmol) in 1,2-dichloroethane (25 mL), and cooled to 0°C was added dropwise trifluoroacetic acid (1.6 mL, 18.8 mmol). The mixture was stirred at rt for 1.5h and KCN (1.2 g, 18.8 mmol) in water (10 mL) was added. The emulsion was vigorously stirred and a saturated solution of $NaHCO_3$ (1 mL) was added. Usual workup (CH_2Cl_2) gave an oil that was purified by flash chromatography (E/EP : 20/80). Compound **18** was obtained as a clear oil (430 mg, 69%). Rf 0.5 (E/EP : 50/50); $[\alpha]_D^{20}$: -80 (*c* 0.35, $CHCl_3$); IR (film): 2250, 1670, 1490, 1450, 700; ^{1}H NMR: 1.60-1.76 (m, 2H), 1.94-2.03 (m, 1H), 2.17-2.24 (m, 1H), 3.70 (dd, J = 7.2 and 8.4, 1H), 3.81 (bs, 1H), 3.84 (bs, 1H), 3.90 (bs, 1H), 4.17-4.23 (m, 2H), 4.67 (d, J = 12.3, 1H), 4.89 (d, J = 12.3, 1H), 7.27-7.40 (m, 10H); ^{13}C NMR: 23.2, 25.4, 47.4, 63.6, 71.0, 72.6, 73.1, 91.8, 115.7, 127.3, 128.0, 128.3, 128.6, 128.9, 136.5, 139.2.

(3R,5S,8R,9R)-8-Benzyloxy-5-dodecyl-3-phenyl-hexahydrooxazolo-[3,2-a]-pyridine-5-carbonitrile **19** (from **18**)

To a solution of diisopropylamine (0.087 mL, 0.66 mmol) in dry THF (1 mL) was added butyllithium (1.6 N solution in hexane, 0.41 mL, 0.66 mmol) at -78°. After 20mn, a solution of **18** (100 mg, 0.3 mmol) in THF (1 mL) was added dropwise and the resulting mixture was stirred for 30mn at -78°. 1-Bromododecane

(0.29 mL, 1.2 mmol) was then added, and the solution was stirred for 3h. The reaction was then quenched by addition of an aqueous saturated solution of NH_4Cl (2 mL). Usual workup gave a residue that was purified by flash chromatography (E/EP : 10/90). Compound **19** was obtained as a clear oil (100 mg, 66%). $[\alpha]_D^{20}$: - 52 (*c* 0.7, $CHCl_3$); IR (film): 2960, 2250, 1360, 1150; ^1H NMR: 0.85 (t, J = 7.2 Hz, 3H), 1.08-1.20 (m, 20H), 1.35-1.45 (m, 2H), 165-1.78 (m, 2H), 1.95-2.07 (m, 2H), 3.49-3.57 (m, 1H), 3.75 (dd, J = 4.3 and 8.4, 1H), 3.96 (dd, J = 4.3 and 8.7, 1H), 4.13 (d, J = 7.8, 1H), 4.21 (d, J = 8.6, 1H), 4..65 (d, J= 11, 1H), 4.84 (d, J = 11, 1H), 7.17-7.35 (m, 10H); ^{13}C NMR: 14.1, 22.7, 23.7, 26.2, 29.0, 29.1, 29.3, 29.6, 31.9, 39.3, 61.3, 62.5, 70.8, 75.5, 74.8, 93.9, 119.0, 127.1, 127.4, 128.2, 128.5, 128.6, 139.2, 144.4.: Anal. Calcd for $C_{33}H_{46}N_2O_2$: C, 78.84; H, 9.22; N, 5.57. Found: C, 78.83; H, 9.25; N, 5.38.

(2R,4R,1'R)-2-(1'-Benzyloxy-4'-hydroxy-hexadecyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **20**

To a suspension of magnesium (710 mg, 29.6 mmol) covered with ether (4 mL) were added a few drops of 1-iododecane. After the reaction had started, the rest of the halide (total volume: 3.65 mL, 2.69 mmol) dissolved in ether (20 mL) was added dropwise. The medium was stirred for 1h at rt after the end of the addition and aldehyde **16** (1.4 g, 3.3 mmol) in ether (20 mL) was then added rapidly at 0°. After 0.5 h, the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl (20 mL). Usual workup gave an oil that was purified by flash chromatography (E/EP : 5/95 and then 50/50). Alcohol **20** was obtained as a clear oil (1.6 g, 82%) (50/50 mixture of diastereoisomers. Rf 0.40 (E/EP: 50%); IR (film): 3400, 2920, 1680, 1360, 1170; ^1H NMR: 0.87 (t, J = 6.8 Hz, 3H) 0.80-1.30 (m, 20H), 1.29 (s, 9H), 1.40-1.50 (m, 2H), 1.52-1.58 (m, 2H), 1.75-1.85 (m, 2H), 3.35 (bs, 1H), 3.55 (bs, 1H), 3.75 (bs, 1H), 4.12 (dd, J = 6.6 and 8.8, 1H), 4.21 (t, J = 8.7, 1H), 4.55 (AB, J = 11.7, 2H), 4.93 (bs, 1H), 5.32 (d, J = 2.9, 1H), 7.17-7.30 (m, 10H); ^{13}C NMR: 22.6, 25.0, 25.7, 28.2, 29.3, 29.6, 31.9, 32.9, 33.3, 37.7, 39.9, 60.8, 71.4, 71.7, 72.5, 72.8, 80.4, 80.9, 90.4, 126.7, 127.3, 127.5, 127.6, 127.8, 128.2, 138.3, 140.1, 154.8.

(2R,4R,1'R)-2-(1'-benzyloxy-4'-oxo-hexadecyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **21**

To a solution of alcohols **20** (700 mg, 1.17 mmol) in dichloromethane (8 mL) was added pyridinium chlorochromate (505 mg, 2.35 mmol). The mixture was stirred at rt for 1 h and water (10 mL) was added. After fitration on celite, the precipitated salts were washed with dichloromethane. Usual workup gave an oil that was flash chromatograpied (E/EP : 20/80). Ketone **21** was obtained as an oil (520 mg, 75 %). Rf 0.80 (E/EP: 30/70); $[\alpha]_D^{20}$: -38 (*c* 0.5, $CHCl_3$); IR (film): 2960, 1710, 1360, 1160; ^1H NMR: 0.79 (t, J = 6.9 Hz, 3H), 0.80-1.25 (m, 20H), 1.30 (s, 9H), 1.65-1.75 (m, 1H), 1.85-1.90 (m, 1H), 2.05-2.15 (m, 2H), 2.30-2.40 (m, 2H), 3.73 (dd, J =3.8 and 4.0, 1H), 4.08 (dd, J = 6.5 and 8.7, 1H), 4.23 (dd, J = 6.5 and 8.7, 1H), 4.47 (d, J = 11.6, 1H), 4.59 (d, J = 11.6, 1H), 4.91 (bs, 1H), 5.34 (d, J = 3.5, 1H), 7.15-7.40 (m, 10H); ^{13}C NMR: 14.1, 22.6, 23.3, 23.8, 28.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 38.2, 42.7, 60.9, 72.5, 73.1, 79.4, 80.9, 90.6, 126.7, 127.3, 127.5, 127.8, 128.2, 128.3, 138.3, 140.1, 154.6, 211.0; Anal. Calcd for $C_{37}H_{55}NO_5$: C, 74.96; H, 9.18; N 2.36. Found: C, 74.90; H, 9.35; N, 2.25.

(3R,5S,8R,9R)-8-Benzyloxy-5-dodecyl-3-phenyl-hexahydrooxazolo-[3, 2-a] pyridine-5-carbonitrile **19** (from **21**)

To a solution of ketone **21** (490 mg, 0.826 mmol) in 1,2-dichloroethane (14 mL) and cooled at 0°C was added dropwise trifluoroacetic acid (0.9 mL, 8.26 mmol). The mixture was stirred at rt for 1.5 h and KCN (540mg, 8.26 mmol) in water (10 mL) was added. The emulsion was vigorously stirred and a saturated

solution of $NaHCO_3$ (1 mL) was added. Usual workup (CH_2Cl_2) gave compound **19** as a clear oil (414 mg, 96%, 82/18 mixture of stereomers). The major stereromer displayed data as described above.

(3R,5S,8R,9R)-8-Benzyloxy-5-dodecyl-3-phenyl-hexahydro-oxazolo-[3, 2-a]-pyridine **22**

To a solution of compound **19** (270 mg, 0.54 mmol) in THF (6 mL) was added at rt silver tetrafluoroborate (157 mg, 0.8 mmol). After 10 min, the resulting suspension of silver cyanide was cooled to -78° and a freshly prepared solution of $Zn(BH_4)_2$ in ether (0.5N solution, 1.1 mL, 0.55 mmol) was added dropwise. The mixture was stirred for 1h, hydrolized by addition of water (2 mL) and allowed to reach rt. Filtration of the suspension on celite, careful washing of the precipitate with ether and usual workup gave an oil that was purified by flash chromatography (E/EP : 10/90). Compound **22** was obtained as an oil (201 mg, 78%). Rf 0.8 (E/EP 20/80); $[\alpha]_D^{20}$: -13 (*c* 0.6 $CHCl_3$); IR (film): 2970, 1680, 1450, 700; ^1H NMR: 0.90 (t, J = 6.8, 3H), 0.9-1.55 (m, 25H), 1.95-2.01 (m, 1H), 2.25-2.40 (m, 1H), 3.62-3.72 (m, 2H), 3.85-3.95 (m, 2H), 4.13 (t, J = 10.6, 1H), 4.74 (d, J = 12.6, 1H), 4.98 (d, J = 12.6, 1H), 7.15-7.55 (m, 10H); ^{13}C NMR: 13.1, 22.3, 23.2, 25.2, 27.4, 28.5, 28.6, 29.3, 61.7, 64.2, 70.6, 70.8, 72.8, 97.1, 126.0, 126.3, 126.4, 127.1, 127.2, 127.3, 129.8, 138.8, 143.5 ; Anal. Calcd for $C_{32}H_{47}NO_2$: C, 80.45; H, 9.92; N, 2.93. Found: C, 80.49; H, 9.92; N, 2.91.

(2S,3R,6S,1'R)-2-(3-Benzyloxy-6-dodecyl-2-vinylpiperidine-1-yl)-2-phenylethanol **23**

To a solution of **22** (1.75 g, 3.67 mmol) in THF (30 mL) was added dropwise at 0°C a solution of vinylmagnesium bromide in THF (1N solution, 11 mL, 11 mmol). The solution was stirred at rt for 15h and hydrolized by addition of an aqueous saturated solution of NH_4Cl. Usual workup followed by flash chromatography (E/EP : 20/80) gave **23** as an oil (1.6 g, 86%). Rf 0.6 (E/EP : 30/70); $[\alpha]_D^{20}$: -40 (*c* 1.5, $CHCl_3$); IR (film): 3350; ^1H NMR: 0.8 (t, J = 6.5, 3H), 1.10-1.18 (m, 22H), 1.36-1.50 (m, 3H), 1.60-1.65 (m, 1H), 2.40 (bs, 1H), 2.89 (bs, 1H), 3.15-3.22 (m, 1H), 3.54 (t, J = 7.7, 1H), 3.59 (dd, J = 6 and 10.3, 1H), 3.77 (dd, J = 9 and 10.3, 1H), 4.17 (dd, J = 6.1 and 8.9, 1H), 4.27 (d, J = 11, 1H), 4.39 (d, J = 11, 1H), 5.26 (dd, 10 and 17, 2H), 5.96 (ddd, J = 7.7, 10.3, 17.6, 1H), 7.17-7.28 (m, 10H); ^{13}C NMR: 14.1, 22.7, 25.1, 25.8, 26.9, 29.3, 29.8, 31.7, 31.9, 51.0, 61.2, 61.3, 62.2, 70.0, 75.8, 79.2, 127.3, 127.5, 127.8, 128.2, 128.3, 128.6, 137.9, 138.6, 140.8; Anal. Calcd for $C_{34}H_{51}NO_2$: C, 80.74; H, 10.16. Found: C, 80.64; H, 10.17.

(2S,3R,6S) 3-Benzyloxy-6-dodecyl-2-vinylpiperidine **25**

To a solution of **24** (554 mg, 1.09 mmol) in THF (15 mL) was added thionyl chloride (0.16 mL, 2.18 mmol). After 0.5 h, addition of an aqueous saturated solution of $NaHCO_3$ (10 mL) was followed by usual workup. The crude chloride thus obtained was dissolved in DMSO (5 mL) and THF (5 mL) and KCN (0.7 g, 10.8 mmol) was added. The mixture was stirred at rt for 18h and water (30 mL) was added. Usual workup followed by flash chromatography (E/EP : 30/70 then 100/0) gave **25** as an oil which cristallized on standing (364 mg, 86%). mp 66°; Rf 0.35 (E/EP: 100/0); $[\alpha]_D^{20}$: -8 (*c* 0.3, $CHCl_3$); IR (nujol): 3200, 1490, 1080, 770; ^1H NMR: 0.80 (t, J = 6.8, 3H), 1.16-1.20 (m, 22H), 1.42-1.50 (m, 2H), 1.66-1.73 (m, 2H), 1.82 bs, 1H), 2.71 (bs), 3.20-3.26 (m, 1H), 3.46 (dd, J = 4.9 and 5.5, 1H), 4.42 (d, J = 11.9, 1H), 4.52 (d, J = 11.9, 1H), 5.13 (dd, J = 9 and 16, 1H), 5.86 (ddd, J = 5.8, 9.5, 16.7, 1H), 7.15-7.25 (m, 10H); ^{13}C NMR: 14.2, 22.7, 24.2, 24.7, 26.2, 27.3, 29.3, 31.9, 34.9, 50.1, 58.0, 70.6, 76.4, 116.3, 127.5, 127.6, 128.3, 138.2, 138.8.

(2S,3R,6S) 3-Benzyloxy-N-benzyloxycarbonyl-6-dodecyl-2-vinylpiperidine **26**

To a solution of **25** (341 mg, 0.91 mmol) and dimethylaminopyridine (600 mg, 4.9 mmol) in dichloromethane (10 mL) was added freshly distilled benzyl chloroformiate (0.35 mL, 4.9 mmol). The mixture was stirred for 4 h at rt, and an aqueous saturated solution of $NaHCO_3$ (10 mL) was added. Usual workup followed by flash chromatography (E/EP : 15/85) gave **26** as a clear oil (396 mg, 83 %). Rf 0.6 (E/EP: 20/80); $[\alpha]_D^{20}$: -2 (*c* 1, $CHCl_3$); IR (film): 2910, 1680, 1400, 1280, 700; ^1H NMR: 0.81 (t, J = 6.9 Hz, 3H), 1.13-1.18 (m, 22H), 1.59-1.68 (m, 2H), 1.73-1.79 (m, 2H), 3.56-3.62 (m, 1H), 3.63-3.70 (m, 1H), 4.39 (d, J = 12, 1H), 4.47 (d, J = 12, 1H), 4.90-4.98 (m, 2H), 5.10-5.20 (m, 2H), 5.84 (ddd, J = 5, 10.7 and 16.2, 2H), 7.16-7.27 (m, 10H); ^{13}C NMR: 14.1, 22.6, 24.1, 29.4, 29.7, 31.9, 32.3, 53.4, 57.8, 66.8, 70.4, 75.4, 116.2, 127.4, 127.9, 136.8, 136.9, 138.5, 156.6.

(2S,3R,6S) 3-Benzyloxy-N-benzyloxycarbonyl-6-dodecyl-2-hydroxymethylpiperidine **27**

To a solution of **26** (184 mg, 0.354 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.5 mL) and cooled to -78° was bubbled a steam of oxygen containing ca. 3% of ozone. After 15 min, the solution turned blue and the excess of ozone was removed by purging with nitrogen. After addition of $P(Ph)_3$ (135 mg, 0.515 mmol), the solution was stirred at -50° for 20min, and $NaBH_4$ (40 mg, 1.06 mmol) was then added. The mixture was allowed to reach rt and was hydrolized after 1h by addition of an aqueous saturated solution of NH_4Cl. Usual workup followed by flash chromatography of the residue (E/EP : 40/60) gave **27** as an oil (151 mg, 41%). Rf 0.45 (E/EP: 50/50); $[\alpha]_D^{20}$: -11 (*c* 0.7, $CHCl_3$); IR (film): 3450, 2910, 1680, 1420, 1320, 1100; ^1H NMR: 0.80 (t, J = 6.9 Hz, 3H), 1.14-1.18 (m, 22H), 1.60-1.80 (m, 4H), 1.85 (bs, 1H), 3.10-3.18 (m, 1H), 3.63-369 (m, 1H), 4.02 (bs, 2H), 4.15-4.20 (m, 1H), 4.52 (s, 2H), 5.07 (s, 2H), 7.19-7.30 (m, 10H); ^{13}C NMR: 14.2, 22.8, 26.1, 26.2, 26.3, 29.5, 29.8, 30.6, 32.0, 54.0, 58.9, 67.3, 69.3, 71.8, 74.3, 127.9, 128.0, 128.5, 128.6, 136.6, 138.5, 156.3; Anal. Calcd for $C_{33}H_{49}NO_4$: C, 75.68; H, 9.43. Found: C, 73.82 ; H, 9.03.

(–)-Desoxoprosopinine **3**

To a solution of **27** (150 mg, 0.286 mmol) in EtOH (1 mL) was added 0.2 mL of 35% HCl and 20% $Pd(OH)_2/C$ (15 mg). The suspension was vigorously stirred under an atmosphere of hydrogen for 24 h and the catalyst was then filtered off on Celite. Ethanol was evaporated under reduced pressure and the residue was dissolved in water (1 mL). This aqueous solution was washed with ether (2x5ml) and basified by addition of 1N NaOH. Usual workup gave (-)-desoxoprosopinine **3** as a white solid (75 mg, 88%). Recristallisation from acetone gave fine needles. mp 88°; Rf 0.2 (MeOH/CH_2Cl_2: 20/80); $[\alpha]_D^{20}$: -16.8 (*c* 0.5, $CHCl_3$); IR (nujol): 3350, 2710, 1150, 1070, 950, 870; ^1H NMR: 0.81 (t, J = 6.3, 3H), 1.18 (bs, 22H), 1.35-1.70 (m, 4H), 2.31 (bs, 3H), 2.70 (bqu, J = 5, 1H), 2.79 (bq, J = 6, 1H), 3.40-3.52 (m, 1H), 3.56 (dd, J = 5.4 and 10.5, 1H), 3.58 (dd, J = 7.4 and 10.6, 1H); ^{13}C NMR: 14.2, 22.8, 26.5, 27.4, 28.6, 29.4, 29.7, 32.0, 33.8, 49.9, 58.0, 62.3, 68.0.

(2R,4R,1'S)-2-(1'-benzyloxy-4'-oxo-butyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **28**

Following the above procedure for the preparation of **16**, aldehyde **28** was prepared from **13** (2.7 g, 6.38 mmol) and was obtained as a clear oil (2.2 g, 80%) after flash chromatography (E/EP : 20/80). Rf 0.50 (E/EP: 30%); $[\alpha]_D^{20}$: +13.9 (*c* 1.4, $CHCl_3$); IR (film): 2720, 1690, 1360, 1170, 1120; ^1H NMR: 1.36 (s, 9H), 2.01-2.15 (m, 2H), 2.41-2.70 (m, 2H), 3.95 (bs, 1H), 4.07 (dd, J = 6.6 and 8.7, 1H), 4.31 (t, J = 8.7, 1H), 4.48 (d, J = 11.3, 1H), 4.67 (d, J = 11.3, 1H), 4.90 (bs, 1H), 5.23 (d, J = 4.3, 1H), 7.15-7.50 (m, 10H), 9.55 (s,

1H); ^{13}C NMR: 23.6, 28.3, 39.9, 61.1, 73.7, 80.6, 92.5, 127.1, 127.6, 127.9, 128.3, 128.4, 128.5, 138.2, 140.2, 154.5, 202.5.

(2R,4R,1'S)-2-(1'-Benzyloxy-4'-hydroxyheptyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **29**

To a suspension of magnesium (380 mg, 15.8 mmol) covered with ether (2 mL) were added a few drops of 1-bromopropane. After the reaction had started, the rest of the halide (total weight: 960 mg, 7.87 mmol) dissolved in ether (10 mL) was added dropwise. The medium was stirred for 1 h at rt after the end of the addition and aldehyde **28** (600 mg, 1.4 mmol) in ether (10 mL) was then added rapidly at 0°. After 0.5 h, the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl (10 mL). Usual workup gave an oil that was purified by flash chromatography (E/EP : 5/95 and then 50/50). Alcohol **29** was obtained as a clear oil (508 mg, 77%) (50/50 mixture of diastereoisomers). Rf 0.47 (E/EP: 30%): IR (film): 3400, 2920, 1680, 1360, 1170; ^1H NMR: 0.87 (t, J = 6.8 Hz, 3H), 1.25-1.90 (m, 9H), 1.34 (s, 9H), 3.44-3.55 (m, 1H), 3.89 (bs, 1H), 3.95-4.05 (m, 1H), 4.12 (td, J =2.7 and 8.8, 1H), 4.49 (d, J = 12.5, 1H), 4.59 (d, J = 12.5, 1H), 4.80 (bs, 1H), 5.10 (d, J = 3.7, 0.5H), 5.19 (d, J = 3.7, 0.5H), 7.11-7.34 (m, 10H).

(2R,4R,1'S)-2-(1-Benzyloxy-4-oxoheptyl)-4-phenyloxazolidine-3-carboxylic acid tert-butyl ester **30**

Following the procedure described above for the preparation of **21**, ketone **30** was prepared starting from alcohol **29** (1.2 g, 2.56 mmol). Clear oil (840 mg, 70%). Rf 0.86 (E/EP: 66/33); $[\alpha]_D^{20}$: +3.4 (*c* 0.9, $CHCl_3$): IR (film): 2960, 1710, 1360, 1160; ^1H NMR: 0.85 (t, J = 7.2 Hz, 3H), 1.31 (s, 9H), 1.52 (q, J = 7.4, 2H), 1.80-2.01 (m, 2H), 1.95 (bt, J = 7.5, 2H), 2.10-2.50 (m, 2H), 2.30-2.40 (m, 1H), 3.90 (bs, 1H), 4.02 (dd, J = 6.7 and 8.6, 1H), 4.45 (d, J = 11.6, 1H), 4.61 (d, J = 11.6, 1H), 4..93 (bs, 1H), 5.34 (d, J = 4.1, 1H), 7.15-7.38 (m, 10H); ^{13}C NMR: 13.8, 17.3, 24.7, 28.3, 38.2, 44.7, 61.1, 73.5, 77.6, 80.2, 92.4, 127.1, 127.5, 127.7, 128.2, 128.4, 138.4, 140.3, 154.4, 210.8; Anal. Calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98. Found: C, 71.97; H, 8.01.

(3R,5S,8S,9R)-8-Benzyloxy-5-propyl-3-phenyl-hexahydrooxazolo-[3, 2-a]-pyridine-5-carbonitrile **31**

Following the procedure used for the preparation of **19** from **21**, compound **31** was obtained starting from ketone **30** (0.8 g, 1.71 mmol).This compound was obtained as an oil (613 mg, 92%). Rf 0.7 (E/EP : 50/50); $[\alpha]_D^{20}$: -1.6 (*c* 0.25, $CHCl_3$); IR (film): 2960, 2250, 1355, 1150; ^1H NMR: 0.45 (t, J = 6.8, 3H), 0.9-2.1 (m, 8H), 3.45-3.62 (m, 1H), 3.73 (dd, J = 4.2 and 8.4, 1H), 3.96 (dd, J = 4.2 and 8.4, 1H), 4.19 (t, J = 4, 1H), 4.29 (d, J = 5, 1H), 4.62 (d, J = 12, 1H), 4.85 (d, J= 12, 1H), 7.15-7.70 (m, 10H); ^{13}C NMR: 15.7, 19.4, 29.2, 35.7, 43.4, 63.4, 63.9, 74.1, 77.4, 79.0, 97.8, 121, 129.7, 129.8, 129.9, 130.5, 130.7, 140.8, 146.2.

(3R,5S,8S,9R)-8-Benzyloxy-5-propyl-3-phenyl-hexahydrooxazolo-[3, 2-a]-pyridine **32**

To a solution of **31** (243 mg, 0.64 mmol) in EtOH (15 mL) was added sodium borohydride (243 mg, 6.4 mmol). The mixture was refluxed for 2 h and water (10 mL) was added.. Ethanol was distilled under reduced pressure and ether was then added. Usual workup followed by flash chromatography (E/EP : 20/80) gave **32** as a white solid (180 mg, 80%). mp 74°; Rf 0.55 (E/EP : 30/70); $[\alpha]_D^{20}$: -28.1 (*c* 0.7, $CHCl_3$); IR (nujol): 2980, 1450, 710; ^1H NMR: 0.45 (t, J = 6.8, 3H), 0.8-1.2 (m, 6H), 1.45-1.65 (m, 1H), 1.95-2.05 (m, 1H), 2.31(bt, J = 8, 1H), 3.45-3.80 (m, 4H), 4.17 (t, J = 8, 1H), 4.63 (d, J = 12, 1H), 4.85 (d, J= 12, 1H), 7.15-7.45 (m, 10H); ^{13}C NMR: 13.5, 18.4, 29.1, 29.3, 29.7, 36.3, 60.5, 64.4, 71.5, 74.9, 77.8, 99.0, 126.6, 126.7, 127.0, 127.9, 128.1, 138.8, 144.3; Anal. Calcd for $C_{24}H_{29}NO_2$: C, 79.3; H, 8.04. Found: C, 79.13; H, 8.07.

(+)-Pseudoconhydrine **4**. HCl

To a solution of **32** (160 mg, 0.458 mmol) in EtOH (1 mL) was added 0.2 mL of 35% HCl and 20% $Pd(OH)_2/C$ (20 mg). The suspension was vigorously stirred under an atmosphere of hydrogen for 24 h and the catalyst was then filtered off on celite. Ethanol was evaporated under reduced pressure and the residue was triturated with ether and then with dry acetone. The remaining solid was crystallized by slow evaporation of a methanolic solution, and the crystals were dried under reduced pressure. Hydrochloride of **4** was obtained as colorless cristals (75 mg, 85%): mp 208°(dec.); Rf 0.15 (($MeOH/CH_2Cl_2$: 20 80); IR (nujol): 3400, 2900, 2580, 2505, 1610, 1420, 1210, 1090; $[\alpha]_D^{20}$:+2.6 (*c* 0.47, MeOH); ^1H NMR: 0.83 (t, J = 6.7, 3H), 1.15-1.60 (m, 6H), 1.92 (bd, J = 11, 1H), 2.55 (bt, J = 11, 1H), 2.90-3.02 (m, 1H), 3.20-3.28 (m, 1H), 3.60-3.72 (m, 1H); ^{13}C NMR: 13.3, 18.9, 26.6, 31.3, 35.0, 49.2, 56.3, 64.0.

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