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Diastereoselective Reduction of Bicyclic β-Enamino Carbonyl Piperidines – Application to the Total Synthesis of (–)-Deoxocassine

Romain Noël,[a] Corinne Vanucci-Bacqué,*[a] Marie-Claude Fargeau-Bellassoued,[a] and Gérard Lhommet*[a]

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The chemo- and diastereoselective reduction of chiral piperidine β-enamino esters **4** and **6** and β-enamino ketones **5** and **7** was studied and found to afford 2,3- or 2,3,6-substituted piperidines. This approach was successfully applied to the total synthesis of (–)-deoxocassine.

Introduction

The diastereoselective synthesis of chiral polysubstituted piperidines is of considerable current interest because these heterocycles are versatile precursors of naturally occurring alkaloids, many of which are well known to exhibit various biological activities. In a previous report,[1] we described the efficient preparation of chiral bicyclic β-enamino carbonyl derivatives **1** (Figure 1) by condensation of (*S*)-phenylglycinol with various tricarbonyl compounds. We wish now to report a study aimed at the diastereoselective reduction of the double bond of the β-enamino carbonyl moiety of these oxazolidino piperidines in order to obtain the corresponding fully saturated piperidines. The latter compounds were envisioned as obvious precursors of alkaloids because they possess a 2,3- or 2,3,6-substituted piperidine moiety. Among this subclass of compounds, 3-hydroxy-2,6-disubstituted piperidines such as *Cassia* and *Prosopis* alkaloids[2] have generated particular attention from many research groups[3] because of their important biological activities. In line with this interest, we selected enantiopure (–)-deoxocassine (**2**),[4] a simple analogue of natural alkaloid (–)-cassine **3**[5] (Figure 1), to apply our methodology to the field of the total synthesis of alkaloids.

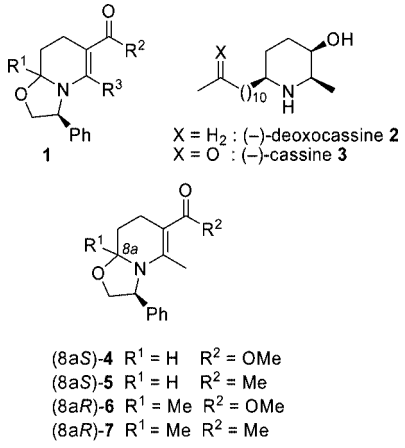


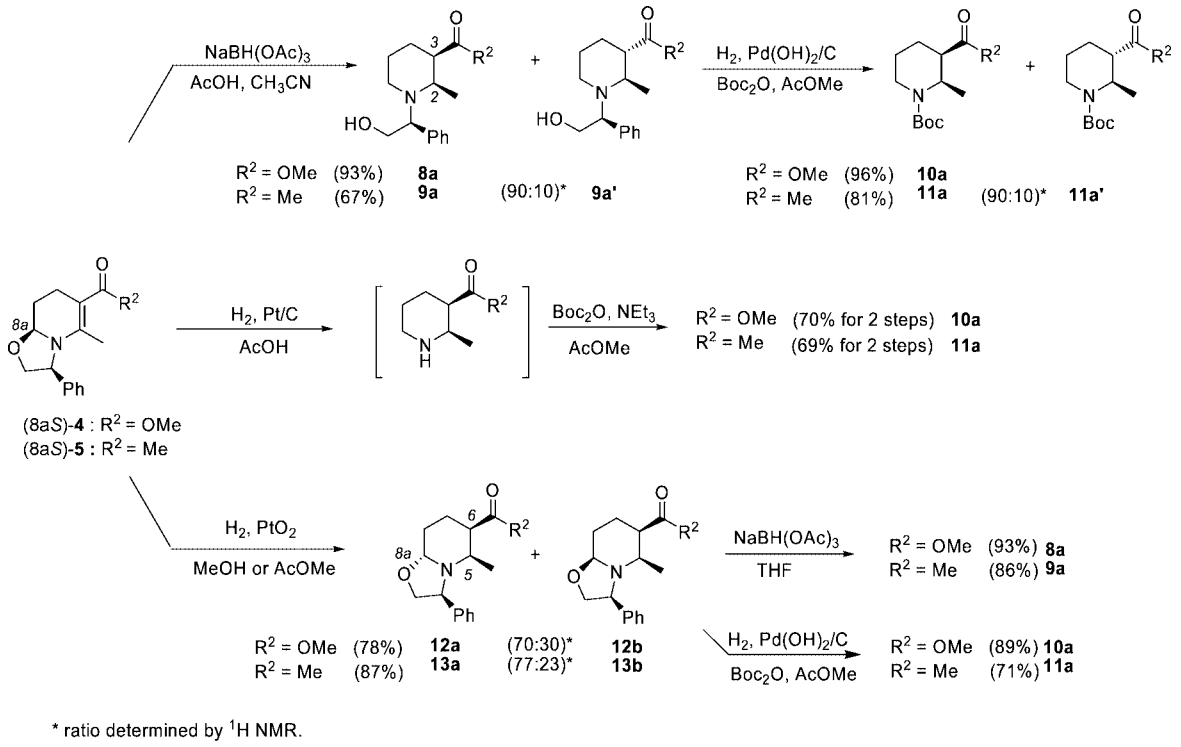
Figure 1. Structures of compounds **1**–**7**.

Results and Discussion

We first focused our work on the reductions of methylated compounds **1** (R^3 = Me), which possess either an angular hydrogen atom [(8a*S*)-**4** and (8a*S*)-**5**] or an angular methyl group [(8a*R*)-**6** and (8a*R*)-**7**][6] (Figure 1). In order to assess the influence of the reducing agent on the chemo- and stereoselectivity of the reaction, these compounds were reacted either with sodium triacetoxy borohydride in acetic acid,[7] or under catalytic hydrogenation conditions, at atmospheric pressure, with $Pd(OH)_2$/C, Pt/C, and PtO_2 as catalysts.

We initially examined the reduction of piperidine bicyclic β-enamino ester (8a*S*)-**4** and β-enamino ketone (8a*S*)-**5**, which both contain an angular hydrogen atom (Scheme 1). Treatment of **4** and **5** with in situ generated sodium triacetoxy borohydride in acetic acid[8] led to the diastereoselective reduction of the C–C double bond along with the cleavage of the oxazolidine ring to give, respectively, compounds **8a** (*de* > 98%) and **9** (*de* = 80%) in good yields. X-ray analysis performed on the picric salt of β-amino ester **8a** allowed us to assign the (2*R*,3*R*) absolute configuration to

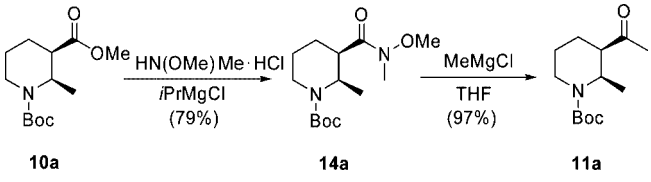
[a] Université Pierre et Marie Curie-Paris 6, Laboratoire de Chimie Organique (UMR CNRS 7611), Equipe de Chimie des Hétérocycles, Institut de Chimie Moléculaire (FR 2769),
4 place Jussieu, 75252 Paris cedex 05, France
Fax: +33-1-44-27-30-56
E-mail: vanucci@ccr.jussieu.fr
lhommet@ccr.jussieu.fr



Scheme 1. Reduction of (8a*S*)-**4** and (8a*S*)-**5**.

this compound whereas assignment of the stereochemistry of β-amino ketones **9** was secured by chemical correlation (see below). Compound **8a** was submitted to hydrogenolysis in the presence of $Pd(OH)_2/C$ and Boc_2O to yield in a one-pot procedure *tert*-butoxycarbonyl derivative (2*R*,3*R*)-**10a** in 96% yield (Scheme 1). Compound **10a** was then efficiently converted in two steps into amino ketone (2*R*,3*R*)-**11a** by reaction of methylmagnesium chloride with Weinreb amide **14a** (Scheme 2). On the other hand, the 90:10 mixture of **9** that results from the reduction of enamino ketone **5** was also hydrogenated into a 90:10 mixture of *tert*-butoxycarbonyl derivatives **11** (Scheme 1). Comparison of the spectroscopic data of the major isomer with that of **11a** (obtained as described above) established that this compound was **11a**. Consequently, the major isomer of compounds **9** was assigned as *cis* (2*R*,3*R*)-**9a**. Moreover, when treated under epimerizing basic conditions (DBU, THF, room temp., 15 h), the 90:10 mixture of compounds **9a** and **9a′** evolved into a 50:50 mixture. This result was attributed to the epimerization at the C-3 center, and allowed us to assign the absolute stereochemistry of minor isomer **9a′** (and so that of **11a′**) to be (2*R*,3*S*). Under the acidic conditions of the reduction step, the presence of compound **9a′** in the final reaction mixture was also attributed to the C-3 epimerization of *cis* piperidine **9a** because of the prolonged reaction time (48 h).

In the presence of $Pd(OH)_2/C$, the catalytic hydrogenation of β-enamino carbonyl derivatives **4** and **5** was found to leave the substrates unchanged. With Pt/C, hydrogenation in methanol also left the compounds unchanged. However, when conducted in acetic acid,[9] hydrogenation of **4** and **5** in the presence of Pt/C led to the corresponding *N*-debenzylated piperidines which were not isolated but instead readily transformed, respectively, into *tert*-butyl carbamates **10** and **11** for easier isolation and identification (Scheme 1). Noteworthy was the excellent diastereoselectivity that was obtained in both cases, which resulted in only *cis* 2,3-disubstituted piperidines **10a** and **11a**.[10]



Scheme 2. Synthesis of **11a** from **10a**.

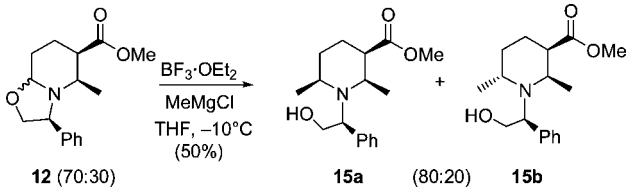
Alternatively, catalytic hydrogenation in the presence of PtO_2 as the catalyst, in methanol or methyl acetate, chemoselectively reduced compounds **4** and **5** into, respectively, bicyclic piperidines **12** and **13** as inseparable mixtures of isomers (ratio 70:30 for **12** and 77:23 for **13**) (Scheme 1). It was noteworthy that the same reaction conditions, applied to a 80:20 epimeric mixture of β-enamino esters (8a*S*)-**4** and (8a*R*)-**4** yielded a mixture of compounds **12** in a 70:30 ratio that was identical to the one obtained starting from pure (8a*S*)-**4**. Moreover, hydride reduction of the mixtures of **12** and **13** by triacetoxy borohydride in THF led to **8a** and **9a**, respectively, in high yields as single *cis* isomers. These results demonstrate that the initial mixtures of **12** and **13** were composed of epimers at C-8a with the *cis* relative stereochemistry between the substituents at C-5 and C-6 of the

oxazolidino piperidines. Besides, NOE experiments conducted on each mixture allowed us to assign the relative stereochemistries between the substituents at C-5 and C-8a: the major isomers **12a** and **13a** exhibited the (8a*R*) configuration. Moreover, these NOE experiments showed a transfer of saturation from one species to the other, which confirmed that both inseparable epimeric mixtures of oxazolidines were in equilibrium, as previously reported for related compounds.[11] The interest of these reduction conditions lies in the preservation of the oxazolidine substructure, which could allow the introduction of substituents at C-6 of the piperidine ring by subsequent reaction with organometallic reagents or silyl enol ethers while keeping in mind that the stereochemistry of the C-8a center of such bicyclic oxazolidines is of little importance for the stereochemistry of the final products.[12]

Finally, hydrogenolysis in the presence of $Pd(OH)_2/C$ as the catalyst and in situ *tert*-butoxycarbonylation was conducted on the mixtures of **12** and **13** and respectively afforded compounds **10a** and **11a** (Scheme 1).

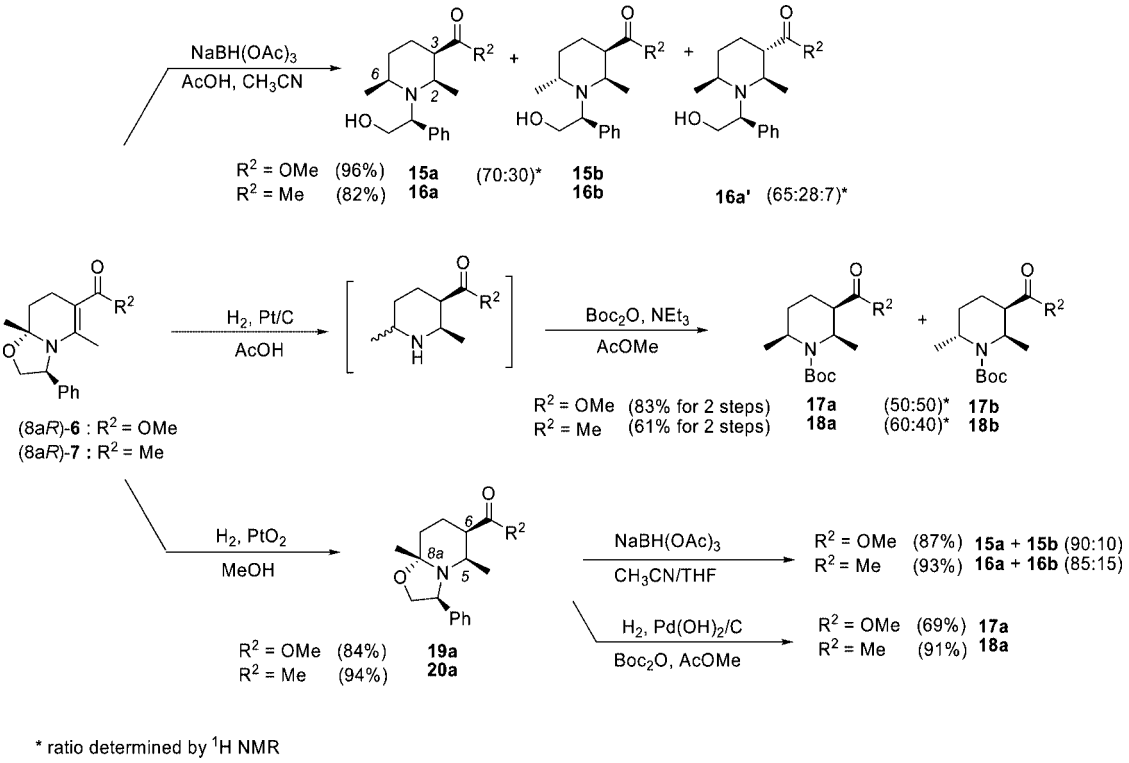
In summary, reduction of angularly hydrogen-substituted compounds (8a*S*)-**4** and (8a*S*)-**5** allowed us to efficiently prepare, in high yields, enantiopure *cis* 2,3-disubstituted piperidines or *cis* 5,6-disubstituted oxazolidino piperidines depending on the reaction conditions. In all cases, attack of the hydride/hydrogen on the double bond stereoselectively proceeded *anti* to the phenyl substituent.

We next turned our attention to the reductions of angularly methyl-substituted compounds (8a*R*)-**6** and (8a*R*)-**7** (Scheme 3). Reduction of β-enamino ester **6** with sodium triacetoxy borohydride in acetic acid[13] afforded monocyclic amino esters **15** as an inseparable 70:30 mixture of isomers (Scheme 3). In order to assign the stereochemistry of the newly created stereocenters, we reacted the mixture of oxazolidines **12** (a mixture 70:30 stemming from the reduction of **4**) with methylmagnesium chloride in the presence of boron trifluoride etherate. This reaction afforded an 80:20 mixture of piperidines **15a** and **15b** (Scheme 4). We assigned the (2*R*,3*R*,6*S*) stereochemistry to major isomer **15a** and (2*R*,3*R*,6*R*) to minor isomer **15b** on the basis of the following considerations. First, it is known that alkylations of similar oxazolidines by organometallic reagents in the presence of Lewis acids give *cis* 2,6-disubstitued piperidines as the major products.[12a,14] Moreover, the respective *cis* and *trans* relationship between the 2- and 6-methyl groups in **15a** and in **15b** was fully confirmed by the difference between the ^{13}C NMR chemical shifts corresponding to the methine and methylene carbons of the chiral auxiliary.[15]



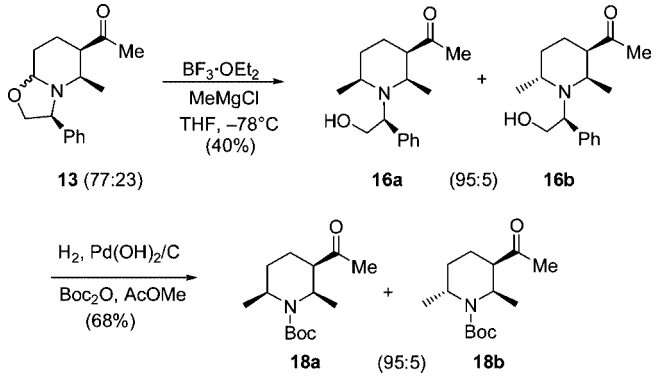
Scheme 4.

Concerning β-enamino ketone **7**, we similarly obtained, under the same reaction conditions as above, a 65:28:7 mixture of three isomers **16**. As previously mentioned, the reaction of oxazolidines **13** (a 70:30 mixture stemming from the



Scheme 3. Reduction of (8a*R*)-**6** and (8a*R*)-**7**.

reduction of **5**) with methylmagnesium chloride, in the presence of boron trifluoride etherate, yielded piperidine (2*R*,3*R*,6*S*)-**16a** as the major product along with a small amount of (2*R*,3*R*,6*R*)-**16b** (ratio 95:5) (Scheme 5), which allowed us to identify the two major isomers of reduced mixture as **16a** and **16b**. Moreover, a 65:28:7 mixture of **16** treated in acidic epimerizing conditions (3 N HCl, MeOH, 3 h) evolved into a 45:26:29 mixture. The minor compound could thus be attributed to the C-3 epimer of major isomer **16a**, that is **16a′** (the product resulting from the epimerization of minor isomer **16b** was not detectable). Thus, we assumed that the stereochemical control of the reduction of the double bond was excellent, with an exclusive *cis* relative stereochemistry of the substituents at C-2 and C-3, but epimerization at the C-3 center, which resulted from prolonged reaction time under acidic conditions, occurred and could not be avoided. Moreover, reductive cleavage of the C–O bond of the oxazolidine moiety of **7** proceeded with a modest selectivity generating a mixture of isomers among which all *cis* compound **16a** was the major product.



Scheme 5.

As previously observed, hydrogenation of compounds **6** and **7** in the presence of $Pd(OH)_2$/C was inefficient. However, hydrogenation conducted in the presence of Pt/C in acetic acid[9] followed by *tert*-butoxycarbonlylation, respectively, gave rise to mixtures of piperidines **17** and **18**[10] with poor diastereoselectivities (ratio 50:50 and 60:40, respectively) (Scheme 3). The stereochemistry of amino esters **17** was established after comparison of their spectroscopic data with that of the compounds obtained by hydrogenolysis of compounds **15** (stemming from hydride reduction of **6**) in the presence of $Pd(OH)_2$/C and Boc_2O, whereas the stereochemistry of amino ketones **18** was established by comparison of their spectroscopic data with that of the *tert*-butoxycarbonyl derivatives obtained from **16**, compounds which in turn had been obtained from **13** (Scheme 5).

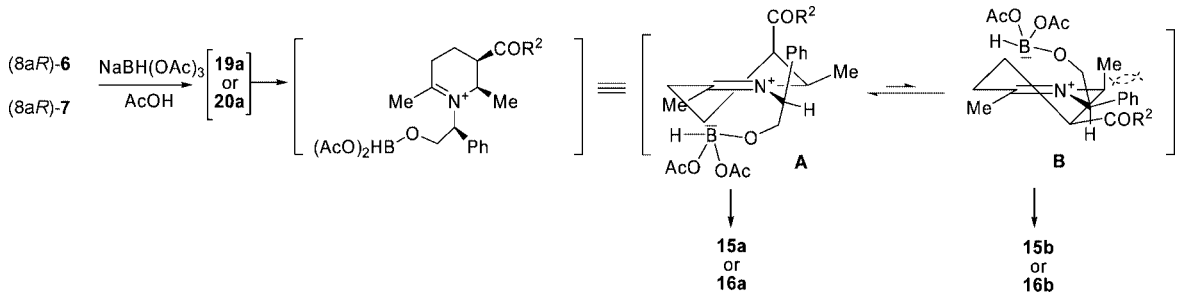
Finally, compounds **6** and **7** were submitted to catalytic hydrogenation in the presence of PtO_2 as the catalyst to respectively give in high yields bicyclic piperidines **19a** and **20a** as single isomers (Scheme 3). In order to establish the absolute configuration of compounds **19a** and **20a**, these compounds were treated with commercially available triacetoxy borohydride[16] to afford mixtures of compounds **15a**–**15b** (90:10) and **16a**–**16b** (85:15), in 87% and 93% yield, respectively. NOE experiments performed on **19a** and **20a** established the *cis* relationship between the methyl groups at C-5 and C-8a. These results allowed us to assign the (5*R*,6*R*,8a*R*) configuration to oxazolidines **19a** and **20a**.

On the other hand, we also conducted a catalytic hydrogenation on the 80:20 epimeric mixture of β-enamino ester (8a*R*)-**6** and (8a*S*)-**6**. Once again, we obtained isomer **19a** as a single product. This result showed that, as previously observed for homologous compounds **12**, epimerization had occurred at the quaternary angular carbon. In the present case, this process was completely in favor of the thermodynamic isomer.

Furthermore, oxazolidines **19a** and **20a**, when subjected to hydrogenolysis in the presence of $Pd(OH)_2$/C and subsequent in situ *tert*-butoxycarbonylation, respectively, yielded compounds **17a** and **18a** as single isomers in good yields. Overall, the two step procedure consisting of two successive hydrogenations [in the presence first of PtO_2 and then $Pd(OH)_2$/C] constitutes a very attractive strategy to access the "all *cis*" 2,3,6-substituted piperidines.

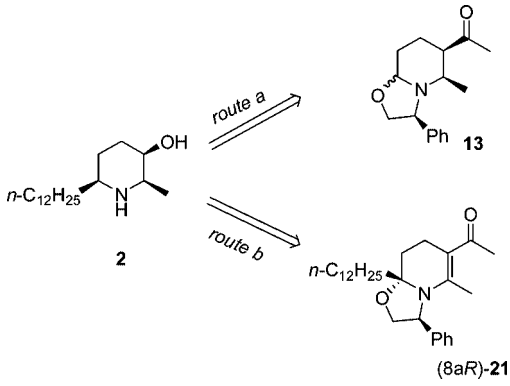
The above study showed that bicyclic β-enamino carbonyl piperidines **4**–**7**, which possess three bonds that may be reduced, displayed different behaviors according to the reductive conditions. In all cases, we observed total stereocontrol of the C–C double bond reduction as the result of the *syn* approach of the reductive reagent from the less hindered face that is *anti* to the phenyl group of the chiral auxiliary. Whatever the reductive conditions, addition to the C–C double bond was always the first reduction to occur leading to intermediate oxazolidino piperidines. In the case of angularly methyl substituted compounds **19a** and **20a**, hydrogenations, in the presence of $Pd(OH)_2$/C as the catalyst, of these bicyclic compounds afforded diastereoselectively "all *cis*" substituted piperidines as the consequence of the initial reduction of the C–O bonds from the *endo* face followed by *N*-debenzylation. In contrast, catalytic hydrogenations in the presence of Pt/C as the catalyst yielded piperidines with poor diastereoselectivities at the methyl-substituted C-6 centers, which suggested that early *N*-debenzylation had occurred. Regarding the triacetoxy borohydride mediated reaction, the stereocontrol of the C-6 center was better and the chiral auxiliary on the nitrogen atom was preserved. The bicyclic oxazolidino piperidine was supposed to be in equilibrium with a monocyclic borohydride-containing iminium[17] that would subsequently evolve through intramolecular axial delivery of the hydride to the iminium under stereoelectronic control (Scheme 6). The minor isomers formed would stem from reactive conformation **B**, which is slightly disfavored compared to conformation **A** because of steric interactions between the phenyl ring of the chiral auxiliary and the C-2 methyl substituent[18] (Scheme 6).

In order to illustrate the synthetic potential of our methodology, we decided to carry out the total synthesis of (–)-deoxocassine (**2**),[4] a simple 3-hydroxy piperidine analogue of piperidine alkaloid (–)-cassine (**3**) that was isolated from the leaves of the *Cassia* species.[5] Access to target compound **2** was envisioned according to two strategies, which



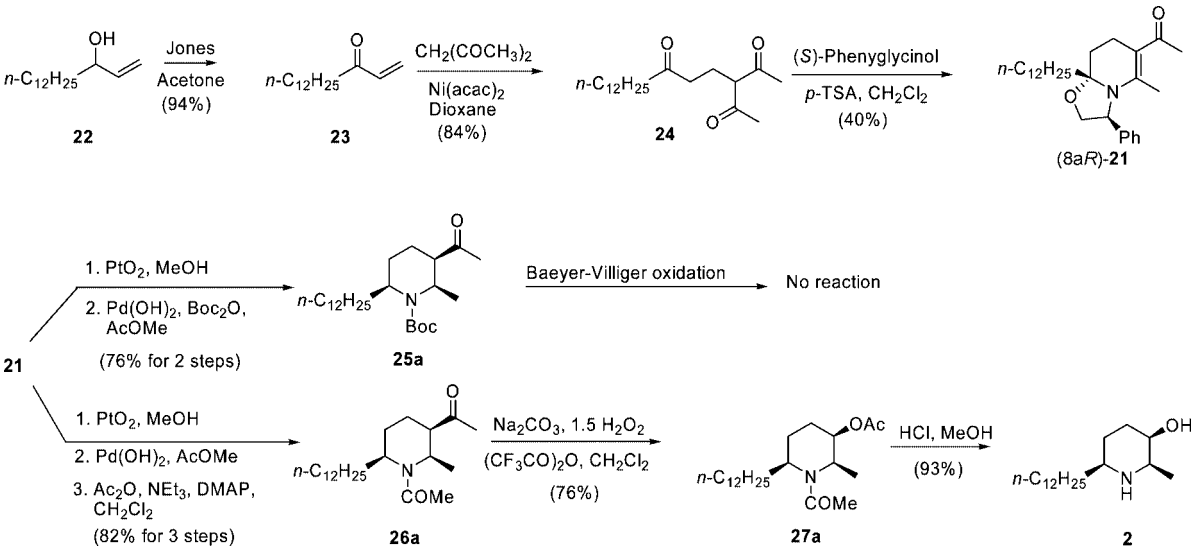
Scheme 6. Proposed mechanism for $NaBH(OAc)_3$ mediated reductions.

rely either on the alkylation of β-amino ketone **13** (Scheme 7, route a), or on the diastereoselective reduction of oxazolidino piperidine (8a*R*)-**21** that bears an angular dodecyl group (Scheme 7, route b).



Scheme 7.

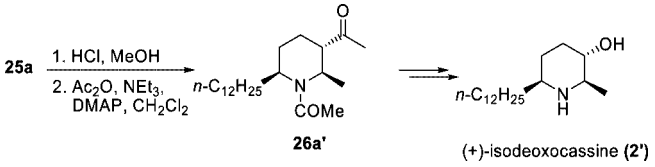
We initially focused our attention on route a (Scheme 7). The introduction of the required dodecyl moiety at C-6 was achieved by reaction of dodecylmagnesium bromide on oxazolidino piperidine **13** in the presence of boron trifluoride etherate as a Lewis acid. Unfortunately, the conversion rate of the reaction did not exceed 35% (according to ^1H NMR), whatever the conditions used (temperature, ratio of reagents, etc.). Therefore, we turned our attention to alternative route b (Scheme 7), that is the synthesis and the subsequent reduction of bicyclic β-enamino ketone **21** (Scheme 8). Following the procedure we previously described for compounds **1**,[1] compound **21** was obtained starting from allylic alcohol **22**[19a,19b] in three steps. Jones oxidation of **22** gave rise in 94% yield to conjugated ketone **23** that was then reacted with methyl acetoacetate, in the presence of $Ni(acac)_2$ as a catalyst, to afford tricarbonyl compound **24** in 84% yield. The latter was condensed with (*S*)-phenylglycinol under various experimental conditions[20] to give rise to oxazolidino piperidine **21** as a single isomer, which was assumed to possess a (8a*R*) absolute configuration, by analogy with our previous results.[1] The best conditions (*p*-toluenesulfonic acid as a catalyst, in refluxing CH_2Cl_2) afforded the expected compound but in a disappointing 40% yield. The two step reduction procedure involving initial PtO_2-catalyzed hydrogenation followed by hydrogenolysis in the presence of $Pd(OH)_2/C$ and Boc_2O afforded piperidine **25a** as a single isomer initially considered as "all *cis*" by analogy with methyl analogue **20a**. This relative stereochemistry was ultimately secured by the obtention of **2** (see below). Attempted Baeyer–Villiger oxidation of compound **25a** under various experimental conditions[21] left the product unchanged. This failure was attributed to the *tert*-butoxycarbonyl protecting group of **25a**. As



Scheme 8. Total synthesis of (–)-deoxocassine (**2**).

a consequence of this hypothesis, we decided to shift to an *N*-acetyl protecting group on the basis of a previous report by other authors[4c] where a related *N*-trifluoroacetyl-3-acetyl piperidine had successfully undergone a Baeyer–Villiger oxidation. After the two step catalytic reduction of **21a**, the free piperidine was acetylated to give compound **26a** in 82% overall yield from **21**. Baeyer–Villiger oxidation of **26a** was carried out with sodium percarbonate and trifluoroacetic anhydride[22] to afford ester **27a** as a single isomer in 76% optimized yield. Hydrolysis under acidic conditions gave rise to the corresponding hydroxypiperidine in 93% yield. Comparison of the spectroscopic data of the resulting compound with that reported in the literature[4a,4b] confirmed the obtention of (–)-deoxocassine (**2**).

During the course of this study, we attempted the transformation of *tert*-butoxycarbonyl piperidine **25a** into *N*-acetyl piperidine **26a** by deprotection in acidic medium followed by *N*-acetylation (Scheme 9). Surprisingly, resulting compound **26a′** exhibited different spectroscopic data from that of **26a**. This discrepancy was hypothesized to result from the epimerization at the C-3 center during the deprotection step. Compound **26a′** was then subjected to the Baeyer–Villiger oxidation–hydrolysis sequence to afford hydroxypiperidine **2′** whose spectroscopic data corresponded to that of (+)-isodeoxocassine,[4a] the C-3 epimer of (–)-deoxocassine {$[\alpha]_D^{20}$ = +11.0 (*c* 0.136, $CHCl_3$) compared to $[\alpha]_D^{24}$ = +13.1 (*c* 0.16, $CHCl_3$)[4a]}. This result confirmed that total epimerization at C-3 had occurred during acidic treatment of compound **25a**. This unexpected observation suggests that acidic treatment of piperidines such as **25a** or **26a** could constitute a convenient method to access *trans* 2,3-substituted piperidines such as **26a′**.



Scheme 9.

Conclusions

In conclusion, the reported study enabled us to prepare enantiopure 2,3- and 2,3,6-substituted β-amino carbonyl piperidines by diastereoselective controlled reduction of bicyclic chiral β-enamino esters and ketones. In particular, our strategy provides efficient access to "all *cis*" substituted piperidines that are useful intermediates for the synthesis of alkaloids. As an illustration, we achieved the total synthesis of (–)-deoxocassine (**2**), a simple analogue of natural (–)-cassine, in five steps and 58% overall yield from oxazolidino piperidine **21**.

Experimental Section

General: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone ketyl immediately prior to use. CH_2Cl_2 was distilled from calcium hydride. Thin layer chromatography analyses were performed with Merck precoated silica gel (60 F_{254}) plates and column chromatography on silica gel Gerudan SI 60 (40–60 μm) (Merck). Melting points are uncorrected. IR spectra were recorded with a Philips PU 9700 instrument. Gas chromatography was performed with capillary Chrompack CP-SIL5 columns. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Elemental analyses were performed by Service de Microanalyse of ICSN (Gif sur Yvette). HRMS were recorded with a JEOL MS 700 mass spectrometer. NMR spectra were recorded with a Bruker ARX 250 spectrometer. Chemical shifts (δ) are expressed in ppm relative to TMS at δ = 0 ppm for ^{1}H NMR and to $CDCl_3$ at δ = 77.16 ppm for ^{13}C NMR.

General Procedure for $NaBH(OAc)_3$ Mediated Reductions: Procedure A: A solution of $NaBH(OAc)_3$ was prepared by portion wise addition of $NaBH_4$ (5 mmol) to glacial acetic acid (50 mmol) in acetonitrile (1.5 mL) at 0 °C. After hydrogen gas evolution ceased (30 min), a solution of the substrate (1 mmol) in acetonitrile (1 mL) was added. After stirring for 48 h at room temperature, water (10 mL) was added and solid Na_2CO_3 was slowly added until pH = 9. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. **Procedure B:** To a solution of the substrate (1 mmol) in THF (20 mL) was added $NaBH(OAc)_3$ (2.5 mmol), and the reaction mixture was stirred at room temperature for 48 h. Saturated $NaHCO_3$ solution was added (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo.

Methyl (2*R*,3*R*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-2-methylpiperidine-3-carboxylate (8a): From **4**: General procedure A was followed for the reduction of compound **4** (404 mg, 1.48 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 7:3) afforded **8a** (391 mg, 95%) as a white solid. From **12**: General procedure B was followed for the reduction of compound **12** (75 mg, 0.272 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 7:3) afforded **8a** (70 mg, 93%) as a white solid. M.p. 41 °C. $[\alpha]_D^{20}$ = +17.4 (*c* 1.02, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3420, 1720 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.75 Hz, 3 H), 1.33–1.55 (m, 1 H), 1.55–1.83 (m, 3 H), 2.38 (td, *J* = 2.5 and 12.25 Hz, 1 H), 2.55–2.65 (m, 1 H), 2.73 (br. s, 1 H), 2.81 (td, *J* = 4.25 and 12 Hz, 1 H), 3.60–3.80 (m, 4 H), 3.65 (s, 3 H), 7.20–7.35 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.9, 20.5, 25.1, 40.8, 46.7, 51.6, 53.8, 62.4, 68.7, 127.7, 128.4, 128.7, 140.2, 174.0 ppm. $C_{16}H_{23}NO_3$ (277.36): calcd. C 69.29, H 8.36, N 5.05; found C 69.05, H 8.38, N 4.91.

X-ray Diffraction Data for the Picric Salt of 8a: $C_{22}H_{25}N_4O_{10}$ (505.46). Trigonal, space group R3, *a* = 24.7915(9), *b* = 24.7915(14) and *c* = 10.0592(12) Å, α = 90, β = 90, γ = 120°, *V* = 5356.6(2) Å^3, *Z* = 9, $D_{calcd.}$ = 1.41 gcm^{-3}, μ (Mo-K_α) = 1.129 cm^{-1}. Data were recorded at room temperature with a Kappa-CCD Bruker diffractometer with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) and the ω-scan technique. Orientation matrix and lattice parameters were obtained by least-squares refinement of the diffraction data of 48 reflections within the range of 3° < θ < 18°. The index ranges of data collection were $-30 \le h \le 32$, $-31 \le k \le 20$, $-5 \le l \le 13$. Intensity data were collected in the θ range 2.0–27.5°, 1841 have $(F_o)^2 \ge 3\sigma(F_o)^2$. All the measured independent reflections were used in the analysis. The structure was solved by direct methods by using SHELXS86[23] and refined with full-matrix least-squares technique on *F* using the CRYSTALS[24]

programs. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were either set in calculated positions or isotropically refined. The values of the discrepancy indices R_1 (R_{w2}) for all data were 0.0840 (0.0993). The final Fourier–difference map showed maximum and minimum height peaks of 1.30 and –0.38 e Å^{-3}. The values of number of variable parameters are 326, and those of the goodness-of-fit are 0.9832. CCDC-615564 (for **8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

1-{(2*R*,3*R*,*S*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-2-methylpiperidin-3-yl}ethanone (9a and 9a′): From **5**: General procedure A was followed for the reduction of compound **5** (250 mg, 0.972 mmol). Purification of the crude product (90:10 mixture of isomers) by silica gel column chromatography (AcOEt/cyclohexane, 1:1) afforded a 90:10 mixture of **9a** and **9a′** (171 mg, 67%). From **13**: General procedure B was followed for the reduction of compound **13** (75 mg, 0.29 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 1:1) afforded pure **9a** (65 mg, 86%) as a colorless oil. For **9a**: $[\alpha]_D^{20}$ = –18.5 (*c* 1.07, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3420, 1700 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.75 Hz, 3 H), 1.35–1.72 (m, 4 H), 2.08 (s, 3 H), 2.42 (dt, *J* = 2.5 and 12 Hz, 1 H), 2.57–2.68 (m, 1 H), 2.75–2.83 (m, 1 H), 2.93 (s, 1 H), 3.62–3.82 (m, 4 H), 7.15–7.38 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.1, 19.7, 24.6, 28.1, 41.0, 53.0, 54.2, 62.5, 68.4, 127.6, 128.4, 128.5, 140.1, 209.6 ppm. $C_{16}H_{23}NO_2$ (261.36): calcd. C 73.53, H 8.87, N 5.36; found C 73.23, H 8.98, N 5.46. For **9a′** (characteristic signals from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.75 Hz, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.6, 21.6, 23.6, 42.0, 51.3, 62.2, 66.9, 140.8, 211.2 ppm.

Methyl (2*R*,3*R*,6*R*,*S*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-2,6-dimethylpiperidine-3-carboxylate (15a and 15b): From **6**: General procedure A was followed for the reduction of compound **6** (197 mg, 0.685 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **15** (193 mg, 96%) as an inseparable colorless oily 70:30 mixture of isomers. From **19a**: General procedure B was followed for the reduction of compound **19a** (31 mg, 0.107 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **15** (27 mg, 87%) as an inseparable colorless oily 90:10 mixture of isomers. IR (neat): $\tilde{\nu}$ = 3430, 1720 cm^{-1}. For major **15a** (from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 7 Hz, 3 H), 1.07 (d, *J* = 6.5 Hz, 3 H), 1.45–1.67 (m, 3 H), 1.67–1.96 (m, 1 H), 2.25 (dt, *J* = 4.5 and 12.25 Hz, 1 H), 2.80 (s, 1 H), 2.89–3.00 (m, 1 H), 3.55–3.68 (m, 1 H), 3.61 (s, 3 H), 3.71 (dd, *J* = 5 and 10.25 Hz, 1 H), 3.84–4.00 (m, 2 H), 7.23–7.40 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.7, 17.3, 19.7, 29.6, 44.1, 48.6, 49.7, 51.6, 62.0, 65.8, 126.5, 128.5, 129.1, 139.3, 174.5 ppm. For minor **15b** (characteristic signals from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.75 Hz, 3 H), 3.25–3.40 (m, 1 H), 3.51 (dd, *J* = 5.25 and 10.25 Hz, 1 H), 3.56 (s, 3 H), 4.24 (dd, *J* = 5.25 and 10.25 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.3, 20.8, 21.5, 31.5, 41.7, 48.2, 48.9, 51.5, 59.4, 60.3, 140.2, 174.5 ppm. $C_{17}H_{25}NO_3$ (291.39): calcd. C 70.07, H 8.65, N 4.81; found C 70.01, H 8.95, N 4.57.

1-{(2*R*,3*R*,6*R*,*S*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-2,6-dimethylpiperidin-3-yl}ethanone (16a and 16b): From **7**: General procedure A was followed for the reduction of compound **7** (100 mg, 0.369 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **16** (83 mg, 82%) as an inseparable colorless oily 65:28:7 mixture of isomers. From **20a**: General procedure B was followed for the reduction of compound **20a** (60 mg, 0.219 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 7:3) afforded **16a** and **16b** (57 mg, 93%) as an inseparable colorless oily 85:15 mixture of isomers. IR (neat): $\tilde{\nu}$ = 3420, 1705 cm^{-1}. For major **16a** (from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 7 Hz, 3 H), 1.13 (d, *J* = 6.5 Hz, 3 H), 1.35–1.70 (m, 3 H), 1.78–1.96 (m, 1 H), 1.88 (s, 3 H), 2.02–2.16 (m, 1 H), 2.90–3.10 (m, 2 H), 3.53–3.64 (m, 1 H), 3.72 (dd, *J* = 4.75 and 10.25 Hz, 1 H), 3.87–3.94 (m, 1 H), 4.02 (dd, *J* = 5.0 and 8.5 Hz, 1 H), 7.20–7.50 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.8, 18.7, 20.7, 28.3, 29.1, 47.8, 50.0, 51.0, 61.3, 65.1, 128.0, 128.4, 128.5, 138.8, 209.5 ppm. For minor **16b** (characteristic signals from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 7 Hz, 3 H), 1.86 (s, 3 H), 3.29–3.37 (m, 1 H), 4.29 (dd, *J* = 5.25 and 10 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.6, 31.6, 48.0, 48.9, 59.1, 60.3, 140.2, 209.9 ppm. For **16a′** (characteristic signals from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.24 (s, 3 H). $C_{17}H_{25}NO_2$ (275.32): calcd. C 74.14, H 9.15, N 5.09; found C 73.81, H 9.36, N 5.02.

General Procedure for $Pd(OH)_2$/C Catalyzed Hydrogenations and in situ *tert*-Butoxycarbonylation: A solution of the substrate (1 mmol) in methyl acetate (10 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2$/C (0.2 equiv. in weight) and Boc_2O (2.1 equiv.), at room temperature. The progress of the reaction was monitored by GC. The reaction mixture was filtered, the residue thoroughly washed with MeOH and the combined filtrates were concentrated in vacuo.

1-*tert*-Butyl 3-Methyl (2*R*,3*R*)-2-Methylpiperidine-1,3-dicarboxylate (10a): From **8a**: The general procedure was followed for the reduction of compound **8a** (70 mg, 0.252 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded **10a** (62 mg, 96%) as a white solid. From **12**: The general procedure was followed for the reduction of compound **12** (73 mg, 0.265 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded **10a** (61 mg, 89%) as a white solid. M.p. 37 °C. $[\alpha]_D^{20}$ = –71.3 (*c* 1.015, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1730, 1685 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7 Hz, 3 H), 1.25–1.55 (m, 1 H), 1.47 (s, 9 H), 1.62–1.92 (m, 3 H), 2.63 (dt, *J* = 4.75 and 12.25 Hz, 1 H), 2.70–2.90 (m, 1 H), 3.69 (s, 3 H), 3.75–4.10 (m, 1 H), 4.55–4.90 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, rotamers): δ = 12.1, 20.5 and 24.6, 24.8, 28.5, 37.5 and 38.6, 44.9 and 45.2, 46.8 and 48.0, 51.7, 79.7, 154.7, 173.4 ppm. $C_{13}H_{23}NO_4$ (257.33): calcd. C 60.68, H 9.01, N 5.44; found C 60.85, H 8.84, N 5.39.

***tert*-Butyl (2*R*,3*R*)-3-Acetyl-2-methylpiperidine-1-carboxylate (11a):** From **9**: The general procedure was followed for the reduction of compound **9** (91 mg, 0.348 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded a 90:10 mixture of **11a** and **11a′** (68 mg, 81%). From **13**: The general procedure was followed for the reduction of compound **13** (41 mg, 0.158 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded pure **11a** (27 mg, 71%) as a white solid. M.p. 47 °C. $[\alpha]_D^{20}$ = –113.8 (*c* 1.015, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1705, 1690 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 7.5 Hz, 3 H), 1.25–1.45 (m, 1 H), 1.47 (s, 9 H), 1.60–1.80 (m, 3 H), 2.25 (s, 3 H), 2.45–2.90 (m, 2 H), 3.80–4.05 (m, 1 H), 4.60–4.95 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, rotamers): δ = 12.1, 19.6 and 19.9, 24.7, 28.4, 28.5, 37.6 and 38.8, 46.5 and 47.7, 53.0, 79.8, 154.7, 208.6 ppm. $C_{13}H_{23}NO_3$ (241.33): calcd. C 64.70, H 9.61, N 5.80; found C 64.93, H 9.37, N 5.71.

1-*tert*-Butyl 3-Methyl (2*R*,3*R*,6*R*,*S*)-2,6-Dimethylpiperidin-1,3-dicarboxylate (17a and 17b): From **15**: The general procedure was followed for the reduction of a 70:30 mixture of compounds **15a**/**15b** (83 mg, 0.285 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded **17a** and **17b** (68 mg, 88%) as a 70:30 mixture of isomers. From **19a**: The general procedure was followed for the reduction of compound **19a** (74 mg, 0.256 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded pure **17a** (48 mg, 69%) as a white solid. For **17a**: M.p. 44 °C. $[\alpha]_D^{20}$ = –19.6 (*c* 1.005, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1740, 1690 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.75 Hz, 3 H), 1.17 (d, *J* = 7 Hz, 3 H), 1.48 (s, 9 H), 1.58–2.02 (m, 4 H), 2.56–2.65 (m, 1 H), 3.69 (s, 3 H), 4.29 (br. s, 1 H), 4.62 (br. s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.9, 16.8, 20.7, 28.6, 29.3, 45.5, 47.0, 51.8, 79.6, 154.9, 173.6 ppm. $C_{14}H_{25}NO_4$ (271.35): calcd. C 61.97, H 9.29, N 5.16; found C 61.99, H 9.41, N 5.19. For **17b** (characteristic signals from a mixture): ^1H NMR (250 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6 Hz, 3 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 2.67–3.06 (m, 1 H), 3.70 (s, 3 H), 3.85–4.00 (m, 1 H), 4.40–4.50 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.6, 17.0, 21.4, 25.7, 28.6, 41.6, 48.3, 51.9, 79.3, 154.8, 173.5 ppm.

***tert*-Butyl (2*R*,3*R*,6*R*,*S*)-3-Acetyl-2,6-dimethylpiperidine-1-carboxylate (18a and 18b):** From **16**: The general procedure was followed for the reduction of a 95:5 mixture of compound **16a**/**16b** (103 mg, 0.374 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded a 95:5 mixture of compounds **18a** and **18b** (65 mg, 68%) as a white solid. From **20a**: The general procedure was followed for the reduction of compound **20a** (71 mg, 0.260 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded **18a** (60 mg, 91%). For **18a**: M.p. 75 °C. $[\alpha]_D^{20}$ = –49.5 (*c* 1.040, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1705, 1680 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 7 Hz, 3 H), 1.16 (d, *J* = 7.25 Hz, 3 H), 1.49 (s, 9 H), 1.55–1.68 (m, 3 H), 1.75–2.00 (m, 1 H), 2.18 (s, 3 H), 2.59–2.67 (m, 1 H), 4.27 (br. s, 1 H), 4.79 (br. s, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.9, 16.7, 20.8, 28.5, 29.2, 45.9, 46.4, 53.3, 79.7, 154.9, 208.8 ppm. $C_{14}H_{25}NO_3$ (255.35): calcd. C 65.85, H 9.87, N 5.49; found C 65.78, H 10.01, N 5.24. For **18b** (characteristic signals from a mixture): ^1H NMR (250 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.75 Hz, 1 H), 1.23 (d, *J* = 6.75 Hz, 3 H), 1.46 (s, 9 H), 2.20 (s, 3 H), 2.97–3.06 (m, 1 H), 3.85–4.10 (m, 1 H), 4.50–4.60 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.4, 17.0, 21.5, 25.8, 28.6, 29.8, 46.8, 47.9, 49.7, 79.5, 154.9, 207.8 ppm.

General Procedure for Grignard Reactions: To a solution of the substrate (1 mmol) in THF (10 mL) at –10 °C was added $BF_3{\cdot}OEt_2$ (1.3 mmol). After stirring for 15 min, 3 M solution of MeMgCl in THF (1.2 mmol) was added. The reaction mixture was stirred overnight at this temperature and quenched by addition of 10% NH_4Cl solution (15 mL). The mixture was warmed to room temperature, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo.

Synthesis of 15 from 12: The general procedure was followed starting from compound **12** (93 mg, 0.338 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded a 80:20 mixture of compounds **15a** and **15b** (49 mg, 50%) along with recovered starting material **12** (45 mg, 48%).

Synthesis of 16 from 13: The general procedure was followed (except that the reaction mixture was cooled to –78 °C prior to MeMgCl addition and stirred overnight at this temperature) starting from compound **13** (90 mg, 0.347 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded a 95:5 mixture of compounds **16a** and **16b** (40 mg, 40%) along with recovered starting material **16** (44 mg, 49%).

General Procedure for Pt/C Catalyzed Hydrogenation and Subsequent *tert*-Butoxycarbonylation: A solution of the substrate (1 mmol) dissolved in AcOH (20 mL) was subjected to hydrogenation (1 atm) in the presence of 5% Pt/C (0.4 equiv. in weight) at room temperature for 12 h. The reaction mixture was filtered. Saturated Na_2CO_3 solution was slowly added (20 mL) followed by solid Na_2CO_3 until pH = 9. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and partially concentrated in vacuo until 10 mL of CH_2Cl_2 remained. To this solution, NEt_3 (13 mmol) and Boc_2O (2.6 mmol) were added. After stirring overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2, and the organic layer was successively washed with saturated aqueous NH_4Cl solution (30 mL), $NaHCO_3$ (30 mL) brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo.

Synthesis of 10a from 4: The general procedure was followed for the reduction of compound **4** (73 mg, 0.265 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded **10a** (75 mg, 70%) as a white solid.

Synthesis of 11a from 5: The general procedure was followed for the reduction of compound **5** (70 mg, 0.272 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **11a** (45 mg, 69%) as a white solid.

Synthesis of 17 from: 6: The general procedure was followed for the reduction of compound **6** (200 mg, 0.696 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 15:85) afforded a 1:1 mixture of isomers **17a** and **17b** (157 mg, 83%).

Synthesis of 18 from 7: The general procedure was followed for the reduction of compound **7** (70 mg, 0.258 mmol). Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded a 6:4 mixture of isomers **18a** and **18b** (40 mg, 61%).

General Procedure for PtO_2 Catalyzed Hydrogenations: A solution of the substrate (1 mmol) dissolved in MeOH or AcOMe (30 mL) was subjected to hydrogenation (1 atm) in the presence of PtO_2 (0.25 equiv. in weight) at room temperature for 30 min to 1 h. The reaction mixture was filtered, the residue thoroughly washed with MeOH, and the organic layer was concentrated in vacuo.

Methyl (3*S*,5*R*,6*R*,8a*R*,*S*)-5-Methyl-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-6-carboxylate (12a and 12b): The general procedure was followed for the reduction of compound **4** (100 mg, 0.366 mmol) in MeOH. Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **12a** and **12b** (79 mg, 78%) as an inseparable colorless oily 7:3 mixture of isomers. IR (neat): $\tilde{\nu}$ = 1730 cm^{-1}. For major **12a** (from a mixture): ^1H NMR (250 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 7 Hz, 3 H), 1.50–1.68 (m, 2 H), 1.76–1.98 (m, 2 H), 2.69–2.85 (m, 1 H), 3.29–3.34 (m, 1 H), 3.59 (s, 3 H), 3.60–3.68 (m, 1 H), 4.23–4.34 (m, 2 H), 4.98 (dd, *J* = 3.50 and 9.25 Hz, 1 H), 7.15–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.3, 19.6, 27.0, 39.6, 49.8, 51.5, 61.9, 73.4, 87.1, 127.6, 128.3, 128.7, 140.1, 174.3 ppm. For minor **12b** (from a mixture): ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.75 Hz, 3 H), 1.76–1.98 (m, 2 H), 2.11–2.24 (m, 2 H), 2.42–2.48 (m, 1 H), 2.69–2.85 (m, 1 H), 3.60–3.68 (m, 1 H), 3.66 (s, 3 H), 3.67–3.75 (m, 1 H), 3.81 (dd, *J* = 2.75 and 9.75 Hz, 1 H), 4.16 (t,

J = 8 Hz, 1 H), 7.15–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.9, 25.4, 27.2, 45.6, 51.0, 58.2, 65.0, 74.5, 96.1, 127.1, 127.6, 127.8, 144.2, 173.2 ppm. HRMS (CI): calcd. for $C_{16}H_{22}NO_3$ $[M + H]^+$ 276.1600; found 276.1598.

1-{(3*S*,5*R*,6*R*,8a*R*,*S*)-1-(5-Methyl-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-6-yl}ethanone (13a and 13b): The general procedure was followed for the reduction of compound **5** (300 mg, 1.17 mmol) in AcOMe. Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 3:7) afforded **13a** and **13b** (262 mg, 87%) as an inseparable colorless oily 77:23 mixture of isomers. IR (neat): $\tilde{\nu}$ = 1700 cm^{-1}. For major **13a** (from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (d, J = 7.25 Hz, 3 H), 1.51–1.64 (m, 1 H), 1.70–1.93 (m, 3 H), 2.03 (s, 3 H), 2.83–2.88 (m, 1 H), 3.34–3.40 (m, 1 H), 3.61–3.72 (m, 1 H), 4.27–4.36 (m, 2 H), 5.01 (dd, J = 4 and 10 Hz, 1 H), 7.20–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.9, 18.7, 27.1, 28.7, 47.5, 49.4, 61.7, 73.6, 87.0, 127.6, 127.9, 128.8, 139.7, 209.9 ppm. For minor **13b** (from a mixture): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.76 (d, J = 7.0 Hz, 3 H), 1.70–1.93 (m, 1 H), 1.98–2.07 (m, 3 H), 2.34 (s, 3 H), 2.45–2.48 (m, 1 H), 2.71–2.77 (m, 1 H), 3.61–3.72 (m, 2 H), 3.81 (dd, J = 3.75 and 8.50 Hz, 1 H), 4.17–4.24 (m, 1 H), 7.20–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 19.6, 24.7, 27.1, 31.8, 53.6, 58.0, 65.9, 74.5, 96.1, 127.3, 127.5, 128.5, 143.6, 210.7 ppm. HRMS (CI): calcd. for $C_{16}H_{22}NO_2$ $[M + H]^+$ 260.1651; found 260.1646.

Methyl (3*S*,5*R*,6*R*,8a*R*)-5,8a-Dimethyl-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-6-carboxylate (19a): The general procedure was followed for the reduction of compound **6** (500 mg, 1.74 mmol) in MeOH. Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 1:9) afforded **19a** (423 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ = +93.7 (c 0.983, CH_2Cl_2). IR (neat), $\tilde{\nu}$ = 1730 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (d, J = 7.25 Hz, 3 H), 1.54 (s, 3 H), 1.68–2.05 (m, 4 H), 2.81–2.91 (m, 1 H), 3.26–3.37 (m, 1 H), 3.57 (s, 3 H), 3.62 (t, J = 8 Hz, 1 H), 4.15 (t, J = 7.5 Hz, 1 H), 4.32 (t, J = 7.5 Hz, 1 H), 7.25–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.6, 19.5, 27.7, 32.2, 39.2, 49.8, 51.5, 65.7, 72.2, 92.3, 127.5, 127.7, 128.6, 140.9, 174.5 ppm. HRMS (CI): calcd. for $C_{17}H_{24}NO_3$ $[M + H]^+$ 290.1751; found 290.1753.

1-{(3*S*,5*R*,6*R*,8a*R*)-5,8a-Dimethyl-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-6-yl)}ethanone (20a): The general procedure was followed for the reduction of compound **7** (156 mg, 0.575 mmol) in MeOH. Purification of the crude product by silica gel column chromatography (AcOEt/cyclohexane, 2:8) afforded **20a** (147 mg, 94%) as a white solid. M.p. 60 °C. $[\alpha]_D^{20}$ = +36.3 (c 1.005, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1700 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.01 (d, J = 7.5 Hz, 3 H), 1.53 (s, 3 H), 1.65–2.00 (m, 4 H), 2.00 (s, 3 H), 2.89–2.97 (m, 1 H), 3.30–3.41 (m, 1 H), 3.66 (t, J = 8 Hz, 1 H), 4.17 (t, J = 7.5 Hz, 1 H), 4.36 (t, J = 7.75 Hz, 1 H), 7.25–7.45 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.5, 18.8, 27.8, 28.5, 32.2, 47.5, 49.6, 65.8, 72.2, 92.5, 127.5, 127.9, 128.7, 140.7, 209.9 ppm. $C_{17}H_{23}NO_2$ (273.37): calcd. C 74.69, H 8.48, N 5.12; found C 74.65, H 8.42, N 4.91.

Synthesis of 11a from 10a via 14a: To a cooled (–20 °C) solution of compound **10a** (165 mg, 0.641 mmol) and *N*,*O*-dimethylhydroxylamine chlorohydrate (97 mg, 0.994 mmol) in dry THF (13 mL) was added a solution of isopropylmagesium chloride in THF (2 M, 0.96 mL, 1.92 mmol). After stirring for 20 min, a 10% aqueous solution of NH_4Cl (10 mL) was added at –20 °C. The reaction mixture was warmed to room temperature and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4 and the solvents evaporated in vacuo. Purification by silica gel column chromatography (AcOEt/cyclohexane, 3:7) afforded pure **14a** (145 mg, 79%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (d, J = 7.5 Hz, 3 H), 1.30–1.78 (m, 3 H), 1.47 (s, 9 H), 1.87–2.04 (m, 1 H), 2.70–3.04 (m, 2 H), 3.19 (s, 3 H), 3.76 (s, 3 H), 3.80–4.10 (m, 1 H), 4.62–4.85 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, rotamers): δ = 12.0 and 12.3 ppm, 20.6, 24.4 and 24.6, 28.3, 32.2, 37.2 and 38.5, 42.1 and 42.6, 46.0 and 47.0, 61.4, 79.1, 154.3, 173.8 ppm. To a solution of compound **14a** (145 mg, 0.506 mmol) in THF (3 mL) at 0 °C a solution of magnesium chloride in THF (3 M, 0.51 mL, 1.53 mmol) was added dropwise. The reaction mixture was stirred for 35 min. The solution was cooled to –20 °C and quenched by addition of 10% ammonium chloride solution (10 mL). The reaction mixture was warmed to room temperature, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (AcOEt/cyclohexane, 2:8) afforded pure **11a** (119 mg, 97%) as a colorless oil.

Pentadec-1-en-3-one (23): To a solution of **22**[19a,19b] (3.55 mL, 15.7 mmol) in acetone (125 mL) at 0 °C was added Jones reagent (5.9 mL) over 15 min. After stirring for 30 min at this temperature, 2-propanol (40 mL) and water (100 mL) were successively added. The reaction mixture was concentrated in vacuo, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (AcOEt/cyclohexane 5:95) afforded compound **23** (3.32 g, 94%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1705, 1685, 1620 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H), 1.19–1.38 (m, 18 H), 1.56–1.67 (m, 2 H), 2.58 (t, J = 7.25 Hz, 2 H), 5.81 (dd, J = 1.5 and 10.25 Hz, 1 H), 6.16–6.41 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2, 22.8, 24.1, 29.4, 29.6, 29.7, 32.0, 39.7, 127.9, 136.7, 201.1 ppm. $C_{15}H_{28}O$ (224.38): calcd. C 80.29, H 12.58; found C 80.29, H 12.48.

3-Acetyloctadecane-2,6-dione (24): A mixture of **23** (1.9 g, 8.46 mmol), acetylacetone (0.87 mL, 8.47 mmol) and $Ni(acac)_2$ (22 mg, 0.086 mmol) in dioxane (17 mL) was heated at 85 °C for 3 d. The reaction mixture was concentrated in vacuo and purified by column chromatography to afford **24** (2.3 g, 84%) as a white solid. M.p. 41–42 °C. IR (neat): $\tilde{\nu}$ = 1725, 1710 cm^{-1}. In $CDCl_3$, **24** is partially enolized (40%) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H), 1.20–1.30 (m, 18 H), 1.50–1.60 (m, 2 H), 2.03–2.12 (m, 1.2 H), 2.14 (s, 2.3 H), 2.19 (s, 3.6 H), 2.33–2.45 (m, 3.3 H), 2.50–2.52 (m, 1.6 H), 3.68 (t, J = 6.75 Hz, 0.6 H), 13.25 (s, 0.4 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2, 21.6, 22.8, 23.1, 23.9, 29.3, 29.5, 29.6, 29.7, 32.0, 39.6, 43.1, 43.2, 67.1, 109.2, 191.2, 204.3, 210.2, 210.3 ppm. HRMS (CI): calcd. for $C_{20}H_{36}O_3Na$ $[M + Na]^+$ 347.2556; found 347.2556.

1-{(3*S*,8a*R*)-8a-Dodecyl-5-methyl-3-phenyl-2,3,8,8a-tetrahydo-7*H*-[1,3]oxazolo[3,2-*a*]pyridin-6-yl}ethanone (21): To a solution of **24** (130 mg, 0.401 mmol) in CH_2Cl_2 (4 mL) was added (*S*)-phenylglycinol (61 mg, 0.445 mmol), 4 Å molecular sieves (400 mg), and *p*-TsA (8 mg, 0.042 mmol). The reaction mixture was stirred and heated at reflux for 24 h and then filtered through a Celite pad. The organic layer was concentrated in vacuo and column chromatography on silica gel (AcOEt/cyclohexane, 2:8) afforded pure **21** (69 mg, 40%) as a colorless oil. $[\alpha]_D^{20}$ = +307 (c 1.000, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1630, 1520 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.5 Hz, 3 H), 1.20–1.55 (m, 21 H), 1.60–1.82 (m, 2 H), 2.15 (s, 3 H), 2.19 (s, 3 H), 2.20–2.45 (m, 2 H), 2.58–2.66 (m, 1 H), 3.85 (dd, J = 7 and 9 Hz, 1 H), 4.39 (dd, J = 7.5

and 9 Hz, 1 H), 4.92 (t, J = 7.25 Hz, 1 H), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.1, 20.3, 22.7, 23.1, 23.4, 28.3, 29.3, 29.6, 29.8, 29.9, 31.9, 34.0, 62.8, 71.6, 95.6, 105.2, 125.7, 127.7, 129.0, 141.3, 152.8, 196.5 ppm. HRMS (CI): calcd. for $C_{28}H_{44}NO_2$ $[M + H]^+$ 426.3367; found 426.3364.

***tert*-Butyl (2*R*,3*R*,6*S*)-3-Acetyl-6-dodecyl-2-methylpiperidine-1-carboxylate (25a):** A solution of **21** (192 mg, 0.451 mmol) in MeOH (9 mL) was subjected to hydrogenation (1 atm) in the presence of PtO_2 (38 mg) at room temperature for 3 h. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in AcOMe (4.5 mL). Boc_2O (197 mg, 0.903 mmol) and $Pd(OH)_2/C$ (76 mg) were added, and the reaction mixture was stirred overnight under a hydrogen atmosphere. After filtration and concentration in vacuo, column chromatography on silica gel (AcOEt/cyclohexane, 1:9) gave pure **25a** (141 mg, 76%). M.p. 32 °C. $[\alpha]_D^{20}$ = –41.3 (c 1.000, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1705, 1685 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, rotamers): δ = 0.88 (t, J = 6.75 Hz, 3 H), 1.00 (d, J = 7 Hz, 3 H), 1.10–1.40 (m, 22 H), 1.40–1.95 (m 4 H), 1.48 (s, 9 H), 2.17 (s, 3 H), 2.55–2.61 (m, 1 H), 3.95–4.22 (m, 1 H), 4.55–4.95 (m, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, rotamers): δ = 14.2, 15.1 and 15.5, 16.2 and 16.7, 22.8, 26.9, 27.7, 28.6, 29.4, 29.7, 32.0, 35.1, 46.2 and 47.2, 49.6 and 50.6, 53.7, 79.7, 155.3, 208.8 ppm. $C_{25}H_{47}NO_3$ (409.65): calcd. C 73.30, H 11.56, N 3.42; found C 73.46, H 11.86, N 3.26.

1-[(2*R*,3*R*,6*S*)-1-Acetyl-6-dodecyl-2-methylpiperidin-3-yl]ethanone (26a): A solution of **21** (80 mg, 0.188 mmol) in MeOH (3.7 mL) was subjected to hydrogenation (1 atm) in the presence of PtO_2 (16 mg) at room temperature for 3 h. The reaction mixture was filtered, concentrated in vacuo, and the residue was dissolved in AcOMe (1.9 mL). $Pd(OH)_2/C$ (32 mg) was added, and the reaction mixture was stirred under a hydrogen atmosphere overnight. The reaction mixture was filtered, concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (0.75 mL). To this solution, NEt_3 (0.09 mL. 0.646 mmol), DMAP (2 mg, 0.016 mmol) and Ac_2O (0.08 mL, 0.575 mmol) were added. The reaction mixture was stirred overnight at room temperature and diluted in CH_2Cl_2 (10 mL). The organic layer was successively washed with saturated NH_4Cl solution (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (AcOEt/cyclohexane, 1:1) afforded **26a** (54 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ = –58.3 (c 1.025, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1715, 1645 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, rotamers): δ = 0.88 (t, J = 6.5 Hz, 3 H), 0.99 (d, J = 7 Hz, 1.8 H), 1.13 (d, J = 7 Hz, 1.2 H), 1.20–1.35 (m, 20 H), 1.40–2.0 (m, 6 H), 2.13, 2.18, 2.19 and 2.20 (4s, 6 H), 2.56–2.64 (m, 1 H), 3.70–3.80 (m, 0.6 H), 4.35–4.45 (m, 0.4 H), 4.58–4.70 (m, 0.4 H), 5.27–5.38 (m, 0.6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, rotamers): δ = 14.2, 15.1 and 16.1, 16.2 and 17.2, 22.3 and 22.5, 22.8, 26.7 and 27.0, 27.8 and 27.9, 29.4, 29.7, 32.0, 34.8 and 35.3, 44.1, 47.8; 49.6, 53.5, 54.1, 169.6 and 170.2, 208.6 ppm. HRMS (CI): calcd. for $C_{22}H_{42}NO_2$ $[M + H]^+$ 352.3210; found 352.3210.

(2*R*,3*R*,6*S*)-1-Acetyl-6-dococyl-2-methylpiperidin-3-yl Acetate (27a): To a suspension of **26a** (88 mg, 0.25 mmol) and sodium percarbonate (628 mg, 4 mmol) in CH_2Cl_2 (3.6 mL), trifluoroacetic anhydride (0.14 mL, 1.01 mmol) was added dropwise. The reaction mixture was stirred overnight. 10% $NaHCO_3$ solution (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel (AcOEt: cyclohexane 3:7) afforded pure **27a** (70 mg, 76%) as a colorless oil. $[\alpha]_D^{20}$ = +15.5 (c 0.965, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1735, 1645 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.5 Hz, 3 H), 1.14–1.40 (m, 23 H), 1.40–1.90 (m, 6 H), 2.05 (s, 1.5 H), 2.07 (s, 1.5 H), 2.11 (s, 3 H), 3.65–3.75 (m, 0.5 H), 4.17–2.28 (m, 0.5 H), 4.55–4.65 (m, 0.5 H), 4.70–4.90 (m, 1 H), 4.90–5.03 (m, 0.5 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2, 14.4 and 15.2, 19.9, 21.3, 22.2 and 22.5, 22.8, 25.7 and 26.3, 27.7 and 27.9, 29.4, 29.7, 32.0, 34.4 and 35.4, 45.5 and 47.3, 50.4 and 52.9, 71.4 and 72.1, 170.1, 170.3 ppm. HRMS (CI): calcd. for $C_{22}H_{42}NO_2$ $[M + H]^+$ 368.3159; found 368.3158.

(–)-Deoxocassine (2): To a solution of **27a** (60 mg, 0.163 mg) in MeOH (1 mL), water (5 mL) was added. MeOH was evaporated in vacuo and 36% HCl solution (5 mL) was added. The reaction mixture was stirred and heated at reflux for 48 h. To the cooled reaction mixture was added, dropwise, a saturated Na_2CO_3 solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel (1 N NH_3 in AcOEt/cyclohexane, 1:1) gave pure **2** (43 mg, 93%) as a white solid whose spectroscopic data are in accordance with the literature.[4a,4b] M.p. 50 °C (ref[4a] m.p. 47.5–48.5°). $[\alpha]_D^{20}$ = –12 (c 0.25, $CHCl_3$) {ref[4a] $[\alpha]_D^{18}$ = –12.3 (c 0.19, $CHCl_3$)}.

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[21] Among the different reaction conditions screened: (a) 50% $H_2O_2/(CF_3CO)_2O/Na_2HPO_4/CH_2Cl_2$; (b) *m*-CPBA/$CH_2Cl_2$; (c) $Na_2CO_3{\cdot}1.5H_2O_2/(CF_3CO)_2O/CH_2Cl_2$.
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