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Stereoselective divergent synthesis of 1,2-aminoalcohol-containing heterocycles from a common chiral nonracemic building block

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ABSTRACT

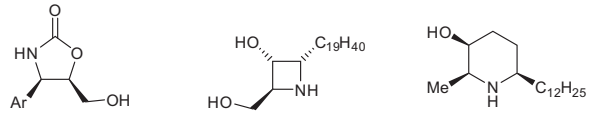
γ-*N*,*N*-Dibenzylamino-β-hydroxysulfoxide **1** proved to be an excellent chiral building block for the synthesis of a range of 1,2-amino alcohol-containing heterocycles. Thus, **1** was converted into 4,5-disubstuted oxazolidin-2-one **4** and aminoepoxides **2** and **3**. Aminoepoxide **2** proved to be an excellent precursor to access oxazolidin-2-one **5** and azetidin-3-ol **6**. Finally, **2** was used as a key intermediate that allowed the development of a divergent strategy to access *cis*-2-methyl-6-substituted piperidin-3-ol alkaloids. (+)-Deoxocassine **7** and a C-6 ethyl analogue **8** were prepared to illustrate this approach and to demonstrate that this strategy should be adaptable to the production of other members of this alkaloid family.

1. Introduction

The advance of biology has revealed the imperative need of developing structural diversity for a rapid and efficient lead generation in drug discovery. Analogously to biosynthetic pathways provided by Nature, and as an alternative to the traditional 'single target' strategy, the design of divergent pathways to produce collections of biologically active compounds from a single building block presents significant challenges to synthetic chemists.[1]

Among the naturally occurring and synthetic cyclic amino alcohols, in which a 1,2-amino alcohol moiety is contained within the ring,[2] oxazolidin-2-ones are of special importance because of their use as chiral auxiliaries[3] and their occurrence in synthetic pharmaceuticals.[4] Representatives of this class of compound include befloxatone, streptazolin, and cytoxazone (Fig. 1). Besides oxazolidinones, azetidines are also an extraordinary class of azaheterocyclic compounds. In particular, azetidin-3-ols can be found in natural products, as the sphingosine type alkaloids Penaresidines A and B and Penazetidin A,[5] and can be considered as potential building blocks of diverse enantiopure bioactive nitrogen-containing compounds. Therefore, the synthesis of optically active oxazolidin-2-ones and azetidin-3-ols still remains challenging to synthetic chemists.

On the other hand, *cis*-2-methyl-6-substituted piperidin-3-ol alkaloids, which have been isolated from leaves and twigs of the plant genera *Cassia* and *Prosopis*,[6] have as a common stereochemical feature an 'all-*cis*' relative configuration. The structural diversity is due to a long side chain at C-6. Considerable effort has been invested in the development of syntheses based on a chiral pool approach[7] or the use of asymmetric synthesis.[8] However, most of the synthetic approaches disclosed to date, have the major drawback that they do not allow adequate diversity and substitution. In light of this, short, efficient, and versatile strategies providing diverse access to C-6 analogues of 'all-*cis*' 2-methyl-6-substituted piperidin-3-ols, continue to be a subject of importance in synthetic organic chemistry.



(-)-Cytoxazone
Ar = 4-MeOPh

Penazetidin A

(+)-Deoxocassine

Figure 1. Examples of 1,2-aminoalcohol containing heterocycles.

As part of our ongoing efforts to develop the synthetic possibilities of (2*R*,3*S*)-3-(dibenzylamino)-1-[(*R*)-*p*-tolylsulfinyl]butan-2-ol **1** as a valuable chiral building block, we herein report a divergent strategy allowing access to relevant chiral heterocycle compounds containing a 1,2-amino alcohol moiety (Fig. 2). Thus, **1** has been further elaborated by taking advantage of the versatility of the sulfoxide chemistry leading to oxirane **3** and oxazolidin-2-one **4**. We then transformed intermediate **1** into *N*,*N*-dibenzylaminoepoxide **2**, and focussed our attention on the use of this second synthetic intermediate as a common precursor to obtain oxazolidin-2-one **5**, azedidin-3-ol **6** and notably to access 'all-*cis*' 2-methyl-6-substituted-3-piperidinols alkaloids as the natural product (+)-deoxocassine **7** and its synthetic analogue **8**.[9]

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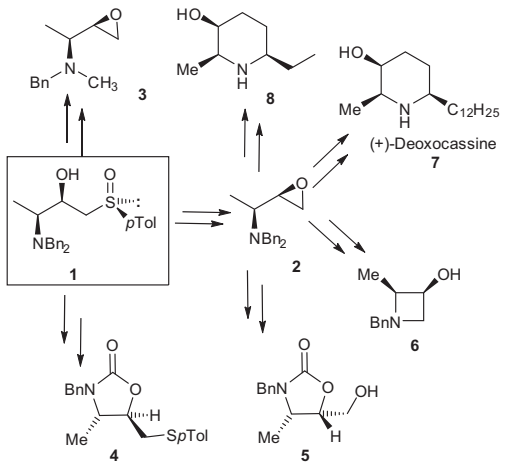
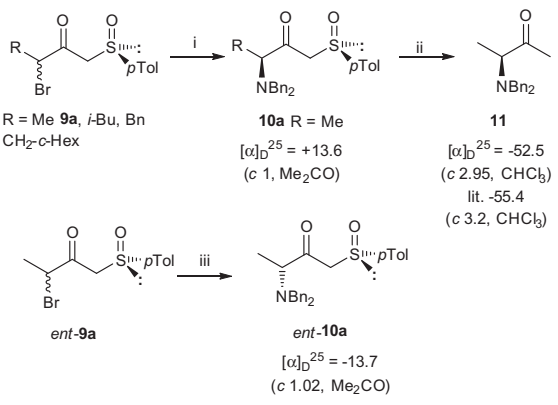


Figure 2. Our divergent strategy to access diverse 1,2-amino alcohol-containing heterocycles.

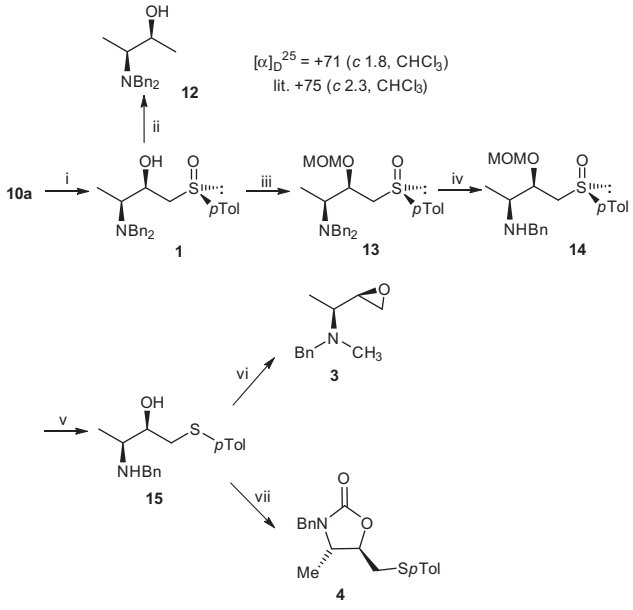
2. Results and discussion

Recently,[10] we put forward a novel and efficient strategy that allowed the recovery of enantiomerically pure α-*N*,*N*-dibenzylamino-α′-(*R*)-sulfinylketones **10**, starting from an epimeric mixture of α-bromo-α′-(*R*)-sulfinylketones **9**,[11] through a combined in situ substitution–epimerization process, a so-called dynamic kinetic resolution (Scheme 1). Our approach involved a nucleophilic displacement of the more reactive bromine epimer by dibenzylamine and epimerization of the less reactive one. This is a 1,4-stereoinduction process whereby the stereochemical information of the sulfoxide group guides the generation of the new stereocenter. Compound **10a** was isolated as a single diastereoisomer in 84% yield, after washing the crude solid material with diethyl ether. The absolute configuration of the newly formed stereogenic center was previously assigned as (*S*) by using X-ray crystallographic analysis;[10] herein we report a correlation with the known dibenzylaminoketone **11**, which was obtained in 60% yield by cleavage of the C–S bond of **10a** with Raney nickel. The specific rotation observed for **11** {$[\alpha]_D^{25} = -52.5$ (*c* 2.95 $CHCl_3$)} was consistent with that reported in the literature[12] {$[\alpha]_D = -55.4$ (*c* 3.2 $CHCl_3$)}. Moreover, since both enantiomers of methyl-*p*-tolylsulfoxide are readily available, this simple and easy methodology enabled the preparation of the corresponding (*R*)-dibenzylaminoketones; for example we obtained *ent*-**10a** from *ent*-**9a** by using the same reaction conditions. Having demonstrated that the methodology could be adapted to several side chains (R = Me, *i*-Bu, Bn and CH_2-*c*-Hex), we selected **10a** (R = Me) as a model substrate to develop, as illustrated herein, further applications of this dibenzylaminoketone synthon.



Scheme 1. Reagents and conditions: (i) Bn_2NH, THF, rt, 84% **10a**; (ii) Raney Ni, EtOH, 0 °C, 15 min, 60%; (iii) Bn_2NH, THF, rt, 70%.

We next focused our attention on the preparation of γ-*N*,*N*-dibenzylamino-β-hydroxysulfoxide **1** starting from enantiomerically pure α-*N*,*N*-dibenzylamino-α′-(*R*)-sulfinylketone **10a** by means of a sulfoxide-controlled highly stereoselective reduction of the carbonyl group using diisobutylaluminium hydride (DIBAL-H) as a reducing agent, in the presence of ZnI_2 (Scheme 2).[13] We improved the yield of this two-step sequence by reacting crude **10a** without previous isolation. Thus, starting from **9a** (R = Me), the desired derivative **1** was obtained in 94% yield in multigram amounts and with an excellent stereoselectivity (>95:5). The relative *syn*-configuration of **1** was confirmed by chemical correlation with the amino alcohol **12**, obtained in 72% yield by cleavage of the C–S bond of **10a** with Raney nickel. The specific rotation observed for **12** {$[\alpha]_D^{25} = +71$ (*c* 1.8 $CHCl_3$)} was consistent with that reported in the literature[14] {$[\alpha]_D = +75$ (*c* 2.3 $CHCl_3$)}.

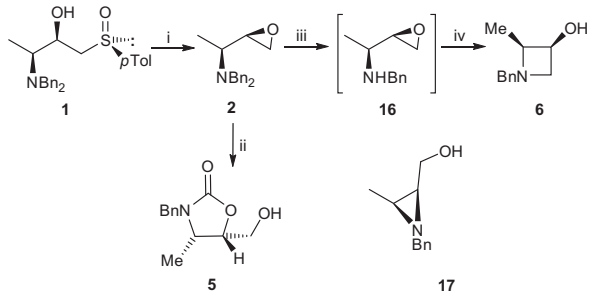


Scheme 2. Reagents and conditions: (i) ZnI_2, rt, 30 min, then DIBAL-H, THF, −78 °C, 94% from **9a**; (ii) Raney Ni, EtOH, rt, 72%; (iii) MOMCl, Et*N*iPr_2, CH_2Cl_2, reflux, 87%; (iv) NIS (3 equiv), CH_2Cl_2, MS 4 Å, rt, 67%; (v) *t*BuBr, $CHCl_3$, reflux, 87%; (vi) (a) Me_3OBF_4, CH_2Cl_2; (b) K_2CO_3, H_2O, 58%; (vii) CDI, NEt_3, CH_2Cl_2, rt, 78%.

With the chiral building block **10a** in hand, we next investigated its use as a synthetic intermediate to obtain both oxirane **3** and the 4,5-disubstituted oxazolidin-2-one **4**. Thus, protection of the free alcohol as methoxy methyl ether (MOM) was achieved upon treatment of **1** with MOMCl in the presence of Hünig's base to give **13** in 87% yield. Amine monodebenzylation using NIS[15] to afford **14** in 67% yield was followed by sulfoxide reduction by exposure to an excess amount of *tert*-butyl bromide in refluxing chloroform[16] to furnish the corresponding sulfide **15** in 87% yield. Concomitant cleavage of the methoxy methyl ether occurred. To the best of our knowledge, cleavage of MOM ethers with *t*BuBr had never been described before and under neutral conditions could be an alternative to the diverse methodologies described in the literature, which have the major drawback of employing acidic conditions.[17] Derivative **15** was then reacted with Meerwein's salt (Me_3OBF_4) and the resulting sulfonium salt was treated with aqueous K_2CO_3 to afford oxirane **3**, which was isolated in 58% yield, along with methyl *p*-tolylsulfide after this two-step procedure.[13] Alternatively, in the presence of Et_3N, sulfide **15** was converted into oxazolidin-2-one **4** using CDI in 78% yield. The *anti*-relationship between the

oxazolidin-2-one substituents was confirmed by NOESY experiments.

Next, the chiral building block **1** was transformed into another useful chiral synthon, oxirane **2** (Scheme 3). This conversion was achieved following a similar protocol described for compound **14** (vide supra). Thus, a three-step sequence involving sulfinyl reduction with *t*BuBr in refluxing chloroform,[16] subsequent sulfur methylation by Me_3OBF_4 in anhydrous CH_2Cl_2, without further purification of the resulting β-sulfenyl derivative, and treatment of the corresponding sulfonium salt by aqueous K_2CO_3, furnished epoxide **2** in 78% yield from **1**, after purification by column chromatography on silicagel.



Scheme 3. Reagents and conditions: (i) (a) *t*BuBr, $CHCl_3$, reflux; (b) Me_3OBF_4, CH_2Cl_2, rt, 5 h, then K_2CO_3, 78% (from **1**); (ii) CAN, $NaHCO_3$, 84%; (iii) NIS (3 equiv), CH_2Cl_2, MS 4 Å, t.a.; (iv) *i*PrOH, MW, 100 °C, 1.5 h, 48% from **2**.

We next focused our efforts in exploring new synthetic applications of vicinal *syn*-*N*,*N*-dibenzylamino oxirane **2**. The latter could be transformed in a straightforward manner into oxazolidin-2-one **5** using a two-step procedure.[18] Thus, **2** was reacted with CAN and treatment of the subsequent monobenzylated amine[19] reaction crude with a saturated solution of $NaHCO_3$ resulted in a regioselective intramolecular epoxide opening to afford oxazolidin-2-one **5** in 84% yield. The *cis*-relationship between the oxazolidin-2-one substituents was confirmed by NOESY experiments. This *cis*-2,4-disubstituted oxazolidin-2-one can be considered a pseudo epimer of the *trans*-oxazolidin-2-one **4**.

Epoxide ring expansion with nucleophiles has received only limited attention in the literature.[20] In this context, we envisioned the use of oxirane **2** as a precursor of *N*-protected azetidin-3-ol **6**. Compound **2** was treated with 3 equiv of NIS in dry dichloromethane[15] and the crude of the resulting monobenzylated product was heated in *i*PrOH at 100 °C under microwave irradiation, giving rise, by ring expansion process, to the formation of an 85:15 mixture of *N*-protected azetidin-3-ol **6** and aziridinol **17**. The major product, enantiopure *N*-protected azetidin-3-ol **6**, was isolated in 48% yield from **2**.[21]

Finally, it was our expectation to develop a general divergent strategy leading to the synthesis of 'all-*cis*' 2-methyl-6-substituted-3-piperidinol alkaloids by using *syn*-(2*R*,1′*S*)-2-(1-dibenzylaminomethyl)epoxide **2** as common building block. Hence, we decided to prepare (+)-deoxocassine **7** (R = $C_{12}H_{25}$) and a synthetic analogue **8** (R = Et). In our retrosynthetic analysis depicted in Figure 3, both target piperidinols would derive from a debenzylation and concomitant intramolecular reductive amination of dibenzylamino ketone **18**. To access dibenzylamino ketone **18**, two pathways (a and b in Fig. 3) were envisaged. Firstly, we planned to prepare **18** by alkylation of methylketone **19**, which was obtained by oxirane ring opening of **2** with an allylic organometallic. In a second approach, the key step leading to dibenzylamino ketone **18** involved an oxirane ring opening of **2** by the nucleophilic lithiated anion of hydrazones **20a** or **20b** and subsequent hydrazone hydrolysis.

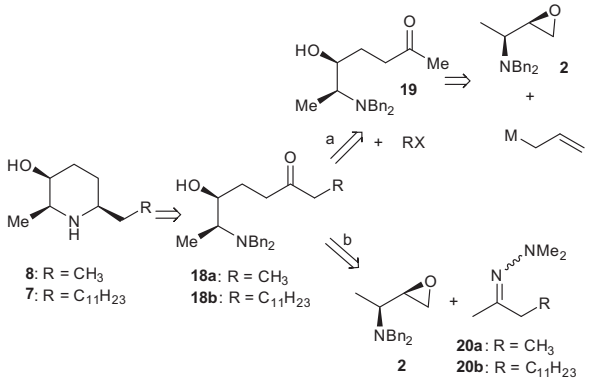
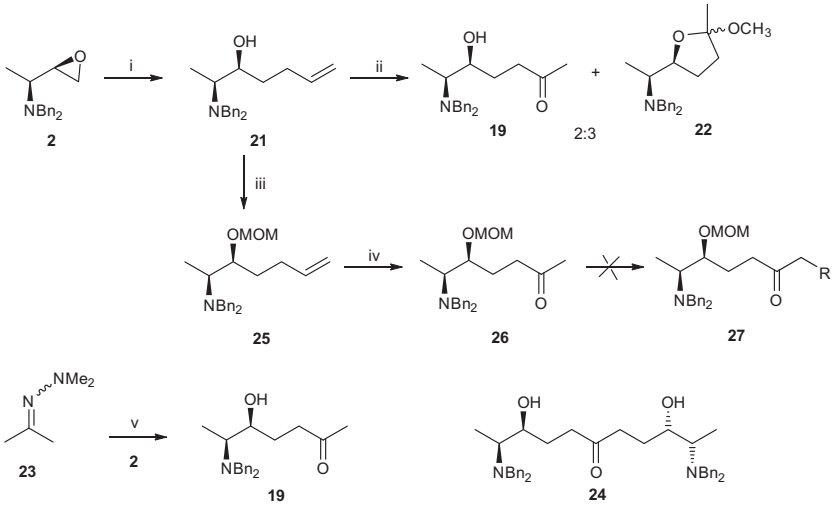


Figure 3. Retrosynthetic analysis for (+)-deoxocassine **7** and its synthetic analogue **8**.

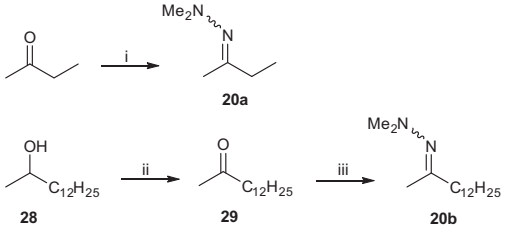
Regarding the first approach, the oxirane ring opening of key compound **2** depended on the treatment of the latter with an excess of magnesium allyl chloride in the presence of CuI in THF



Scheme 4. Reagents and conditions: (i) Magnesium allyl chloride, CuI, THF, −40 °C, 76%; (ii) $PdCl_2(CH_3CN)_2$, $CuCl_2{\cdot}2H_2O$, MeOH, O_2, rt; (iii) MOMCl, DIPEA, CH_2Cl_2, reflux, 88%; (iv) $PdCl_2(CH_3CN)_2$, $CuCl_2{\cdot}2H_2O$, MeOH, O_2, rt, 56%; (v) (a) BuLi, THF, 0 °C, then **2**; (b) SiO_2, THF, H_2O, rt, 54%.

at −40 °C (Scheme 4). The corresponding amino alcohol **21** with a *syn*-relative configuration was obtained in 76% yield. The reaction was totally regioselective and no other regioisomer was observed by ^{1}H NMR analysis of the crude reaction. The *anti*-amino alcohols of this type are normally obtained by addition of an organometallic reagent to the corresponding α-aminoaldehyde under Felkin–Ahn control, however the *syn*-diastereoisomers are difficult to access.[22] We attempted to convert allylic alcohol **21** into methyl ketone **19** through a Wacker oxidation[23] by exposure to $PdCl_2(CH_3CN)_2$ and $CuCl_2{\cdot}2H_2O$ as catalysts. We obtained a 2:3 inseparable mixture composed of the desired methyl ketone **19** and ketal **22**, which consequently could not be isolated. Alternatively, methyl ketone **19** was obtained in 54% yield by alkylation of the lithium anion of acetone dimethylhydrazone **23** with oxirane **2** and subsequent in situ hydrazone hydrolysis. Concomitant formation of dimer **24** hampered the reaction yield. On the basis of the formation of the ketal by-product **22** by the Wacker oxidation, we protected the hydroxyl group of the allylic alcohol **21** as a MOM ether and **25** was obtained in 88% yield. Exposure of **25** to Wacker oxidation conditions provided the desired methylketone **26** in a reasonable 56% yield. Nevertheless, attempts to obtain **27** by alkylating **26** with 1-iodoundecane ($C_{11}H_{23}I$) using LDA as base were unsuccessful. Since ketone anions have proven to be quite unreactive toward epoxides,[24] we applied the procedure leading to *N*,*N*-dimethylhydrazone formation from **26** and subsequent alkylation of the corresponding lithium anion. The procedure turned out to be very troublesome and despite much experimentation, the formation of **27** was not observed.

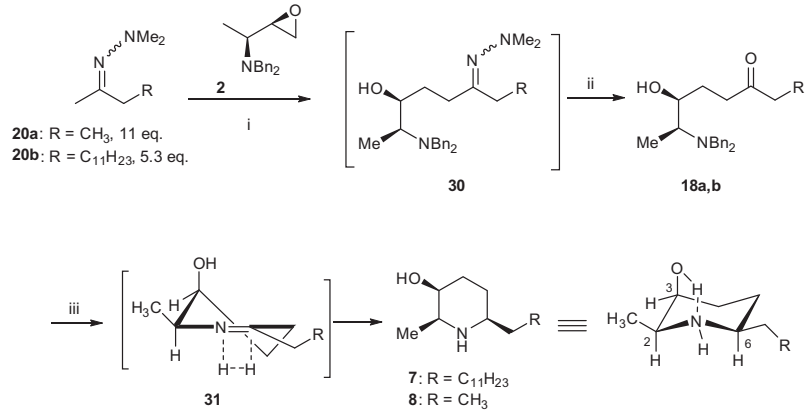
The frustrating outcome for the first strategy aiming to obtain ketones **18** turned our attention to the second approach, which focused on the study of hydrazone **20a** and **20b** alkylations with the common chiral building block **2**. Among the methodologies leading to the C–C bond formation, the use of *N*,*N*-dimethylhydrazones has found a wide applicability.[25] Indeed, *N*,*N*-dialkylhydrazones offer many advantages such as the high nucleophilicity of their organolithium derivatives, regioselectivity and controlled α-monoalkylation. Even though azaenolates can react with quite a number of electrophiles, oxiranes have rarely been employed.[24,26] In this context, our initial efforts focused on the preparation of dimethyl hydrazones **20a** and **20b** (Scheme 5). Thus, the reaction of 2-butanone with dimethyl hydrazine in refluxing CH_2Cl_2 gave the corresponding dimethyl hydrazone **20a** in 82% yield. On the other hand, analogue **20b** could be obtained by a two step sequence starting from commercially available alcohol **28**, which was oxidized into the corresponding ketone **29** in 95% yield by using PCC. Dimethyl hydrazone **20b** was obtained in quantitative yield by using a procedure similar to that used for **20a**.



Scheme 5. Reagents and conditions: (i) NH_2Me_2, CH_2Cl_2, reflux, 82%; (ii) PCC, CH_2Cl_2, 95%; (iii) NH_2NMe_2, CH_2Cl_2, reflux, 100%.

At this point, we proceeded to attempt an oxirane ring opening of the common precursor **2** with the lithium aza-enolate of dimethylhydrazones **20a** or **20b** (Scheme 6). Considerable endeavors were necessary to optimize the reaction conditions. The use of either $BF_3{\cdot}OEt_2$ as a catalyst or of an excess of anhydrous LiCl as additive, according to a known literature procedure for enolate oxirane ring opening,[26c,27] were unsuccessful. Finally, the reaction was successfully implemented by adding oxirane **2** to an excess of aza-enolate (11 equiv for **20a** and 5.3 equiv for **20b**), generated from the corresponding hydrazones and butyllithium at 0 °C, allowing the reaction mixture to warm to room temperature. The corresponding hydrazones **30** were converted in a one-pot procedure into the desired ketones **18a** and **18b** by exposure of the crude to SiO_2, in a 1:1 mixture of water and tetrahydrofuran (THF) in a one-pot procedure in 63% and 79% yield, respectively, after silica gel chromatography.

At this stage, completion of the targeted 2-methyl-6-substituted-3-piperidinols was conveniently and efficiently accomplished by in situ amine debenzylation and concomitant reductive cyclization of the ensuing aminoketones. Thus, dibenzylaminoketones **18a** and **18b** afforded specifically, in a two-step sequence, upon hydrogenation in the presence of 20% $Pd(OH)_2$ on carbon at room temperature and atmospheric pressure, (+)-deoxocassine **7**[28] and its C-6 ethyl analogue **8** in 75% and 61% yield, after silica gel chromatography. From a mechanistic point of view, as described in the literature,[7e] the Δ^1-piperidine intermediate **31** was hydrogenated from the less hindered α-face of the molecule leading to an 'all-*cis*' configuration with a high degree of stereocontrol, since not even a trace of the C-6 epimer could be detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The spectroscopic data (^{1}H NMR, ^{13}C NMR, and mass



Scheme 6. Reagents and conditions: (i) BuLi, THF, 0 °C–rt then **2**; (ii) SiO_2, THF–H_2O, 63% **18a** and 79% **18b** from **2**; (iii) H_2, $Pd(OH)_2$/C, EtOH.

spectra), the melting point and the specific rotation of synthetic **7** were in complete agreement with those previously reported {$[\alpha]_D^{25}$ = +11.6 (*c* 0.95, $CHCl_3$); lit.[7h] {$[\alpha]_D$ = +11.8 (*c* 1.0, $CHCl_3$)}. The deoxocassine C-6 ethyl analogue **8**, which to our knowledge has never been described, exhibited a specific rotation of $[\alpha]_D^{25}$ = +8.8 (*c* 1.1, $CHCl_3$). The 'all-*cis*' relationship between the substituents in compounds **7** and **8** was confirmed by the small $J_{2,3}$ value (1.3 Hz), typical for the axial–equatorial H-2 and H-3 protons in the major conformer of *cis*-2-methyl-6-substituted piperidine-3-ols.[7b,29] Moreover, the *cis* relationship between the substituents at the 2,6-positions for compound **8** was confirmed by NOESY experiments.

3. Conclusion

Among the four *syn*-*N*,*N*-dibenzylamino alcohols that we have prepared in a previous study, we used compound **1** as a model substrate to develop a divergent and efficient strategy allowing access to six different saturated heterocycles bearing a 1,2 aminoalcohol moiety. This key chiral non-racemic building block **1** allowed the synthesis of oxirane **3** and oxazolidinone **4**. Additionally, compound **1** furnished a second chiral building block, oxirane **2**. This precursor permitted access to both enantiopure and synthetically useful oxazolidinone **5**, a pseudo epimer of oxazolidinone **4**, and azetidin-3-ol **6**. The synthetic potential of oxirane **2** as precursor was further exemplified by the development of a flexible total synthesis of (+)-deoxocassine **7** and its C-6 ethyl analogue **8** by using a new, general, and efficient protocol. This approach involved as a key step, the coupling of aza-enolates of hydrazones **20a** and **20b** with the key oxirane **2**. Compared to previous reported syntheses, our route avoids the use of a protecting group for the 3-hydroxyl function. The obvious synthetic potential of this short reaction sequence arises from its convergent nature. Of great significance is the fact that the key oxirane intermediate of this synthesis **2** should facilitate the synthesis of other members of the 'all-*cis*' 2-methyl-6-substituted piperidine-3-ol alkaloids by judicious choice of the ketone moiety. Further applications of this divergent strategy to the synthesis of other valuable chiral synthons and bioactive products are currently going on in our laboratory.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources. THF was dried by distillation on sodium/benzophenone. Diisopropylamine was distilled on KOH. Reactions were conducted in flame dried glassware under an argon atmosphere. ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz (or 400 MHz/100 MHz, or 600 MHz/150 MHz), respectively, either in $CDCl_3$ or MeOD using a Bruker Avance spectrometer. Chemical shifts are given in ppm and reported to the residual solvent peak ($CHCl_3$ 7.26 ppm and 77.16 ppm or MeOH 4.87, 3.31 ppm and 49.15 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (*J*, Hz), and integration. Analytical TLC was performed on silica gel $60F_{254}$ plates. Column chromatography was carried out on silica gel 60 (63–200 μm). High resolution mass spectra (HRMS) were measured on a Micromass spectrometer using electrospray ionization (ESI) and Q-Tof detection. Melting points were obtained with a Büchi apparatus and are uncorrected. Optical rotations values were measured with a Perkin–Elmer apparatus at 20 °C, 589 nm (sodium ray), and concentrations are given in g/100 mL.

4.2. Experimental procedures

4.2.1. (*S*)-3-(Dibenzylamino)butan-2-one 11

To a solution of **10a** (240 mg, 0.592 mmol) in anhydrous EtOH (8 mL) was added a large excess of activated Raney Ni in EtOH (about 2 mL) at 0 °C. The suspension was stirred rapidly at 0 °C for 15 min, then filtered through a Celite pad, and washed with EtOH. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 40:1) to afford **11** as a colorless oil (94 mg, 60%). R_f = 0.63 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = −52.5 (*c* 2.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36–7.19 (m, 10H), 3.65 (d, *J* = 13.7 Hz, 2H), 3.41 (d, *J* = 13.7 Hz, 2H), 3.30 (q, *J* = 6.7 Hz, 1H), 2.19 (s, 3H), 1.11 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.1, 139.4, 128.9, 128.6, 127.3, 63.0, 54.7, 27.8, 7.1; ESIMS *m*/*z* 268.2 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1701, found: 268.1707.

4.2.2. (S_S,3*R*)-3-(Dibenzylamino)-1-(*p*-tolylsulfinyl)butan-2-one *ent*-10a

3-Bromo-1-[(*S*)-*p*-tolylsulfinyl]butan-2-one *ent*-**9a** (500 mg, 1.73 mmol) was dissolved in THF (10 mL) and dibenzylamine (0.86 mL, 4.34 mmol) was added. The reaction mixture was stirred for 5 h at room temperature and treated with saturated aqueous $KHCO_3$ (10 mL). The phases were separated and the aqueous one was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a 10% $KHSO_4$ aqueous solution (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was washed with Et_2O to afford *ent*-**10a** as a white solid (489 mg, 70%). R_f = 0.60 (cyclohexane/EtOAc, 2:1); $[\alpha]_D^{25}$ = −13.7 (*c* 1.02, Me_2CO); mp 89 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.12 (m, 14H), 4.20 (d, *J* = 13.2 Hz, 1H), 4.10 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 2H), 3.33 (d, *J* = 13.4 Hz, 2H), 2.83 (q, *J* = 6.6 Hz, 1H), 2.36 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 203.1, 142.1, 140.1, 138.7, 130.1, 127.2, 128.8, 127.8, 124.5, 66.3, 63.6, 55.0, 21.6, 6.0; ESIMS *m*/*z* 406.3 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{25}H_{28}NO_2S$ $[M+H]^+$: 406.1841; found 406.1850.

4.2.3. (2*S*,3*S*)-3-(Dibenzylamino)butan-2-ol 12

A solution of aminohydroxysulfoxide *syn*-**1** (100 mg, 0.245 mmol) in anhydrous EtOH (4 mL) was added to a large excess of activated Ni Raney in EtOH (approx. 1 mL). The suspension was stirred at room temperature for 4 h, then filtered through a Celite pad, and washed with EtOH. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 95:5) to afford **12** as a colorless oil (47 mg, 72%). R_f = 0.15 (cyclohexane/EtOAc 95:5); $[\alpha]_D^{25}$ = +71 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.32–7.20 (m, 10H), 4.34 (br s, 1H), 3.80 (d, *J* = 13.3 Hz, 2H), 3.60 (dq, *J* = 9.4, 6.0 Hz, 1H), 3.29 (d, *J* = 13.3 Hz, 2H), 2.45 (dq, *J* = 9.4, 6.7 Hz, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.2, 129.2, 128.7, 127.4, 67.2, 60.5, 53.5, 19.6, 8.1; ESIMS *m*/*z* 270.0 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1858; found 270.1852.

4.2.4. (S_R,2*R*,3*S*)-*N*,*N*-Dibenzyl-2-(methoxymethoxy)-1-(*p*-tolylsulfinyl)butan-3-amine 13

To a solution of aminohydroxysulfoxide **1** (50 mg, 0.123 mmol) in CH_2Cl_2 (2 mL) were added MOMCl (0.06 mL, 0.795 mmol) and $EtNiPr_2$ (0.13 mL, 0.746 mmol). The solution was heated at reflux for 2 h, and then diluted with CH_2Cl_2 (3 mL), washed with water (3 × 5 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 2:1) to afford **13** as a colorless oil (48 mg, 87%). R_f = 0.4 (cyclohexane/EtOAc 2:1); $[\alpha]_D^{25}$ = +7.5 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (d, *J* = 8.2 Hz, 2H), 7.33–7.25 (m, 12H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.54 (d, *J* = 6.9 Hz, 1H),

3.96 (d, J = 13.5 Hz, 2H), 3.74 (ddd, J = 5.8, 5.8, 3.5 Hz, 1H), 3.39 (s, 3H), 3.35 (d, J = 13.5 Hz, 2H), 3.25 (dd, J = 13.0, 6.0 Hz, 1H), 3.19 (dd, J = 13.0, 5.6 Hz, 1H), 2.94 (qd, J = 6.8, 3.5 Hz, 1H), 2.44 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.5, 141.2, 140.1, 129.9, 129.1, 128.3, 127.0, 124.5, 96.6, 77.3, 61.0, 56.1, 55.4, 55.0, 21.5, 9.2; ESIMS m/z 452.2 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{27}H_{33}NO_3S$ $[M+H]^+$: 452.2259; found 452.2241.

4.2.5. (*S*$_R$,2*R*,3*S*)-*N*-Benzyl-2-(methoxymethoxy)-1-(*p*-tolylsulfinyl)butan-3-amine 14

Powdered molecular sieves 4 Å (605 mg) were flame-dried and cooled under argon. Next, *N*-iodosuccinimide (603 mg, 2.68 mmol) was added. To this solid mixture was added a solution of **13** (405 mg, 0.897 mmol) in anhydrous CH_2Cl_2 (15 mL). The suspension was stirred at room temperature for 2 h, and then the mixture was filtered and washed with CH_2Cl_2 (10 mL). The organic layer was washed with aqueous saturated $Na_2S_2O_3$ (3 × 10 mL), H_2O (10 mL), and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (cyclohexane/EtOAc 2:1 + 2% NEt_3) to afford **14** as a colorless oil (215 mg, 66%). R_f = 0.2 (cyclohexane/EtOAc 1:1 + 1% Et_3N); $[\alpha]_D^{25}$ = +83 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.57 (d, J = 8.2 Hz, 2H), 7.33–7.24 (m, 7H), 4.64 (d, J = 7.0 Hz, 1H), 4.59 (d, J = 7.0 Hz), 3.83–3.78 (m, 1H), 3.74 (d, J = 13.0 Hz, 1H), 3.56 (d, J = 13.0 Hz), 3.40 (s, 3H), 3.32 (dd, J = 13.2, 5.0 Hz, 1H), 3.11 (dd, J = 13.2, 6.5 Hz, 1H), 3.02 (qd, J = 6.5, 4.0 Hz, 1H), 2.40 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.7, 141.3, 140.5, 130.1, 128.4, 128.2, 127.1, 124.5, 96.5, 75.5, 59.6, 56.1, 54.2, 51.3, 21.5, 15.8; ESIMS m/z 362.1 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{20}H_{28}NO_3S$ $[M+H]^+$: 362.1790; found 362.1799.

4.2.6. (2*R*,3*S*)-3-(Benzylamino)-1-(*p*-tolylthio)butan-2-ol 15

A solution of **14** (101 mg, 0.279 mmol) and *t*BuBr (0.64 mL, 5.52 mmol) in $CHCl_3$ (5 mL) was heated at reflux for 9 h and then cooled to room temperature. The solvents were then evaporated in vacuo and the crude material was purified by column chromatography on silica gel (cyclohexane/EtOAc 1:2 + 2% NEt_3) to afford **15** as a colorless oil (73 mg, 87%). R_f = 0.25 (cyclohexane/EtOAc 1:2 + 2% Et_3N); $[\alpha]_D^{25}$ = −6.3 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.32–7.25 (m, 7H), 7.09 (d, J = 8.0 Hz, 2H), 3.90 (d, J = 13.0 Hz, 1H), 3.70 (d, J = 13.0 Hz, 1H), 3.46 (ddd, J = 7.8, 6.9, 3.8 Hz, 1H), 3.17 (dd, J = 13.5, 3.8 Hz, 1H), 2.95 (dd, J = 13.5, 7.8 Hz, 1H), 2.76 (d, J = 6.5 Hz, 1H), 2.32 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 140.3, 136.7, 132.3, 130.7, 129.9, 128.6, 128.3, 127.2, 73.1, 56.2, 51.6, 39.6, 21.1, 16.9; ESIMS m/z 302.2 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{18}H_{24}NOS$ $[M+H]^+$: 302.1579; found 302.1573.

4.2.7. (2*R*,1′*S*)-2-[1-(*N*-Benzyl-*N*-methylamino)ethyl]oxirane 3

To a solution of **15** (65 mg, 0.217 mmol) in CH_2Cl_2 (2 mL) was added trimethyloxonium tetrafluoroborate (37 mg, 0.25 mmol) and the reaction mixture was stirred at room temperature for 4 h, after which additional Me_3OBF_4 (37 mg, 0.25 mmol) was added and the stirring was continued for 2 h. The resulting heterogeneous mixture was treated with saturated aqueous K_2CO_3 (2 mL) and stirred overnight. The aqueous phase was recovered and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 4:1) to afford **3** as a colorless oil (24 mg, 58%). R_f = 0.2 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = +12 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.23 (m, 5H), 3.74–3.67 (m, 2H), 3.09 (ddd, J = 6.8, 4.1, 2.8 Hz, 1H), 2.78–2.76 (m, 1H), 2.55–2.48 (m, 2H), 2.29 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.2, 128.4, 127.7, 126.3, 59.9, 58.3, 53.5, 43.6, 37.6, 12.2; ESIMS m/z 192.2 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388; found 192.1382.

4.2.8. (4*S*,5*R*)-3-Benzyl-4-methyl-5-((*p*-tolylthio)methyl) oxazolidin-2-one 4

To a solution of **15** (54 mg, 0.179 mmol) in CH_2Cl_2 (1 mL) were added NEt_3 (0.03 mL, 0.212 mmol) and DIC (49 mg, 0.302 mmol). The reaction mixture was stirred at room temperature for 3 h, and diluted with CH_2Cl_2 (4 mL). The solution was washed with a 0.5 M HCl aqueous solution (3 × 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel using cyclohexane/EtOAc 4:1 as eluent **4** as a colorless oil (46 mg, 78%). R_f = 0.32 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = +20.6 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.22 (m, 7H), 7.08 (d, J = 8.0 Hz, 2H), 4.76 (d, J = 15.2 Hz, 1H), 4.08–40.5 (m, 2H), 3.45 (pent, J = 6.2 Hz, 1H), 3.22 (dd, J = 13.9, 4.4 Hz, 1H), 2.85 (dd, J = 13.9, 8.5 Hz, 1H), 2.31 (s, 3H), 1.21 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.1, 137.4, 135.9, 131.0, 130.4, 130.0, 128.9, 128.1, 127.9, 78.8, 54.9, 45.7, 38.0, 21.1, 18.6; ESIMS m/z 328.1 $[M+H]^+$, 655.3 $[2M+H]^+$; HRMS (ES): m/z calcd for $C_{19}H_{22}NO_2S$ $[M+H]^+$: 328.1371; found 328.1367.

4.2.9. (4*S*,5*S*)-3-Benzyl-5-(hydroxymethyl)-4-methyloxazolidin-2-one 5

To a solution of **2** (0.127 g, 0.48 mmol) in 8 mL AcCN:H_2O 5:1 was added CAN (0.55 g, 1 mmol). After 3 h of stirring at room temperature, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (15 ml). After 30 min, water (15 mL) and EtOAc (15 ml) were added. The phases were separated and the organic one was extracted with EtOAc (3 × 25 ml). The beige solid **5** was obtained in 84% yield (89 mg). R_f = 0.24 (cyclohexane/EtOAc 3:2); $[\alpha]_D^{25}$ = +30 (*c* 1.05, Me_2CO); mp 79–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30–7.19 (m, 5H), 4.72 (d, J = 15.3 Hz, 1H), 4.48–4.41 (m, 1H), 3.99 (d, J = 15.3 Hz, 1H), 3.81–3.67 (m, 3H), 2.61 (s, large, 1H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.9, 135.9, 128.9, 128.1, 128.0, 77.1, 60.8, 52.0, 45.7, 12.6; ESIMS m/z 222.1 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{12}H_{16}NO_3$ $[M+H]^+$: 222.1117; found 222.1146.

4.2.10. (2*S*,3*S*)-1-Benzyl-2-methylazetidin-3-ol 6

Powdered molecular sieves 4 Å (150 mg) were flame-dried and cooled under argon and mixed with *N*-iodosuccinimide (248 mg, 1.10 mmol). To this solid mixture was added a solution of epoxide **2** (100 mg, 0.374 mmol) in anhydrous CH_2Cl_2 (7 mL). The suspension was stirred at room temperature for 1.5 h and then the mixture was filtered and washed with CH_2Cl_2 (5 mL). The organic layer was washed with aqueous saturated $Na_2S_2O_3$ (2 × 5 mL) and H_2O (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was dissolved in *i*PrOH (4 mL) and this solution was heated under microwave irradiation (400 W, 10 °C) for 1.5 h. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel (EtOAc + 2% NEt_3) to afford **6** as a colorless oil (32 mg, 48%). R_f = 0.19 (EtOAc); $[\alpha]_D^{25}$ = +44.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27–7.15 (m, 5H), 4.18 (td, J = 5.7, 5.7, 1.5 Hz, 1H), 3.60 (d, J = 12.7 Hz, 1H), 3.45 (d, J = 12.7 Hz, 1H), 3.32–3.25 (m, 1H), 3.13 (dd, J = 8.9, 1.3 Hz, 1H), 3.06 (dd, J = 8.9, 5.6 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.9, 129.0, 128.3, 127.2, 66.8, 66.2, 61.3, 61.0, 13.2; ESIMS m/z 178.1 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232; found 178.1229.

4.2.11. ((2*R*,3*S*)-1-Benzyl-3-methylaziridin-2-yl)methanol 17

Obtained as a by-product with **6** as a pale yellow oil. $[\alpha]_D^{25}$ = +13 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27–7.16 (m, 5H), 3.66 (dd, J = 11.4, 5.0 Hz, 1H), 3.47 (dd, J = 11.4, 6.1 Hz, 1H), 3.46

(s, 2H), 2.06 (s large, 1H), 1.76–1.69 (m, 2H), 1.14 (d, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.5, 128.8, 128.3, 127.5, 64.6, 60.4, 44.5, 39.7, 13.7. ESIMS m/z 355.24 $[2M+H]^+$; HRMS (ES): m/z calcd for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232; found 178.1233.

4.2.12. (2*S*,3*S*)-2-(Dibenzylamino)hept-6-en-3-ol 21

At first, CuI (110 mg, 0.579 mmol) was flame-dried and cooled under argon. Next, THF (1 mL) was added, and the suspension was cooled at −40 °C. Allylmagnesium chloride (2 M in THF, 0.56 mL, 1.12 mmol) was added, and the solution was stirred at −40 °C for 45 min. A solution of epoxide **2** (51 mg, 0.191 mmol) in THF (2 mL) was added, and the stirring was continued at −40 °C for 13 h. Saturated aqueous NH_4Cl (5 mL) was added, the aqueous phase was recovered and was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (EtOAc/cyclohexane 20:1) to afford **21** as a colorless oil (45 mg, 76%). R_f = 0.38 (cyclohexane/EtOAc 8:1); $[\alpha]_D^{25}$ = +52.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.24 (m, 10H), 5.88–5.78 (m, 1H), 5.03–4.93 (m, 2H), 4.51 (s, 1H), 3.85 (d, J = 13.3 Hz, 2H), 3.51 (td, J = 9.5, 2.4 Hz, 1H), 3.33 (d, J = 13.3 Hz, 2H), 2.58 (dq, J = 9.5, 6.7 Hz, 1H), 2.32–2.23 (m, 1H), 2.17–2.08 (m, 1H), 1.61–1.53 (m, 1H), 1.29–1.19 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.1, 139.0, 129.2, 128.7, 127.4, 114.6, 70.3, 58.5, 53.4, 33.3, 30.2, 8.2; ESIMS m/z 310.2 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{21}H_{28}NO$ $[M+H]^+$: 310.2171; found 310.2177.

4.2.13. 2-(Propan-2-ylidene)-1,1-dimethylhydrazine 23

A mixture of acetone (2 mL, 27.2 mmol) and *N*,*N*-dimethylhydrazine (2 mL, 26.2 mmol) was treated with $MgSO_4$ (2 g). The mixture was heated at reflux for 6 h and then allowed to cool to room temperature and filtered. The excess acetone was removed under reduced pressure, to give **23** as a colorless liquid (2.5 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.43 (s, 6H), 1.96 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.0, 47.2, 25.4, 18.3; ESIMS m/z 101.1 $[M+H]^+$; HRMS (ES): m/z calcd for $C_5H_{12}N_2$ $[M+H]^+$: 101.1079; found 101.1072.

4.2.14. (5*S*,6*S*)-6-(Dibenzylamino)-5-hydroxyheptan-2-one 19

n-Butyllithium (2.5 M in hexane, 0.4 mL, 1 mmol) was slowly added to a solution of **23** (97 mg, 0.97 mmol) in THF (2 mL) at 0 °C. The solution was stirred at 0 °C for 1 h. A white precipitate was formed. The solution was then warmed to room temperature, and stirred for 10 min. A solution of epoxide **2** (49 mg, 0.183 mmol) in THF (5 mL) was added, the mixture was stirred 6 h at room temperature, and then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was recovered and extracted with EtOAc (3 × 5 mL). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in THF (2 mL), H_2O (2 mL), and SiO_2 (1 g) was added. The mixture was stirred overnight, filtered off, and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 9:1) to give **19** as a colorless oil (32 mg, 54%). R_f = 0.28 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = +26 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.22 (m, 10H), 4.46 (br s, 1H), 3.81 (d, J = 13.2 Hz, 2H), 3.44 (td, J = 9.2, 2.6 Hz, 1H), 3.30 (d, J = 13.2 Hz, 2H), 2.62–2.46 (m, 3H), 2.08 (s, 3H), 1.86–1.82 (m, 1H), 1.33–1.25 (m, 1H), 1.33–1.25 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 209.1, 138.8, 129.1, 128.5, 127.3, 69.8, 58.2, 53.3, 39.6, 30.0, 27.4, 8.0; ESIMS m/z 326.2 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{21}H_{28}NO_2$ $[M+H]^+$: 326.2120; found 326.2134.

4.2.15. (2*S*,3*S*,9*S*,10*S*)-2,10-Bis-(dibenzylamino)-3,9-dihydroxyundecan-6-one 24

Obtained as a by-product with **19** as a pale yellow oil (4 mg, 7%). R_f = 0.08 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = −37.5 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.22 (m, 20H), 4.42 (br s, 2H), 3.80 (d, J = 13.3 Hz, 4H), 3.41 (td, J = 9.2, 2.4 Hz, 2H), 3.29 (d, J = 13.3 Hz, 4H), 2.58–2.40 (m, 6H), 1.83–1.79 (m, 2H), 1.28–1.22 (m, 2H), 1.02 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 211.3, 139.0, 129.2, 128.6, 127.4, 70.0, 58.4, 53.4, 38.9, 27.6, 8.2; ESIMS m/z 593.3 $[M+H]^+$.

4.2.16. (2*S*,3*S*)-*N*,*N*-Dibenzyl-3-(methoxymethoxy)hept-6-en-2-amine 25

To a solution of **21** (28 mg, 0.090 mmol) in CH_2Cl_2 (2 mL) were added MOMCl (0.04 mL, 0.530 mmol) and $EtNiPr_2$ (0.09 mL, 0.517 mmol). The solution was heated at reflux for 16 h, and then diluted with CH_2Cl_2 (10 mL), washed with water (3 × 5 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 10:1) to afford **25** as a colorless oil (28 mg, 88%). R_f = 0.35 (cyclohexane/EtOAc 10:1); $[\alpha]_D^{25}$ = +19 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43–7.24 (m, 10H), 5.75 (ddt, J = 16.9, 10.5, 6.4 Hz, 1H), 5.00–4.85 (m, 2H), 4.66 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.03 (d, J = 13.7 Hz, 2H), 3.57–3.35 (m, 6H), 2.98–2.76 (m, 1H), 2.06–1.59 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.7, 138.8, 129.0, 128.1, 126.7, 114.3, 96.7, 82.2, 55.8, 55.1, 54.2, 30.8, 29.7, 9.4; ESIMS m/z 353.24 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{23}H_{32}NO_2$ $[M+H]^+$: 354.2433; found 354.2421.

4.2.17. (5*S*,6*S*)-6-(Dibenzylamino)-5-(methoxymethoxy)heptan-2-one 26

To a solution of **25** (72 mg, 0.204 mmol) in MeOH (2.5 mL) were added $PdCl_2(CH_3CN)_2$ (8 mg, 0.031 mmol) and $CuCl_2{\cdot}2H_2O$ (51 mg, 0.299 mmol). Next, O_2 was bubbled through this suspension for 2.5 h at room temperature. The mixture was then filtered off and concentrated in vacuo. The residue was dissolved in EtOAc (5 mL), and H_2O (5 mL) and ammonia (60% in water, 1 mL) were added. The aqueous phase was recovered and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to give **26** as a colorless oil (42 mg, 56%). R_f = 0.20 (cyclohexane/EtOAc 9:1); $[\alpha]_D^{25}$ = +14 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.18 (m, 10H), 4.61 (d, J = 6.8 Hz, 1H), 4.55 (d, J = 6.8 Hz, 1H), 3.97 (d, J = 13.6 Hz, 2H), 3.40–3.31 (m, 6H), 2.73 (qd, J = 6.9, 4.1 Hz, 1H), 2.11–1.72 (m, 7H), 1.15 (d, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 208.6, 140.7, 129.1, 128.2, 126.8, 96.7, 81.9, 55.8, 55.1, 53.9, 39.4, 29.8, 25.1, 9.3; ESIMS m/z 370.3 $[M+H]^+$; HRMS (ES): m/z calcd for $C_{23}H_{32}NO_3$ $[M+H]^+$: 370.2382; found 370.2379.

4.2.18. 2-(Butan-2-ylidene)-1,1-dimethylhydrazine 20a

A solution of 2-butanone (5 mL, 55.9 mmol) and *N*,*N*-dimethylhydrazine (5 mL, 65.8 mmol) in CH_2Cl_2 (20 mL) was heated at reflux for 6 h, and then allowed to cool to room temperature. Water was then removed by the addition of $MgSO_4$. After filtration, the solvent and excess *N*,*N*-dimethylhydrazine were removed under reduced pressure, to give **20a** as a colorless liquid (5.2 g, 82%). R_f = 0.4 (cyclohexane/EtOAc 15: 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.40–2.38 (m, 6H), 2.20–2.14 (m, 2H), 1.92–1.88 (m, 3H), 1.08–1.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.6, 169.0, 47.7, 47.2, 32.4, 24.7, 22.3, 16.2, 11.7, 11.2; ESIMS: m/z = 115.1 $[M+H]^+$; HRMS (ES): m/z calcd for $C_6H_{15}N_2$ $[M+H]^+$: 115.1235, found 115.1226.

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4.2.19. (6*S*,7*S*)-7-(Dibenzylamino)-6-hydroxyoctan-3-one 18a

Oxirane opening: At first, *n*BuLi (2.5 M in hexane, 0.8 mL, 2 mmol) was slowly added to a solution of hydrazone **20a** (224 mg, 1.96 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. A white precipitate was formed. The system was then warmed to room temperature, and stirred for 10 min. A solution of epoxide **2** (48 mg, 0.179 mmol) in THF (5 mL) was added, the mixture was stirred overnight at room temperature and then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was recovered and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure.

Hydrolysis of hydrazone: the residue was dissolved in THF (5 mL), H_2O (5 mL), and then SiO_2 (1 g) was added. The mixture was stirred overnight, filtered off, and the aqueous layer was recovered and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 9: 1) to give **18a** as a colorless oil (38 mg, 63%). R_f = 0.31 (cyclohexane/EtOAc, 9:1); $[\alpha]_D^{25}$ = +30.4 (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.26–7.14 (m, 10H), 3.74 (d, *J* = 13.2 Hz, 2H), 3.32 (td, *J* = 2.5, 9.2 Hz, 1H), 3.23 (d, *J* = 13.3 Hz, 2H), 2.57–2.33 (m, 3H), 2.28 (qd, *J* = 1.7, 7.3 Hz, 2H), 1.84–1.73 (m, 1H), 1.28–1.16 (m, 1H), 0.98–0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 211.8, 138.8, 129.0, 128.5, 127.3, 69.9, 58.2, 53.3, 38.2, 36.0, 27.5, 8.0, 7.8; ESIMS: *m*/*z* = 340.2 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{22}H_{30}NO_2$ $[M+H]^+$: 340.2277, found: 340.2281.

4.2.20. Tetradecan-2-one 29

To a solution of pyridinium chlorochromate (765 mg, 3.55 mmol) in CH_2Cl_2 (5 mL) was added tetradecan-2-ol (512 mg, 2.39 mmol) in CH_2Cl_2 (5 mL), at room temperature. The mixture was stirred for 7 h, and then Et_2O (10 mL) was added. The system was stirred vigorously and filtered on a Celite and florisil pad. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc 10:1) to give pure ketone **21** as a colorless oil (482 mg, 95%). R_f = 0.7 (cyclohexane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.35 (t, *J* = 2.75 Hz, 2H), 2.06 (s, 3H), 1.55–1.47 (m, 2H), 1.19 (br s, 18H), 0.81 (t, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 209.6, 44.1, 32.1, 30.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.6, 29.4, 24.1, 22.9, 14.3; ESIMS: *m*/*z* = 213.3 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{14}H_{28}O$ $[M+H]^+$: 213.2218, found 213.2222.

4.2.21. 2-(Tetradecan-2-ylidene)-1,1-dimethyl-hydrazine 20b

To a solution of ketone **21** (455 mg, 2.14 mmol) and *N*,*N*-dimethylhydrazine (0.25 mL, 3.29 mg) in CH_2Cl_2 (10 mL) was added $MgSO_4$ (500 mg). The mixture was heated at reflux overnight, and then allowed to cool to room temperature. Water was removed by addition of $MgSO_4$. After filtration, the solvent and excess *N*,*N*-dimethylhydrazine were removed under reduced pressure, to give **20b** as a colorless liquid (540 mg, 100%). R_f = 0.7 (cyclohexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.40–2.36 (m, 6H), 2.18–2.10 (m, 2H), 1.91–1.88 (m, 3H), 1.49–1.44 (m, 2H), 1.23 (br s, 18H), 0.85 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 169.9, 168.3, 47.7, 47.2, 44.0, 39.3, 32.1, 31.7, 30.0, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 27.2, 26.7, 24.1, 22.9, 16.6, 14.3; ESIMS: *m*/*z* = 255.3 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{16}H_{35}N_2$ $[M+H]^+$: 255.2800, found 255.2796.

4.2.22. (2*S*,3*S*,6*R*)-6-Ethyl-2-methylpiperidin-3-ol 8

To a solution of **11a** (37 mg, 0.109 mmol) in EtOH (1.5 mL) was added $Pd(OH)_2/C$ (20%, 11 mg, 0.016 mmol), and the mixture was placed under an atmosphere of H_2. After 3 h at room temperature, the mixture was filtered on Celite, washed with EtOH, and concentrated under reduced pressure to afford pure **10** as a colorless oil (13 mg, 75%). R_f = 0.12 (CH_2Cl_2/MeOH, 8:2 + 5% NEt_3); $[\alpha]_D^{25}$ = +8.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (MeOD, 600 MHz): δ = 3.81 (m, 1H), 3.21 (qd, *J* = 6.7, 1.3 Hz, 1H), 2.99–2.94 (m, 1H), 1.95–1.92 (m, 1H), 1.80–1.63 (m, 4H), 1.59–1.51 (m, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (MeOD, 150 MHz): δ = 65.9, 60.0, 57.6, 31.0, 27.7, 23.1, 15.9, 10.0; ESIMS: *m*/*z* = 144.1 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_8H_{18}NO$ $[M+H]^+$: 144.1388, found 144.1389.

4.2.23. (2*S*,3*S*,6*R*)-6-Dodecyl-2-methylpiperidin-3-ol 7 [(+)-deoxocassine]

To a solution of **11b** (36 mg, 0.075 mmol) in EtOH (1.5 mL) was added $Pd(OH)_2/C$ (20%, 20 mg, 0.029 mmol), and the mixture was placed under an atmosphere of H_2. After 3 h at room temperature, the mixture was filtered on short pad of silica and Celite, washed with EtOH, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/MeOH 9:1 + 2% NEt_3) to afford (+)-deoxocassine **1** as a white solid (13 mg, 61%). R_f = 0.15 (EtOAc/MeOH, 9:1 + 2% NEt_3); $[\alpha]_D^{25}$ = +11.6 (*c* 0.95, $CHCl_3$); mp 49–51 °C; ^{1}H NMR ($CDCl_3$, 400 - MHz): δ = 3.48–3.62 (m, 1H), 2.79 (qd, *J* = 6.5, 1.3 Hz, 1H), 2.60–2.54 (m, 1H), 1.95–1.91 (m, 1H), 1.57–1.47 (m, 2H), 1.41–1.30 (m, 23H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 68.1, 57.2, 55.8, 37.1, 32.1, 31.9, 29.8, 29.7, 29.7, 29.6, 29.4, 26.2, 25.9, 22.7, 18.8, 14.1; ESIMS: *m*/*z* = 284.2 $[M+H]^+$; HRMS (ES): *m*/*z* calcd for $C_{18}H_{38}NO$ $[M+H]^+$ 284.2953, found 284.2945.

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