Tetrahedron 69 (2013) 6129–6143

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Henry–Nef reaction: a practical and versatile chiral pool route to 2-substituted pyrrolidine and piperidine alkaloids

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ARTICLE INFO

Article history:
Received 15 March 2013
Received in revised form 13 May 2013
Accepted 15 May 2013
Available online 22 May 2013

Keywords:
Pyrrolidine
Piperidine
Henry
Nef
Chiral pool
2-Substituted
Alkaloids

ABSTRACT

The paper describes the synergistic protocol developed by combinatorial Henry and Nef reaction for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids containing 1,3-aminoketone and 1,3-amino alcohol units. The utility of the protocol is demonstrated by asymmetric synthesis of 12 natural products of which asymmetric synthesis of (−)-*N*-methylpelletierine is presented for the first time. The one-carbon homologation described also provides an alternate route for the synthesis of key intermediates homoprolinol and homopipecolinol used as synthetic precursors for several alkaloids and construction of β-amino acids from α-amino acids.

1. Introduction

2-Substituted pyrrolidines and piperidine alkaloids containing a stereogenic nitrogen centre are ubiquitously found in nature and as active components in the various drug candidates.[1] Some of the alkaloids containing 1,3-aminoketone and 1,3-amino alcohol units are depicted in Fig. 1. These alkaloids are isolated from 60 species of the genus *Sedum* and are usually referred as Sedum[2] alkaloids, which are of immense interest due to their memory-enhancing properties and application as anti-Alzheimer agents.[3] Owing to their vast pharmaceutical applications, the access to these motifs is gaining major importance from industrial prospective.[4] These motifs are also potent key building blocks in organic synthesis.[5] As a consequence, the asymmetric synthesis of 2-substituted pyrrolidine and piperidine alkaloids is of current interest and formidable challenge in synthetic organic chemistry. The protocols designed in the earlier days mainly involve racemic synthesis by polar additions, photocyclizations, cycloadditions and radical cyclizations.[6] The modern asymmetric methods encompass chiral pool strategies,[7] chiral auxiliary mediated synthesis using chiral organo metallic reagents[8] and organocatalysis.[9] All these methods have their advantages and limitations. For example, recent development in organocatalysis nevertheless has tremendous potential is yet to develop for practical applications from industrial point of view. On the other hand, 'chiral pool' strategies, wherein the starting material can easily be carved from the naturally available sources like amino acids, though requires large number of synthetic manoeuvring, but still is the best bet for chiral integrity and accordingly for industrial application.[10] Keeping this in mind, we thought of developing a practical and versatile chiral pool strategy for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids from L-proline and L-pipecolinic acid. The molecules of our interest are those containing 1,3-aminoketone and 1,3-amino alcohol units, principal units present in various natural products.[11] Another attraction was the potential of 1,3-amino alcohol units to act as chiral ligands and chiral auxiliaries.[12] A vast variety of methods are available in the literature for the synthesis of these amino alcohols, however, only few asymmetric methods are reported,[13] mainly involving proline catalyzed α-aminoxylation,[13a] rhodium catalyzed asymmetric transformations[13b] and asymmetric Mannich reaction.[13c]

2. Results and discussion

2.1. Henry-Nef reaction on protected prolinols and pipecolinols

In a preliminary communication we had described the development of Henry–Nef protocol for the synthesis of some of the

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0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.05.055

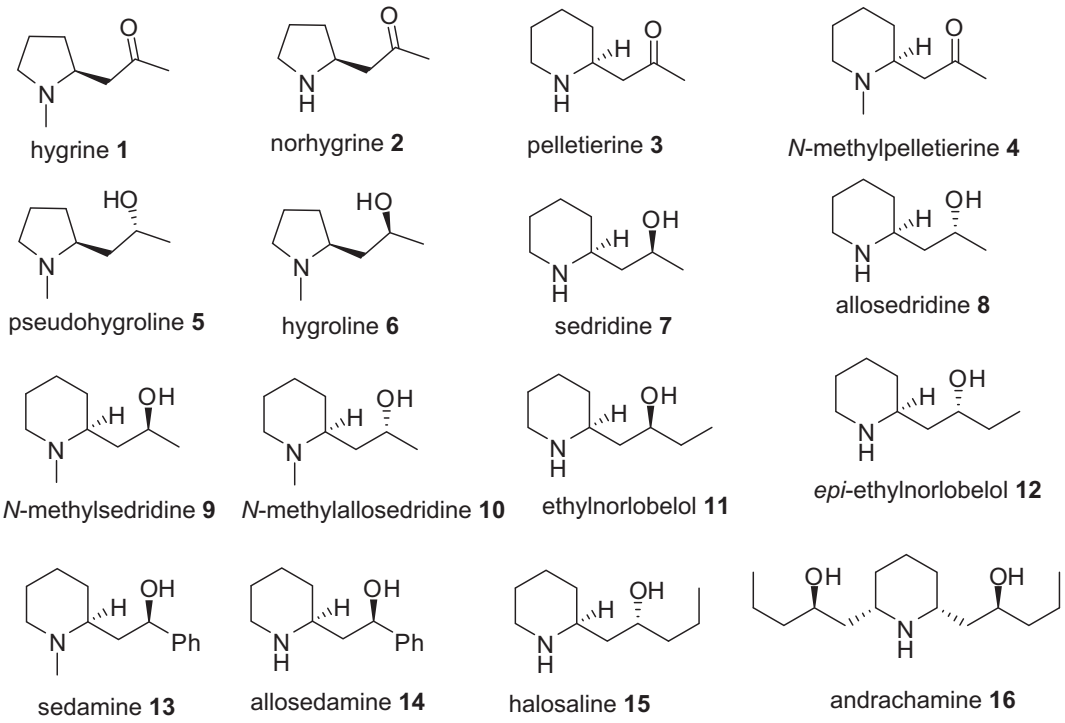
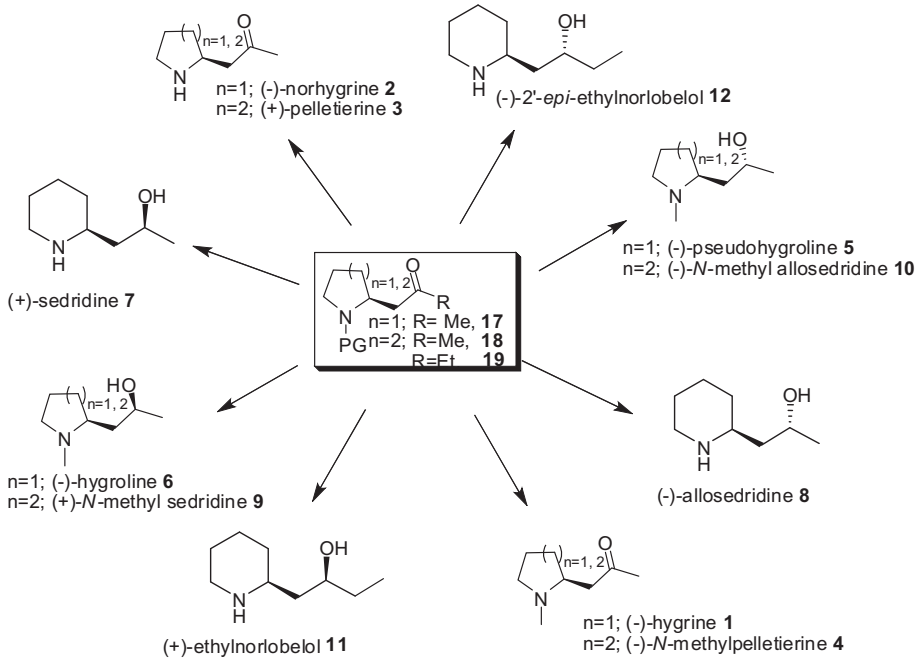


Fig. 1. 2-Substituted pyrrolidine and piperidine alkaloids with 1,3-aminoketone and alcohol units.

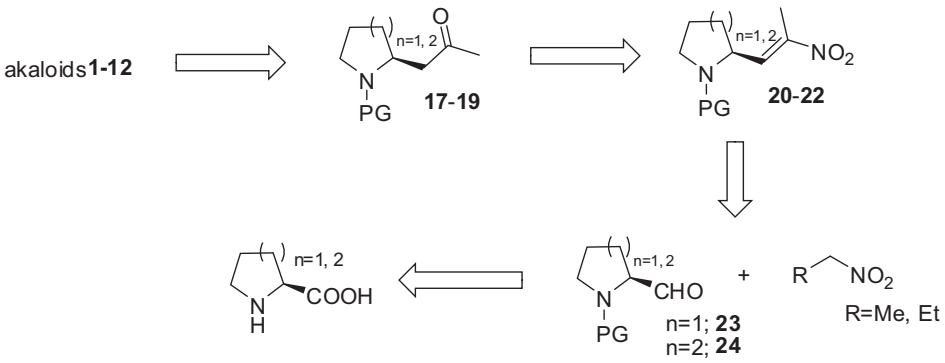
pyrrolidine alkaloids.[14] This paper illustrates the full account of application of this protocol for the synthesis of pyrrolidine and piperidine alkaloids and key homologated prolinol and pipecolinol intermediates, known precursors for the synthesis of large pool of alkaloids.

Henry–Nef protocol is in combination involves two major synthetic steps; the formation of the nitro functionality from carbonyls and successive transformation to next carbonyl unit mainly by oxidative or reductive methods. Even though this method is well documented in the literature,[15] surprisingly, not well explored for synthetic applications, turned our synthetic attention in this area. We envisioned the intermediates **17**–**19** can serve as ideal precursors for the synthesis of our targeted alkaloids (Scheme 1). These units could be derived by performing Nef reaction on the corresponding nitroalkenes **20**–**22**. Based on this we formulated a retrosynthetic sequence as outlined in Scheme 2.

At the outset of our study, we undertook several investigative methods to arrive with the nitrofunctional intermediates **20**–**22**. Despite there are numerous reports available on Henry reaction as a tool for natural products, the application for 2-substutited

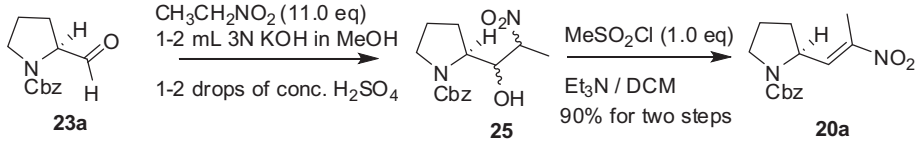


Scheme 1. Synthetic strategy through common intermediates.



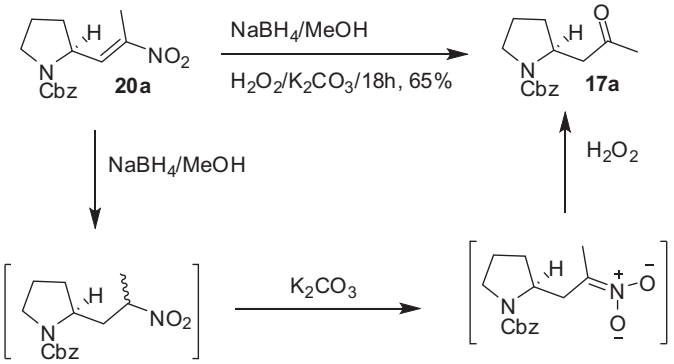
Scheme 2. Retrosynthetic approach.

pyrrolidine and piperidine alkaloids is not yet explored.[16] The integrity of the chirality was of major concern for us since the aldehyde **23** (**24**) having a stereogenic centre existing between carbonyl and nitrogen with a lone pair of electrons was readily racemizable under any drastic condition. Henry reaction of **23** was thus carried out initially with nitroethane using weak bases like piperidine, K_2CO_3, pyridine and Et_3N, but resulted either in the low yield with the starting material remaining unreacted or total decomposition. The change of solvent and reaction conditions did not affect much to improve the fate of the reaction. Recent elegant work carried out by Fioravanti et al. for the diastereoselective synthesis of *E* and *Z* nitroalkenes,[17] prompted us to employ the same method on our substrates. The initial reaction carried out on Cbz-prolinal **23a** with nitroethane gave us the nitroalkenes *E* and *Z* using piperidine base in CH_2Cl_2 over molecular sieves and only one *E*-isomer in toluene at reflux. But unfortunately, in our hand, failed to produce good yield when applied for the large-scale synthesis of it. Then we thought of carrying out the Henry reaction with excess of nitroethane in the presence of catalytic amount of KOH (0.1–0.2 mol %) in methanol. The reaction smoothly took place giving us different possible isomers (four diastereomers) of the nitro alcohol **25** within 1 h. Since the requisite nitro olefin was desired irrespective of *E* and *Z* isomeric forms, the alcoholic mixture **25** was as such subjected to mesylation and subsequent elimination of the mesylate formed in the reaction mixture to furnish **20a** as a single isomer without any epimerization (Scheme 3). On obtaining the requisite nitro olefin **20a**, our next job was to introduce the carbonyl functionality to arrive at the key intermediate **17a** through Nef reaction.



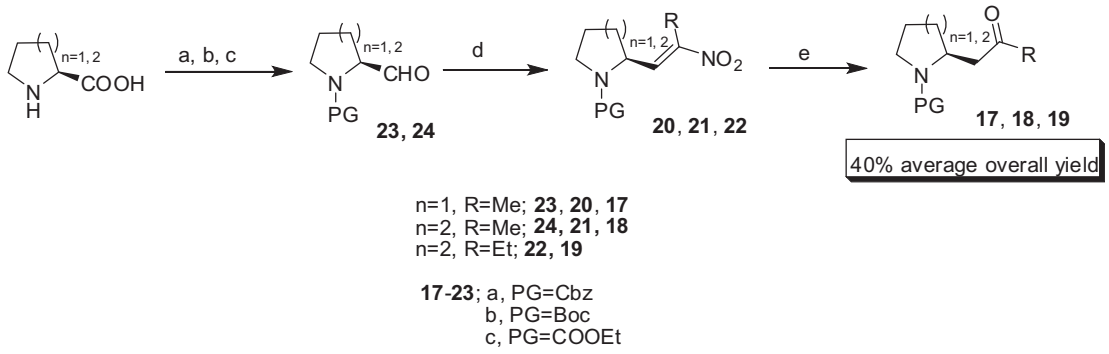
Scheme 3. Successful Henry reaction.

The application of general conventional Nef method using strong acid–base treatment for the generation of carbonyl group from nitro was strictly ruled out in order to avoid the consequences of racemization and deprotection of the carbamate protecting group. The alternate methods were probed for the suitable Nef conditions. Initially we thought of converting nitroalkene **20a** to nitroalkane by reduction using $NaBH_4$ and then transforming to carbonyl. But it was observed reduction gave poor yield with stoichiometric ratio of $NaBH_4$ and slight excess resulted in polymerization.[18] We then directly applied some of the mild Nef methods on the nitro olefin **20a**. Initially we subjected the nitroalkene **20a** for the treatment with activated Al powder in the presence of $NiCl_2$,[19] which resulted in immediate total decomposition of the substrate showing very high exothermic change. The reaction of nitro olefin **20a** with $SnCl_2$[20] also resulted in decomposition. The application of McMurray Nef reaction[21] using $TiCl_3$, which even though produced the product **17a**, the poor yield disfavoured us for adapting it. The substrate **20a** was then subjected to react with $NaBH_4$ in methanol, after 2 h H_2O_2 and K_2CO_3 were added and left overnight.[22] It gave a clean keto product **17a** after column chromatographic purification in 65% yield (Scheme 4).



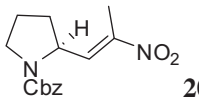
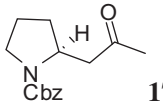
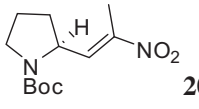
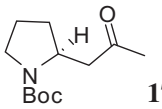
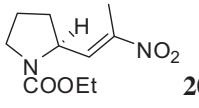
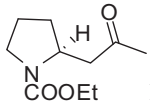
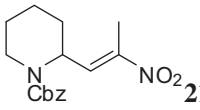
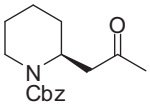
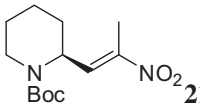
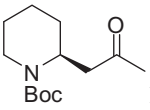
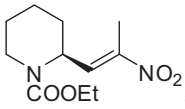
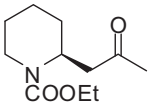
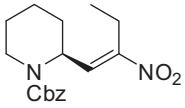
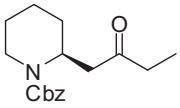
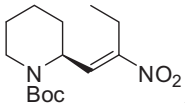
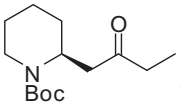
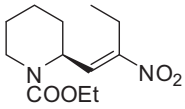
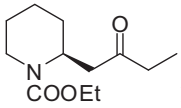
Scheme 4. Successful Nef reaction with plausible mechanism.

Once a platform was set-up for the optimized Nef reaction conditions, we prepared a series of nitro olefinic compounds **20**–**22**(**a**–**c**) starting from proline and pipecolinic acid with different carbamate protecting groups and successfully converted them to carbonyl intermediates **17**–**19**(**a**–**c**) with yield ranging from 55 to 75% using the same method (Scheme 5, Table 1). However, Henry reaction of phenylnitromethane with any of the aldehyde **23** could not be accomplished.



Scheme 5. General synthetic route from L-proline and L-pipecolinic acid. Reagents and conditions: (a) LAH, THF, reflux, 8 h, 90%; (b) For PG=–Cbz: Cbz–Cl, K_2CO_3, CH_3CN, 0 °C, 6 h, 85–90%; For PG=–Boc: $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 80–90%; For PG=–COOEt: ClCOOEt, K_2CO_3, CH_3CN, 0 °C, 80–90%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 95%; (d) (i) $CH_3CH_2NO_2$ (*n*-$PrNO_2$), 0.1–0.2 mol % of 3 N KOH, two drops of concd H_2SO_4; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2 (80–90%, two steps); (e) $NaBH_4$, MeOH, K_2CO_3, H_2O_2, rt, 18 h (56–75%).

Table 1
Preparation of requisite Nef products for the synthesis of natural products

Nitro compounds	Nef product	Yield (%)
 **20a**	 **17a**	65
 **20b**	 **17b**	56
 **20c**	 **17c**	56
 **21a**	 **18a**	65
 **21b**	 **18b**	60
 **21c**	 **18c**	60
 **22a**	 **19a**	75
 **22b**	 **19b**	70
 **22c**	 **19c**	65

2.2. Synthesis of 2-substituted pyrrolidine and piperidine alkaloids

The synthetic utility of the key keto intermediates **17**–**19** achieved through Nef reaction was realized by transforming them to various natural products **1**–**12**.

The target alkaloids **5**–**12** differ with respect to their hydroxyl configuration at the second carbon atom of the aliphatic chain. For achieving this, we explored the diastereoselective reduction of the carbonyls using different reducing agents as shown (Scheme 6). From this study it is clear that the bulky reducing agent tri-*tert*-butoxyaluminium hydride [$LiAl(O^tBu)_3H$] is an effective reducing reagent in getting the cis (*SR*) diastereoselectivity. It gave stereoselectively cis (*SR*)-isomer in all the cases and maximum selectivity was obtained when *tert*-butoxycarbonyl was the protecting group. The other two reducing agents $Zn(BH_4)_2$ and $NaBH_4$ also favoured cis (*SR*)-isomer but with less selectivity. Least selectivity of cis (*SR*) over trans (*SS*) was observed when $NaBH_4$ was used as a reducing agent and when benzyloxycarbonyl was the protecting group. It is interesting to note that trans (*SS*) selectivity over cis (*SR*) was observed when $Zn(BH_4)_2$ was used as a reducing agent for the *tert*-butoxy protecting group in the case of five-membered ring, but the same not shown by six-membered piperidine carbonyls with any of the protecting groups used. The reason for the high diastereoselectivity observed during the reduction of carbonyl using $LiAl(O^tBu)_3H$ is elegantly explained by Davies et al.[23] by invoking a transition state **32** for the six-membered piperidine nucleus (Fig. 2).

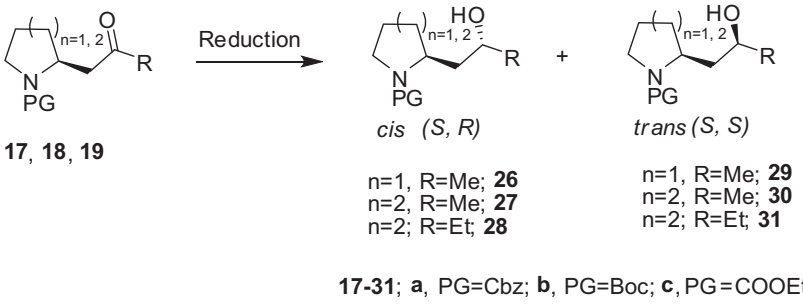
The reduced alcohols **26**–**31** were then separated for completing the total synthesis of targeted natural products.

(−)-Pelletierine, *ent*-**3**, was first isolated by Tanret in 1878 from *Prunica granatum* L.,[24] though its structure remained unresolved partly due to inability of the chemists to synthesize it.[25] The structure was assigned through NMR studies by Gilman and Marion after 83 years[26] and further confirmed by first total synthesis by Beyerman and Maat in 1963.[27a] Many syntheses of it and its analogues thereafter have been elaborated in the literature.[27,9b]

For the synthesis of (+)-pelletierine **3**, the carbobenzyloxy group of **18a** was chemo selectively deprotected using hydrogenation over Pd/C without affecting the carbonyl group (Scheme 7). The physical and spectral properties of thus synthesized **3** as its HCl salt matched very well with the literature values.

Synthesis of compound **3** also constitutes the formal synthesis of natural products like (±)-vertine, 5-*epi*-(+)-cermizine C and (−)-lasubine (Scheme 8).[27j,p,q,28]

(−)-Hygrine **1** and (−)-norhygrine **2** were isolated together from plant extracts[2,29] and numerous racemic and asymmetric syntheses have been reported.[30] The synthesis of (−)-norhygrine **2** was accomplished from **17a** similar to pelletierine **3** (Scheme 7).



Carbonyl compound	Reducing agents	Diastereomeric ratio with different protecting groups		
		PG=Boc	PG=Cbz	PG=COOEt
n=1; R=Me	$NaBH_4$	79:21	50:50	58:42
	$LiAl(O^tBu)_3H$	**99:1**	92:8	81:19
	$Zn(BH_4)_2$	**15:85**	45:55	54:46
n=2; R=Me	$NaBH_4$	72:28	56: 44	62: 38
	$LiAl(O^tBu)_3H$	**99.7: 0.3**	94: 6	75: 25
	$Zn(BH_4)_2$	63: 37	58: 42	60: 40
n=2; R=Et	$NaBH_4$	71: 29	55: 45	62: 38
	$LiAl(O^tBu)_3H$	**99.7: 0.3**	95: 5	75: 25
	$Zn(BH_4)_2$	64: 36	58: 42	60: 40

Scheme 6. Diastereoselective reduction of carbonyls ([**26**/**29**]/[**27**/**30**]/[**28**/**31**]) (diastereomeric ratio was determined by HPLC using Kromasil column, flow rate 1 mL/min, eluent 10% IPA+*n*-hexane).

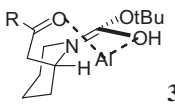
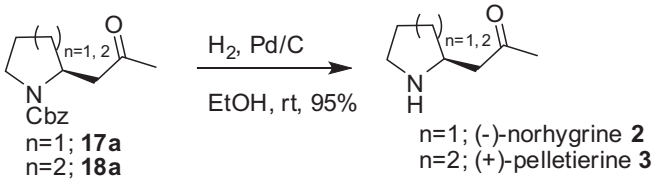


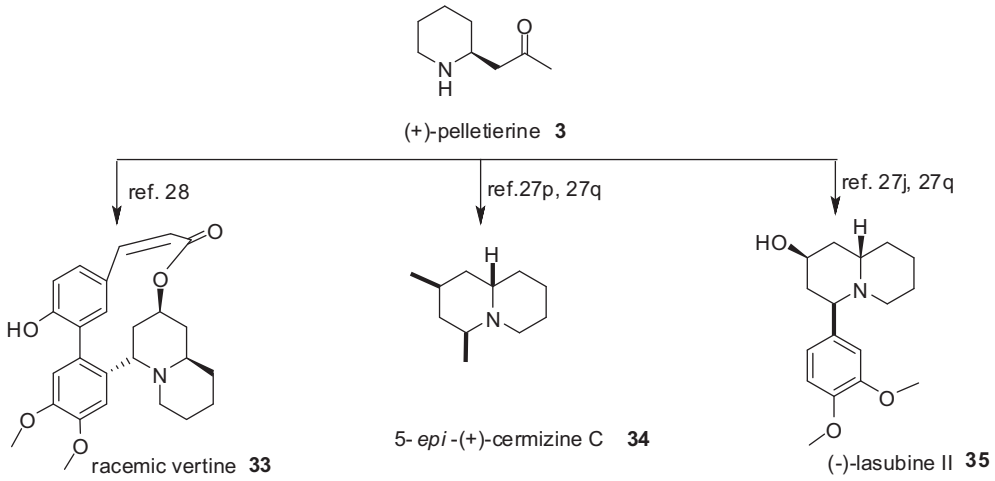
Fig. 2. Transition state for reduction with $LiAl(O^tBu)_3H$.



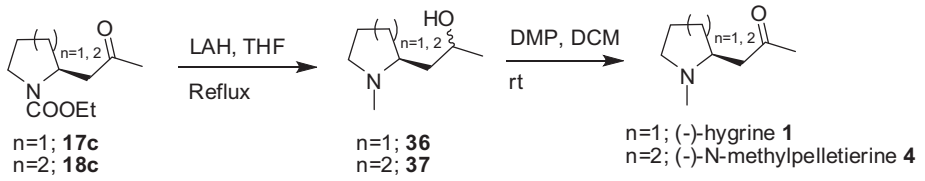
Scheme 7. Synthesis of (−)-norhygrine and (+)-pelletierine.

(−)-*N*-Methylpelletierine **4** was isolated[24c] along with (−) and (±)-pelletierine **3** from the same source and few racemic syntheses of it are reported.[27q–t] To the best of our knowledge no asymmetric synthesis of **4** till date is reported. The LAH reduction of compound **18**c gave the mixture of diastereomers **37**, which as such were oxidized with Dess–Martin periodinane (DMP) to give (−)-*N*-methylpelletierine **4**, the spectral data were well consistent with the reported data (Scheme 8). Incidentally this is a first asymmetric synthesis of (−)-*N*-methylpelletierine **4**. Similarly the synthesis of (−)-hygrine **1** was achieved starting from **17c** (Scheme 9).

(+)-Sedridine **7** was isolated from *Sedum acre*,[27c,31] (−)-allosedridine **8** was isolated from *Sedum nedum*[32] while *N*-methylsedridine **9** and *N*-methylallosedridine **10** were first isolated from *Sedum polytrichoides*[33] and *Sedum sarmentosum*,[2,34] respectively, and different syntheses of these alkaloids have been detailed.[23,27k,35] (−)-Pseudohygroline **5** and (−)-hygroline **6** are the five-membered Sedum alkaloids mainly isolated from *Schizanthus*



Scheme 8. Synthetic approaches from (+)-pelletierine.



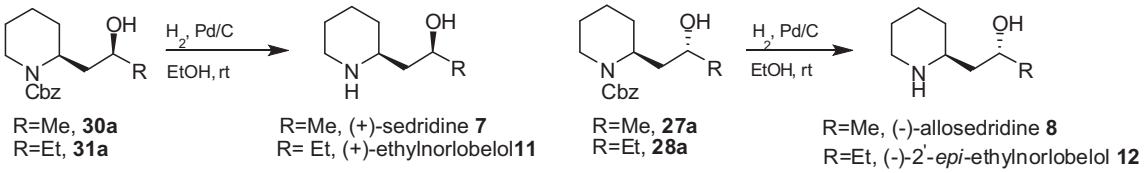
Scheme 9. Synthesis of (−)-hygrine and (−)-*N*-methylpelletierine.

hookeri, *Carallia brachiata* and *Erythroxylon coca*[36] and several asymmetric synthesis of them are described in the literature.[23,35m,37] A straightforward deprotection of benzyloxycarbonyl group of compounds **30a**, **27a**, **31a** and **28a** resulted in accomplishing the synthesis of (+)-sedridine **7**, (−)-allosedridine **8**, (+)-ethylnorlobelol **11** and (−)-*epi*-ethylnorlobelol **12** (Scheme 10).

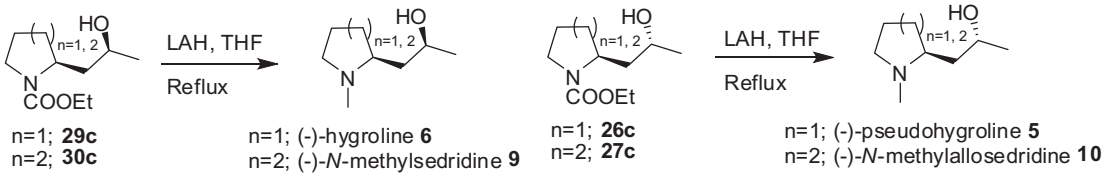
The synthesis of (−)-*N*-methylsedridine **9** and (−)-*N*-methylallosedridine **10** was achieved by LAH reduction of compounds **30c** and **27c** by reducing the ethoxycarbamate to methyl group (Scheme 11). The similar treatment of compounds **29c** and **26c** produced (−)-hygroline **6** and (−)-pseudohygroline **5**, respectively.

terminal nitro olefin to aldehyde, which was further reduced in situ using $NaBH_4$ to furnish the alcohol **38** in an average 45% overall yield starting from proline and pipecolinic acid (Scheme 13).

The homologated prolinol and pipecolinol found application in the synthesis of numerous natural and unnatural products as depicted in Scheme 14.[35j,40,41] The synthesis of histamine H1 antagonist, clamastine **47**, was achieved by Clayden et al. by synthesizing homologated prolinol via Arndst–Eistert method followed by chlorination and subsequent nucleophilic substitution by biphenyl alcoholic compound.[41a,b] A simplest 2-sustituted piperidine alkaloid coniine **48** and some of the Sedum alkaloids have been



Scheme 10. Synthesis of sedridine and norlobelol.



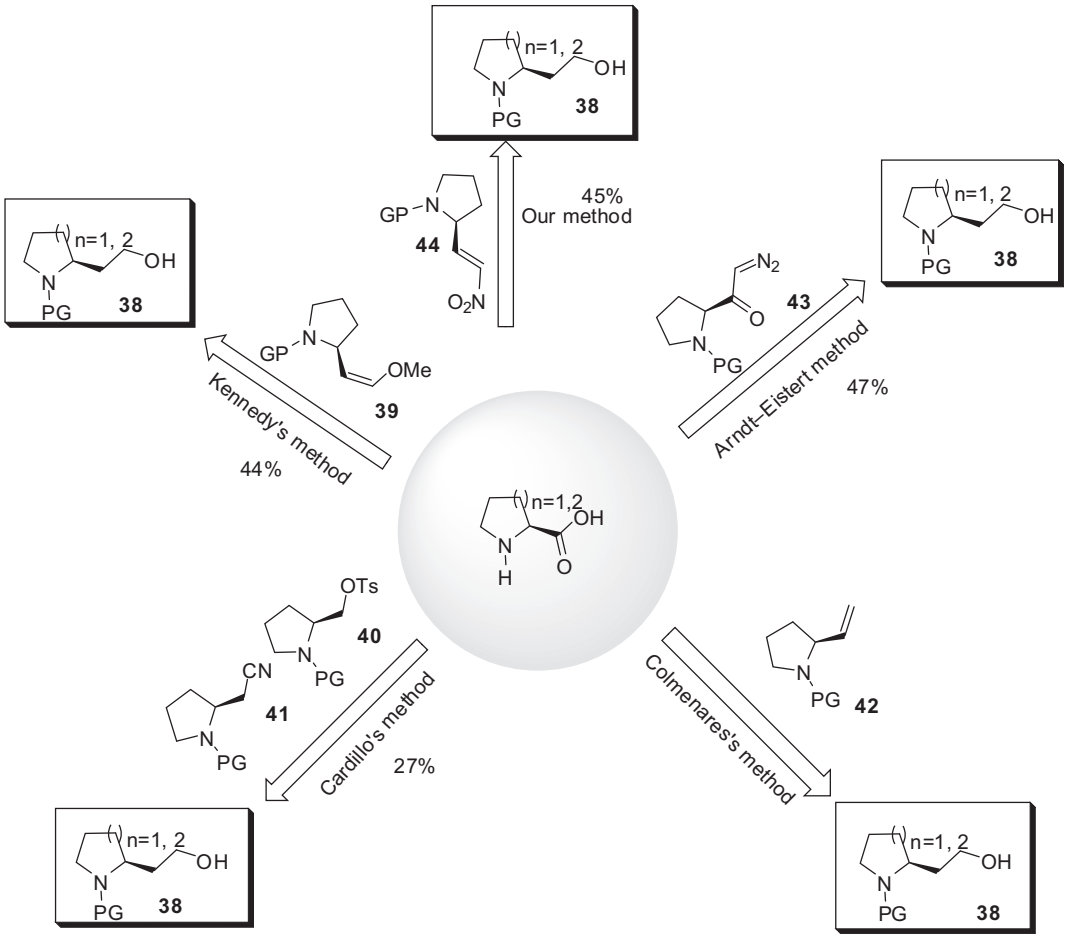
Scheme 11. Synthesis of (−)-*N*-methylsedridine and (−)-*N*-methylallosedridine.

2.3. Homologation of proline and pipecolinic acid via reductive Nef reaction

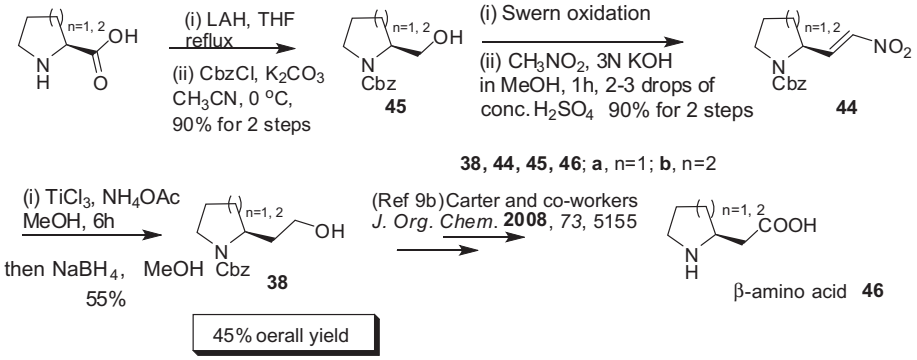
Homologated proline and pipecolinic acids are also important as they constitute important intermediates for the straightforward synthesis of natural products. The very few methods reported in the literature for such homologation are depicted in Scheme 12. The old and frequently used method for homologation of acids is Arndst–Eistert reaction.[38] Cardillo et al. successfully homologated proline through tosylation, cyanation and subsequent reduction during the synthetic evolution of endomorphin-1 analogues[39] whereas Kennedy and Fürstner could achieve this through hydroboration reaction for the synthesis of tylophora alkaloids.[40] The homologation was also done through the Wittig olefination strategy for the synthesis of (+) hygrine.[30i]

We thought of evaluating our Henry–Nef protocol by preparing nitro olefin **44** and subsequent transformations. However our earlier Nef method using $NaBH_4$, H_2O_2 and K_2CO_3 failed in effecting the conversion of nitro olefin **44** to corresponding aldehyde. After several experimentations, McMurray's[21] Nef protocol using $TiCl_3$ and NH_4OAc proved to be effective for the transformation of the synthesized by Paserella et al. using enzymatic reagent based differentiation of protected pipecolinols.[35j,41e,g] Davies and Mackervey have synthesized coniceine **50** involving the synthesis of homologated prolinol as a major step.[41c] Compound **38** has been transformed to alkene **51** whose synthetic utility is well explored and smoothly described recently by Cheng et al. by synthesizing it using Betti base as a chiral auxiliary.[27j] Recent work by Foubelo et al. have demonstrated the applicability of alkene **51** by synthesizing various natural products.[27p] The synthesis of tylophora alkaloid (−)-antofine **52** was accomplished by Fürstner and Kennedy using homologated prolinol.[40] Some of the active drugs like SB-269970 **53** have also been obtained through one-carbon homologation of prolinol.[41d] Very recently Gómez et al. fabulously described the chemoenzymatic synthesis of polyhydroxy indolizidines and quinolizidines starting from racemic **38b**.[41f]

It is noteworthy to mention that conversion of proline/pipecolinic acid to one-carbon homologated proline/pipecolinic acid through our Henry–Nef protocol opens a new route for the synthesis of β-amino acid **46** from α-amino acids.[42] The synthesis of β-amino acids remains challenge for synthetic chemists as they are of paramount importance to pharmaceutical applications.[43]



Scheme 12. Methods for one-carbon homologation of proline and pipecolinic acid.



Scheme 13. Reductive Nef method for homologation of proline and pipecolinic acid.

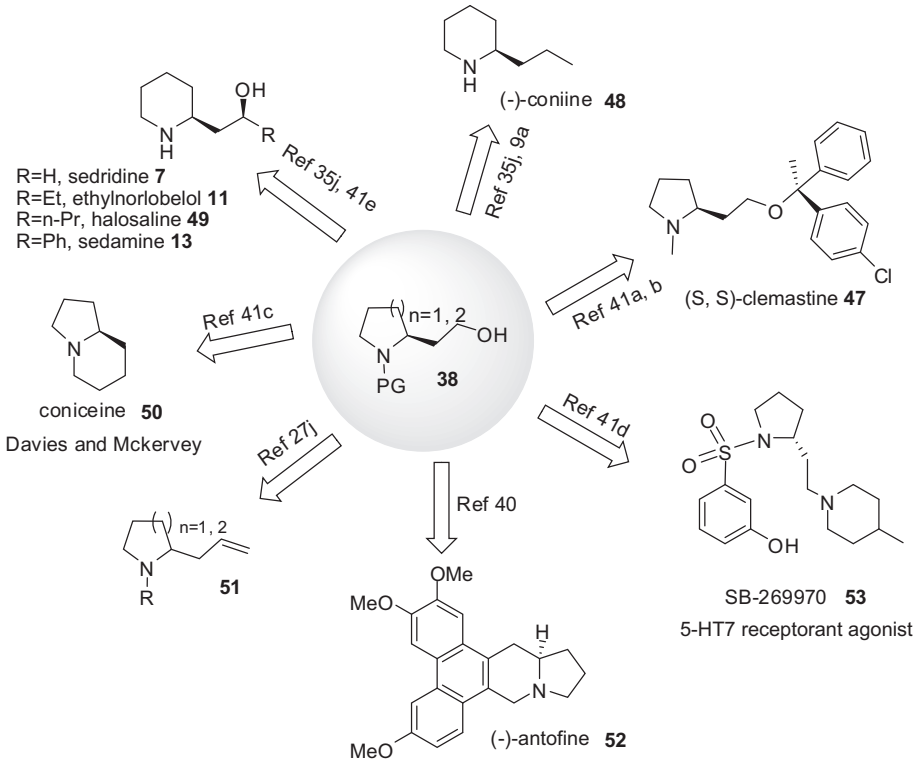
3. Conclusion

In summary, we have developed a practical Henry–Nef reaction protocol for the synthesis of 2-substituted pyrrolidine and piperidine alkaloids containing 1,3-amino alcohol and 1,3-aminoketone units. For Henry reaction catalytic amount of KOH was found to be most appropriate base while for Nef reaction $NaBH_4/H_2O_2$ found to be useful for 1,3-amino secondary alcohols and $TiCl_3$ for 1,3-amino primary alcohols. The versatility of this protocol was demonstrated by synthesizing 12 naturally occurring alkaloids, which include the first asymmetric synthesis of (−)-*N*-methylpelletierine. The synthesis of homoprolinol and homopipecolinol constitutes the formal synthesis of plethora of alkaloids and also opens an alternate route for the synthesis of β-amino acids from α-amino acids.

4. Experimental

4.1. General remarks

Chemicals and solvents were purchased from commercial suppliers and purified by standard techniques whenever necessary. Column chromatography was performed on silica gel (60–120



Scheme 14. Synthetic application of homologated prolinol and pipecolinol.

mesh). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 instrument. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS). The spectra were recorded in $CDCl_3$ as solvent (δ=7.28 ppm for ^{1}H, δ=77.0 ppm for ^{13}C). The multiplicities of carbon signals were obtained from DEPT 135 experiment. Optical rotations (concentration in grams/100 mL solvent) were measured using sodium D line on ADP 220 polarimeter. Infrared (IR) spectra were recorded in a Shimadzu FTIR instrument. High-resolution mass spectra (HRMS) were recorded on a Micro Mass ES-QTOF Mass spectrometer.

4.2. General procedures

I General procedure of Henry reaction

To a stirred solution of nitroethane (11.0 mmol) in methanol (5 mL) was added 3 N KOH (1–2 mL). After 10 min, was added prolinal/pipecolinal **23**/**24**(**a**–**c**) (1.0 mmol) in methanol (5 mL). The reaction mixture was stirred at rt for 1 h. It was then acidified with concd H_2SO_4, diluted with water (20 mL) and extracted with EtOAc (3×25 mL). The combined organic layer was washed with brine (2×25 mL) and dried over anhyd Na_2SO_4. To the crude residue obtained after concentrating the solvent, was added CH_2Cl_2 (20 mL) followed by drop wise addition of CH_3SO_2Cl (2.0 mmol) at 0 °C. The reaction mixture was stirred for 20 min, Et_3N (3.0 mmol) was added and stirring continued further for 20 min. After the reaction mixture had attained the rt, 2 N HCl (15 mL) was added. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with brine (2×25 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was further purified by column chromatography (SiO_2, hexane/EtOAc, 9:1).

Note: for the synthesis of nitro olefins **22**(**a**–**c**) and **44**(**a**, **b**), the intermediate nitro aldol products obtained were purified by column chromatography (SiO_2, hexane/EtOAc, 7:3) giving mixture of diastereomers. The diastereomeric mixture was then treated with of $MeSO_2Cl$ (1.0 mmol) and Et_3N (2.0 mmol) and same procedure was carried out further as earlier.

II General procedure of Nef reaction

To a pre cooled solution of nitroalkene **20**–**22**(**a**–**c**) (1.0 mmol) in MeOH (10 mL) was added $NaBH_4$ (2.0 mmol) in portion. After 2 h stirring at rt, the reaction mixture was cooled to 0 °C. To this cold mixture, 30% H_2O_2 (2.6 mL) and K_2CO_3 (7.9 mmol) were added and the reaction mixture was further stirred for 18 h at rt. The reaction mixture was then acidified with 2 N HCl (5 mL), extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (2×20 mL), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography (SiO_2, hexane/EtOAc, 8.5:1.5).

III General procedures for diastereoselective reduction of keto to hydroxyl group using different reducing agents

(a) Reduction with $LiAl(O^tBu)_3H$

To a cooled solution of $LiAl(O^tBu)_3H$ (3.0 mmol) in THF (5 mL), the ketone **17**–**19**(**a**–**c**) (1.0 mmol) in THF (5 mL) was added drop wise under nitrogen atmosphere. The reaction mixture was stirred further for 8 h at 0 °C and then quenched with ice-cold water (5 mL), acidified with 1 N HCl (2 mL). It was then extracted in ethyl acetate (3×15 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (SiO_2,

eluent hexane/EtOAc, 1:1) to give a diastereomeric mixture ([**26**/**29**]/[**27**/**30**]/[**28**/**31**]) [yield 90–95%]. The diastereomeric mixture (**26**–**31**) was subjected to HPLC using Kromasil column (*n*-hexane/IPA, 9:1) to find the ratio of [**26**/**29**]/[**27**/**30**]/[**28**/**31**] [cis (*SR*)/trans (*SS*)] as shown in the table of Scheme 6.

The separation of diastereomeric mixtures was done using flash chromatography for the characterization purpose (*n*-hexane/EtOAc, 9:1).

(b) Reduction with $NaBH_4$

To a cooled solution of $NaBH_4$ (3.0 mmol) in CH_3OH (5 mL), the ketone **17**–**19**(**a**–**c**) (1.0 mmol) in CH_3OH (5 mL) was added drop wise under nitrogen atmosphere. The reaction mixture was stirred further for 8 h at 0 °C and then quenched with ice-cold water (5 mL) and acidified with 1 N HCl (2 mL). It was then extracted in ethyl acetate (3×15 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (hexane/EtOAc, 1:1) to give a diastereomeric mixture ([**26**/**29**]/[**27**/**30**]/[**28**/**31**]) [yield 90–95%]. The diastereomeric mixture (**26**–**31**) was subjected to HPLC using Kromasil column (*n*-hexane/IPA, 9:1) to find the ratio of [**26**/**29**]/[**27**/**30**]/[**28**/**31**] [cis (*SR*)/trans (*SS*)] as shown in the table of Scheme 6.

The separation of diastereomeric mixture was done using flash chromatography for the characterization purpose (*n*-hexane/EtOAc, 9:1).

(c) Reduction with $Zn(BH_4)_2$

A solution of the ketone **17**–**19**(**a**–**c**) (1.0 mmol) in THF (5 mL) was stirred at 0 °C, $Zn(BH_4)_2$ solution (0.3 mL) [Prepared in the laboratory using $ZnCl_2$ (2.0 g) and $NaBH_4$ (1.3 g) in 28 mL THF according to the reported procedure[44]] was added under nitrogen atmosphere. The reaction mixture was stirred further for 8 h. It was then quenched with ice-cold water and acidified with 1 N HCl (5 mL). It was then extracted with ethyl acetate (3×15 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The residue was column chromatographed (hexane/EtOAc, 1:1) to give a diastereomeric mixture ([**26**/**29**]/[**27**/**30**]/[**28**/**31**]) [yield 90–95%]. The diastereomeric mixture (**26**–**31**) was subjected to HPLC using Kromasil column (*n*-hexane/IPA, 9:1) to find the ratio of ([**26**/**29**]/[**27**/**30**]/[**28**/**31**]) [cis (*SR*)/trans (*SS*)] as shown in the table of Scheme 6.

The separation of diastereomeric mixture was done using flash chromatography for the characterization purpose (*n*-hexane/EtOAc 9:1).

4.3. Experimental procedures and characterization

*4.3.1. Benzyl (2S)-2-[(1′E)-2′-nitroprop-1′-en-1′-yl]pyrrolidine-1-carboxylate (**20a**).* Following the general procedure I, Henry-olefination of compound **23a** (0.23 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave **20a** (0.26 g, 90% for two steps) as pale yellow thick liquid; R_f=0.25 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ +13.0 (*c* 0.1, $CHCl_3$); IR (neat) 3108, 2979, 2934, 2882, 1698, 1526 and 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.64–1.71 (m, 2H, H-3), 1.80–1.87 (m, 2H, H-4), 1.8 (s, 3H, H-3′), 3.51–3.59 (m, 2H, H-5), 4.43–4.57 (m, 1H, H-2), 4.97–5.16 (m, 2H, C*H*$_2$Ph), 7.24–7.26 (m, 1H, H-1′), 7.31–7.36 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3′), 24.4 (C-3), 31.5 (C-4), 46.9 (C-5), 55.0 (C-2), 67.6 (*C*H$_2$–Ph), 127.8 (PhCH), 128.5 (PhCH), 128.5 (PhCH), 135.1 (C-1′), 136.4 (Ph*C*), 148.2 (C-2′), 154.8 (N*C*O); HRMS: *m*/*z* calcd for $C_{15}H_{18}N_2O_4Na$ $[M+Na]^+$: 313.1164; found: 313.1169.

*4.3.2. tert-Butyl (2S)-2-[(1′E)-2′-nitroprop-1′-en-1′-yl]pyrrolidine-1-carboxylate (**20b**).* Following the general procedure I, Henry-olefination of compound **23b** (0.19 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the product **20b** (0.23 g, 90% for two steps) as a pale yellow thick liquid; R_f=0.40 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −12.0 (*c* 0.1, $CHCl_3$); IR (neat) 3100, 2970, 2936, 2880, 1690, 1536 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H, ^{t}Bu*H*), 1.64–1.71 (m, 2H, H-3), 1.8–2.2 (m, 2H, H-4), 2.2 (s, 3H, H-3′), 3.41–3.54 (m, 2H, H-5), 4.40–4.51 (m, 1H, H-2), 6.96 (d, *J*=7.6 Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3′), 24.3 (C-3), 28.8 (OC(*C*H$_3$)$_3$), 32.5 (C-4), 48.0 (C-5), 54.8 (C-2), 89.1 (O*C*Me$_3$), 137.1 (C-1′), 147.5 (C-2′), 154.3 (N*C*O); HRMS: *m*/*z* calcd for $C_{12}H_{20}N_2O_4Na$ $[M+Na]^+$: 279.1321; found: 279.1320.

*4.3.3. Ethyl (2S)-2-[(1′E)-2′-nitroprop-1′-en-1′-yl]pyrrolidine-1-carboxylate (**20c**).* Following the general procedure I, Henry-olefination of compound **23c** (0.17 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the title compound **20c** (0.2 g, 90%) as a pale yellow dense liquid; R_f=0.50 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ +12.0 (*c* 0.1, $CHCl_3$); IR (neat) 3008, 2979, 2934, 1690, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19–2.29 (m, 9H, H-4, H-3, H-3′, OCH$_2$C*H*$_3$), 3.26–3.56 (m, 2H, H-5), 4.10–4.12 (m, 2H, OC*H*$_2$CH$_3$), 4.47–4.54 (m, 1H, H-2), 6.91 (d, *J*=8 Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 12.7 (CH$_2$C*H*$_3$), 14.7 (C-3′), 24.4 (C-3), 32.4 (C-4), 46.7 (C-5), 54.9 (C-2), 61.3 (O*C*H$_2$), 135.4 (C-1′), 155.0 (NCO); HRMS: *m*/*z* calcd for $C_{10}H_{16}N_2O_4Na$ $[M+Na]^+$: 251.1008; found: 251.1006.

*4.3.4. Benzyl (2S)-2-(2′-oxopropyl)pyrrolidine-1-carboxylate (**17a**).* Following the general procedure II, Nef reaction on **20a** (0.29 g, 1.0 mmol) gave **17a** (0.17 g, 65%) as a thick liquid; R_f=0.30 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −38.0 (*c* 0.5, $CHCl_3$); IR (neat) 1711, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.66–2.15 (m, 7H, H-3, H-4, H-3′), 2.42–2.45 (m, 1H, H-1′A), 2.82–3.15 (m, 1H, H-1′B), 3.41–3.42 (m, 2H, H-5), 4.20–4.23 (m, 1H, H-2), 5.08–5.17 (m, 2H, C*H*$_2$Ph), 7.29–7.36 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-3), 30.3 (C-3′), 30.9 (C-4), 46.6 (C-1′), 47.6 (C-5), 54.0 (C-2), 66.6 (CH$_2$Ph), 127.3 (PhCH), 127.6 (PhCH), 128.2 (PhCH), 137.0 (PhC), 153.6 (N*C*O), 206.8 (C-2′); HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_3Na$ $[M+Na]^+$: 284.1263; found: 284.1266.

*4.3.5. tert-Butyl (2S)-2-(2′-oxopropyl)pyrrolidine-1-carboxylate (**17b**).* Following the general procedure II, compound **20b** (0.25 g, 1.0 mmol) on Nef reaction gave **17b** (0.13 g, 56%) as a thick liquid; R_f=0.45 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −43.3 (*c* 0.1, $CHCl_3$); IR (neat) 2974, 1713, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.50 (s, 9H, ^{t}Bu*H*), 1.62–2.15 (m, 4H, H-4, H-3), 2.40–2.42 (m, 1H, H-1′A), 2.90–3.11 (m, 1H, H-1′B), 3.14–3.36 (m, 2H, H-5), 4.10–4.16 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (C-3), 28.5 (OC(*C*H$_3$)$_3$), 30.6 (C-3′), 30.7 (C-4), 46.4 (C-5), 48.6 (C-1′), 53.4 (C-2), 79.5 (O–*C*Me$_3$), 154.3 (N*C*O), 206.9 (C-2′); HRMS: *m*/*z* calcd for $C_{12}H_{21}NO_3Na$ $[M+Na]^+$: 250.1419; found: 250.1418.

*4.3.6. Ethyl (2S)-2-(2′-oxopropyl)pyrrolidine-1-carboxylate (**17c**).* Following the general procedure II, compound **20c** (0.23 g, 1.0 mmol) on Nef reaction gave **17c** (0.11 g, 56%) as a viscous liquid; R_f=0.20 (hexane/EtOAc, 9:1); $[\alpha]_D^{28}$ −39.3 (*c* 0.1, $CHCl_3$); IR (neat) 2974, 1713, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.2 (t, 3H, OCH$_2$C*H*$_3$), 1.65–1.83 (m, 1H, H-3A), 1.85–1.87 (m, 2H, H-4), 2.01–2.05 (m, 1H, H-3B), 2.12 (s, 3H, H-3′), 2.42–2.45 (m, 1H, H-1′A), 2.89–3.23 (m, 1H, H-1′B), 3.36–3.40 (m, 2H, H-5), 4.11–4.21 (m, 3H, H-2, −OC*H*$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7 (−CH$_2$C*H*$_3$), 23.6 (C-3), 30.2 (C-4), 31.7 (C-3′), 46.4 (C-5), 48.5 (C-1′), 53.4 (C-2), 60.8 (OCH$_2$CH$_3$), 154.9 (N*C*O), 206.0 (C-2′); HRMS: *m*/*z* calcd for $C_{10}H_{17}NO_3Na$ $[M+Na]^+$: 222.1106; found: 222.1102.

*4.3.7. tert-Butyl (2S)-2-[(2′R)-2′-hydroxypropyl]pyrrolidine-1-carboxylate (**26b**).* Following the general procedures IIIa–c, reduction of **17b** (0.23 g, 1.0 mmol) gave **26b** (0.12 g, 98%) as a thick liquid (yield after separation of the diastereomers as mentioned in

the general procedures IIIa–c); R_f=0.25 (hexane/EtOAc, 7:3); $[\alpha]_D^{28}$ −11.2 (*c* 0.2, $CHCl_3$) {lit.[23] $[\alpha]_D^{28}$ +10.9 (*c* 0.7, $CHCl_3$) for (*RS*)-isomer}; IR (neat) 3426, 2971, 1694, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.18 (d, 3H, H-3′), 1.46–2.02 (m, 15H, ^{t}Bu*H*, H-3, H-4, H-1′), 3.31–3.34 (m, 2H, H-5), 3.80–3.87 (buried m, 1H, H-2′), 3.90–3.98 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.8 (C-3), 23.9 (C-3′), 28.5 (OC(CH_3)$_3$), 32.5 (C-4), 45.8 (C-1′), 46.4 (C-5), 55.7 (C-2), 66.5 (C-2′), 79.7 (O*C*Me$_3$), 155.6 (N*C*O); HRMS: *m*/*z* calcd for $C_{12}H_{23}NO_3Na$ $[M+Na]^+$: 252.1576; found: 252.1581.

*4.3.8. tert-Butyl (2S)-2-[(2′S)-2′-hydroxypropyl]pyrrolidine-1-carboxylate (**29b**).* Following the general procedures IIIa–c, reduction of **17b** (0.23 g, 1.0 mmol) gave **29b** (0.12 g, 98%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedures IIIa–c); R_f=0.25 (hexane/EtOAc, 7:3); $[\alpha]_D^{28}$ −80.2 (*c* 0.1, $CHCl_3$) {lit.[23] $[\alpha]_D^{23}$ +78.5 (*c* 0.7, $CHCl_3$) for (*RR*)-isomer}; IR (neat) 3426, 2971, 1694, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17–2.01 (d, 3H, H-3′), 1.32–2.01 (m, 6H, H-1′, H-3, H-4), 1.46 (s, 9H, ^{t}Bu*H*), 3.26–3.37 (m, 2H, H-5), 3.65–3.70 (m, 1H, H-2), 3.71–4.18 (m, 1H, H-2′), 4.97 (br s, O*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.5 (C-3), 23.6 (C-3′), 28.4 (OC(CH_3)$_3$), 31.1 (C-4), 45.6 (C-1′), 46.5 (C-5), 53.7 (C-2), 63.6 (C-2′), 79.2 (O*C*Me$_3$), 156.6 (N*C*O); HRMS: *m*/*z* calcd for $C_{12}H_{23}NO_3Na$ $[M+Na]^+$: 252.1576; found: 252.1573.

*4.3.9. 1-[(2S)-Pyrrolidin-2-yl]acetone (**2**).* Acetonyl carbamate **17a** (0.18 g, 6.8 mmol) in EtOH (15 mL) was stirred with 10% Pd/C (20 mg) under H_2 atmosphere (2 kg/cm^2) for 8 h in Parr hydrogenator at rt. The mixture was then filtered, washed with EtOH and then concentrated to give (−)-norhygrine **2** (0.07 g, 81%) as a pale yellow thick liquid; $[\alpha]_D^{30}$ −30.2 (*c* 0.2, $CHCl_3$) {lit.[14] $[\alpha]_D^{33}$ −29.6 (*c* 0.14, $CHCl_3$); ee 99%; IR (neat) 3310, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.62–2.25 (m, 4H, H-4, H-3), 2.22 (s, 3H, H-3′), 2.96 (dd, *J*=6.0, 18.6 Hz, 2H, H-1′), 3.33–3.42 (m, 2H, H-5), 3.89–3.94 (m, 1H, H-2), 9.43 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-3), 30.3 (C-4), 30.1 (C-3′), 44.9 (C-1′), 45.2 (C-5), 55.1 (C-2), 205.8 (C-2′).

*4.3.10. 1-[(2S)-1-Methylpyrrolidin-2-yl]acetone·HCl (**1**·HCl).* To a cooled suspension of LAH (0.114 g, 3.0 mmol) in THF (15 mL) was added compound **17c** (0.20 g, 1.0 mmol) in THF (5 mL) drop wise under nitrogen atmosphere and refluxed further for 6 h. It was quenched with drop wise addition of ice-cold water (1 mL) and further treated with 2 N NaOH (1 mL) solutions. The reaction mass was filtered and directly dried over anhyd Na_2SO_4 to give **36** (0.18 g, 90%). The crude mass was as such dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C under nitrogen atmosphere, added $NaHCO_3$ (0.1 g, 1.2 mmol) and DMP (0.5 g, 1.2 mmol), brought to rt in 30 min. The reaction mass was filtered and concentrated under reduced pressure. The crude mass was then treated with 5 N HCl (2 mL) in 10 mL CH_2Cl_2 for 2 h, concentrated and further purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 8.5:1.5) to afford compound **1**·HCl (0.17 g, 95%) as pale yellow thick liquid; R_f=0.20 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{30}$ −33.2 (*c* 0.2, H_2O) {lit.[30h] $[\alpha]_D^{30}$ +34.5 (*c* 0.5, H_2O) for *R*-isomer]; ee 96%; IR (neat) 3390, 2900, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.87–2.41 (m, 4H, H-3, H-4), 2.27 (s, 3H, H-3′), 2.81 (d, *J*=6.0 Hz, NC*H*$_3$), 2.80–2.82 (m, 1H, H-5A), 3.11 (dd, *J*=6.6, 18.6 Hz, 1H, H-1′A), 3.45 (dd, *J*=6.6, 18.6 Hz, 1H, H-1′B), 3.59–3.75 (m, 1H, H-5B), 3.76–3.83 (m, 1H, H-2), 11.67 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0 (C-3), 30.3 (C-3′), 30.5 (C-4), 40.3 (N*C*H$_3$), 44.2 (C-1′), 56.2 (C-5), 64.2 (C-2), 204.9 (C-2′); GC–MS: *m*/*z* calcd for $C_8H_{15}NO$ $[M]^+$: 141; found: 141.

*4.3.11. (2R)-1-[(2S)-1-Methylpyrrolidin-2-yl]propan-2-ol (**5**).* To a suspension of LAH (0.076 g, 2.0 mmol) in THF (10 mL) cooled at 0 °C was added compound **26c** (0.1 g, 0.5 mmol) in THF (5 mL) drop wise under nitrogen atmosphere. The reaction mixture was then refluxed for 8 h. It was quenched with drop wise addition of ice-cold water (1 mL) and further treated with 2 N NaOH (1 mL) solution. The organic compound was extracted with EtOAc (3×10 mL). The combined organic layer was then dried over anhyd Na_2SO_4. The organic layer was filtered and concentrated in vacuo to get the pure product **5** (0.07 g, 95%) as a very thick liquid; $[\alpha]_D^{28}$ −90 (*c* 0.2, EtOH) {lit.[37f] $[\alpha]_D^{29}$ +70.7 (*c* 2.0, EtOH); lit.[37a] $[\alpha]_D^{29}$ +97.0 (*c* 3.4, EtOH) for (*RR*)-isomer}; ee 92%; IR (neat) 3362, 2964, 1418 cm^{-1}; ^{1}HMR ($CDCl_3$, 400 MHz): δ 1.15 (d, *J*=6.4 Hz, 2H, H-3′), 1.32–1.49 (m, 3H, H-1′A, H-3A), 1.72–1.78 (m, 2H, H-4), 1.97–2.03 (1H, m, H-3B), 2.31–2.36 (m, 4H, NC*H*$_3$, H-5A), 2.67–2.69 (m, 1H, H-2), 3.02–3.06 (m, 1H, H-5B), 3.88–3.92 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6 (C-4), 24.2 (C-3′), 30.4 (C-3), 42.7 (N*C*H$_3$), 42.8 (C-1′), 55.4 (C-5), 65.5 (C-2), 67.3 (C-2′); HRMS: *m*/*z* calcd for $C_8H_{17}NONa$ $[M+Na]^+$: 144.1388; found: 144.1397.

*4.3.12. (2S)-1-[(2S)-1-Methylpyrrolidin-2-yl]propan-2-ol (**6**).* Following the similar procedure described for compound **5**, compound **29c** (0.1 g, 0.5 mmol) on LAH (0.076 g, 2.0 mmol) reduction gave the pure product **6** (0.065 g, 95%) as a very thick colourless liquid; $[\alpha]_D^{23}$ −50 (*c* 0.2, EtOH) {lit.[37a] $[\alpha]_D^{22}$ −49.0 (*c* 0.4, EtOH) for (*RR*)-isomer}; ee 99%; IR (neat) 3362, 2964 cm^{-1}; H NMR ($CDCl_3$, 400 MHz): δ 1.04–1.08 (m, 3H, H-3′), 1.32–1.49 (m, 3H, H-1′A, H-3A), 1.72–1.78 (m, 2H, H-4), 2.01–2.09 (m, 1H, H-3B), 2.20 (s, 3H, NC*H*$_3$), 2.30–2.32 (m, 1H, H-5A), 2.8–2.90 (m, 1H, H-5B), 3.70–3.60 (m, 1H, H-2′), 3.80 (s br, 1H, −O*H*); ^{13}C NMR($CDCl_3$, 100 MHz): δ 23.3 (C-4), 23.7 (C-3′), 28.3 (C-3), 37.1 (C-1′), 40.6 (N*C*H$_3$), 57.1 (C-5), 62.7 (C-2), 64.8 (C-2′); HRMS: *m*/*z* calcd for $C_8H_{17}NONa$ $[M+Na]^+$: 144.1388; found: 144.1384.

*4.3.13. Benzyl (2S)-2-[(1E)-2-nitroprop-1-en-1-yl]piperidine-1-carboxylate (**21a**).* Following the general procedure I, Henry-olefination of compound **24a** (0.25 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the title compound **21a** (0.26 g, 85% for two steps) as pale yellow thick liquid; R_f=0.45 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −33.0 (*c* 0.1, $CHCl_3$); IR (neat) 3108, 2979, 2934, 2882,1698, 1526 and 1356 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.53 (m, 2H, H-4), 1.56–1.84 (m, 4H, H-3 and H-5), 2.17 (s, 3H, H-3′), 2.97–3.03 (t, *J*=12 Hz, 1H, H-6), 4.11–4.15 (m, 1H, H-2), 5.08–5.18 (m, 3H, PhC*H*$_2$ and H-1′), 7.28–7.36 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3′), 19.5 (C-4), 24.9 (C-5), 29.4 (C-3), 40.4 (C-6), 48.8 (C-2), 67.5 (PhC*H*$_2$), 128.0 (Ph*C*H), 128.2 (Ph*C*H), 128.5 (Ph*C*H), 128.6 (Ph*C*H), 131.7 (Ph*C*H), 133.5 (C-1′), 136.3 (Ph*C*), 148.8 (C-2′), 155.4 (N*C*O); HRMS: *m*/*z* calcd for $C_{16}H_{20}N_2O_4Na$ $[M+Na]^+$: 327.1322; found: 327.1321.

*4.3.14. tert-Butyl (2S)-2-[(1E)-2-nitroprop-1-en-1-yl]piperidine-1-carboxylate (**21b**).* Following the general procedure I, Henry-olefination of compound **24b** (0.213 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the product **21b** (0.23 g, 85% for two steps) as a pale yellow crystalline solid; R_f=0.55 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −48.4 (*c* 0.1, $CHCl_3$); mp=80 °C; IR (neat) 3108, 2979, 2934, 2882, 1694, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H, ^{t}Bu*H*), 1.47–1.78 (m, 6H, H-4, H-5, H-3), 2.22 (s, 3H), 2.88 (t, *J*=12.4 Hz, 1H, H-6), 3.99–4.02 (m, 1H, H-6), 4.90–5.10 (buried m, 1H, H-2), 7.27–2.29 (d, *J*=8.8 Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-3′), 19.6 (C-4), 24.9 (C-5), 28.3 (OC(CH_3)$_3$), 29.5 (C-3), 40.1 (C-6), 48.5 (C-2), 80.1 (O*C*Me$_3$), 132.5 (C-1′), 148.4 (C-2′), 154.6 (N*C*O); HRMS: *m*/*z* calcd for $C_{13}H_{22}N_2O_4Na$ $[M+Na]^+$: 293.1477; found: 293.1479.

*4.3.15. Ethyl (2S)-2-[(1E)-2-nitroprop-1-en-1-yl]piperidine-1-carboxylate (**21c**).* Following the general procedure I, Henry-olefination of compound **24c** (0.18 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave **21c** (0.20 g, 85%) as a pale yellow dense liquid; R_f=0.40 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −32.3 (*c* 0.1, $CHCl_3$); IR

(neat) 3108, 2979, 2934, 2882, 1692, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.26–1.30 (buried m, 3H, CH_2CH_3), 1.47–1.90 (m, 6H, H-4, H-5, H-3), 2.26 (s, 3H, H-3′), 2.92–2.98 (m, 1H, H-6A), 4.06–4.13 (m, 3H, H-6B, CH_2CH_3), 5.01–5.07 (buried m, 1H, H-2), 7.28–7.32 (d, J=9.2 Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (CH_2CH_3), 14.5 (C-3′), 19.4 (C-4), 24.9 (C-5), 29.4 (C-3), 40.2 (C-6), 48.6 (C-2), 61.6 (OCH_2CH_3), 131.8 (C-1′), 148.7 (C-2′), 155.5 (NCO); HRMS: m/z calcd for $C_{11}H_{18}N_2O_4Na$ $[M+Na]^+$: 265.1164; found: 265.1162.

*4.3.16. Benzyl (2S)-2-(2-oxopropyl)piperidine-1-carboxylate (**18a**).* Following the general procedure II, Nef reaction on **21a** (0.29 g, 1.0 mmol) gave **18a** (0.18 g, 65%) as a thick liquid; $[\alpha]_D^{28}$ −10.0 (c 0.5, $CHCl_3$) {lit.[27f] $[\alpha]_D^{26}$ +10.2 (c 2.5, $CHCl_3$) for R-isomer}; IR (neat) 2990, 1693, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41–1.66 (m, 6H, H-4, H-5, H-3), 2.01–2.29 (m, 4H, H-3′), 2.69–2.86 (m, 2H, H-1′), 4.01–4.07 (buried m, 1H, H-6A), 4.70–4.72 (buried m, 1H, H-6B), 4.80–4.82 (buried m, 1H, H-2), 5.09–5.19 (m, 2H, CH_2Ph), 7.28–7.37 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 30.1 (C-3′), 39.8 (C-1′), 44.3 (C-6), 47.5 (C-2), 65.3 (OCH_2Ph), 126.9 (PhCH), 127.6 (PhCH), 127.9 (PhCH), 128.5 (PhCH), 128.5 (PhCH), 136.7 (PhC), 155.3 (NCO), 206.9 (C-2′).

*4.3.17. tert-Butyl (2S)-2-(2-oxopropyl)piperidine-1-carboxylate (**18b**).* Following the general procedure II, compound **21b** (0.25 g, 1.0 mmol) on Nef reaction gave **18b** (0.15 g, 60%) as a thick yellow liquid; $[\alpha]_D^{28}$ −14.0 (c 0.1, $CHCl_3$) {lit.[27j] $[\alpha]_D^{33}$ −12.7 (c 0.22, $CHCl_3$)}; IR (neat) 2974, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, 9H, ^{t}Bu*H*), 1.22–1.60 (m, 6H, H-4, H-5, H-3), 2.16 (s, 3H, H-3′), 2.61–2.63 (m, 2H, C-1′), 2.72–2.78 (m, 1H, H-6A), 3.94 (br s, 1H, H-6B), 4.60–4.70 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8 (C-4), 25.2 (C-5), 28.3 (O–C(CH_3)$_3$), 28.4 (C-3), 30.0 (C-3′), 39.3 (C-1′), 44.2 (C-6), 47.2 (C-2), 79.6 ($OCMe_3$), 154.7 (NCO), 207.1 (C-2′).

*4.3.18. Ethyl (2S)-2-(2-oxopropyl)piperidine-1-carboxylate (**18c**).* Following the general procedure II, compound **21c** (0.24 g, 1.0 mmol) on Nef reaction gave **18c** (0.13 g, 60%) as a pale yellow viscous liquid; R_f=0.35 (hexane/EtOAc, 8:2); $[\alpha]_D^{28}$ −10.6 (c 0.1, $CHCl_3$); IR (neat) 2970, 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.21 (t, J=4 Hz, 3H, CH_2CH_3), 1.35–1.60 (m, 6H, H-4, H-5, H-3), 2.15 (s, 3H, H-3′), 2.60–2.65 (m, 2H, H-1′), 2.76–2.82 (m, 1H, H-6A), 3.90–4.00 (buried m, 1H, H-6B), 4.07–4.08 (m, 2H, OCH_2CH_3), 4.70–4.80 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (OCH_2CH_3), 17.8 (C-4), 24.2 (C-5), 27.3 (C-3), 29.0 (C-3′), 38.5 (C-2′), 43.2 (C-6), 46.3 (C-2), 60.2 (OCH_2CH_3), 154.5 (NCO), 205.9 (C-2′); HRMS: m/z calcd for $C_{11}H_{19}NO_3Na$ $[M+Na]^+$: 236.1263; found: 236.1261.

*4.3.19. Benzyl (2S)-2-[(2S)-2-hydroxypropyl]piperidine-1-carboxylate (**30a**).* Following the general procedures IIIa–c, reduction of **18a** (0.29 g, 1.0 mmol) gave **30a** (0.27 g, 95%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedures IIIa–c); $[\alpha]_D^{28}$ −25.82 (c 0.1, $CHCl_3$) {lit.[35l] $[\alpha]_D^{25}$ −28.52 (c 2.920, $CHCl_3$)}; IR (neat) 3420, 2970, 1690, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19–1.76 (m, 10H, H-4, H-5, H-3, H-3′, O*H*), 2.00 (t, J=13.2 Hz, 1H, H-1′A), 2.77 (t, J=12.8 Hz, 1H, H-1′B), 3.20–3.33 (buried m, 1H, H-2′), 3.50–3.55 (buried m, 1H, H-6A), 4.05–4.08 (m, 1H, H-6B), 4.40–4.60 (buried m, 1H, H-2), 5.16–5.19 (m, 2H, PhCH_2), 7.30–7.37 (m, 5H, PhCH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (C-4), 22.5 (C-3′), 25.4 (C-5), 29.3 (C-3), 39.3 (C-1′), 39.3 (C-6), 47.4 (C-2), 65.2 (C-2′), 67.5 (PhCH_2), 126.9 (PhCH), 127.9 (PhCH), 128.1 (PhCH), 128.3 (PhCH), 128.5 (PhCH), 136.5 (PhC), 156.8 (NCO).

*4.3.20. Benzyl (2S)-2-[(2R)-2-hydroxypropyl]piperidine-1-carboxylate (**27a**).* Following the general procedures IIIa–c, reduction of **18a** (0.29 g, 1.0 mmol) gave **27a** (0.27 g, 95%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedures IIIa–c); $[\alpha]_D^{28}$ −50.6 (c 0.1, $CHCl_3$) {lit.[35l] $[\alpha]_D^{25}$ −52.37 (c 1.275, $CHCl_3$)}; IR (neat) 3430, 2990, 1680, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.84 (m, 11H, H-4, H-3′, H-5, H-3, H-1′A, O*H*), 2.21–2.40 (buried m, 1H, H-1′B), 2.88–2.94 (m, 1H, H-6A), 3.70–3.90 (buried m, 1H, H-6B), 4.05–4.07 (m, 1H, H-2), 4.40–4.43 (m, 1H, H-2), 5.14 (s, 2H, CH_2Ph), 7.34–7.37 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9 (C-4), 23.6 (C-3′), 25.4 (C-5), 25.5 (C-3), 28.9 (C-1′), 39.3 (C-6), 48.7 (C-2), 65.8 (C-2′), 67.1 (PhCH_2), 127.8 (PhCH), 127.9 (PhCH), 128.4 (PhCH), 136.7 (PhCH), 136.7 (PhC), 155.7 (NCO).

*4.3.21. tert-Butyl (2S)-2-[(2R)-2-hydroxypropyl]piperidine-1-carboxylate (**27b**).* Following the general procedures IIIa–c, reduction of **18b** (0.25 g, 1.0 mmol) gave **27b** (0.24 g, 94%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedures IIIa–c); $[\alpha]_D^{28}$ −63.4 (c 0.05, $CHCl_3$) {lit.[35j] $[\alpha]_D^{33}$ +56.0 (c 1.15, $CHCl_3$) for (*RS*)-isomer, 85% ee}; IR (neat) 3426, 2971, 1694, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.82 (m, 11H, H-4, H-5, H-3, H-3′, H-1′A, O*H*), 1.45 (s, 9H, ^{t}Bu*H*), 2.67–2.85 (m, 2H, H-1′B, H-6A), 3.80–3.83 (buried m, 1H, H-6B), 3.90–3.94 (buried m, 1H, H-2), 4.30–4.33 (buried m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0 (C-4), 23.5 (C-3′), 25.5 (C-3 and C-5), 29.0 (O–C(CH_3)$_3$), 29.6 (C-1′), 39.9 (C-6), 40.5 (C-2), 66.5 (C-2′), 79.7 ($OCMe_3$), 156.5 (NCO).

*4.3.22. Ethyl (2S)-2-[(2S)-2-hydroxypropyl]piperidine-1-carboxylate (**30c**).* Following the general procedures IIIa–c, reduction of **18c** (0.23 g, 1.0 mmol) gave **30c** (0.23 g, 95%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedures IIIa–c); $[\alpha]_D^{28}$ −16.0 (c 0.04, $CHCl_3$); IR (neat) 3450, 2900, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22–1.90 (m, 12H, H-4, H-5, H-3, OCH_2CH_3, H-3′), 1.90–1.97 (m, 1H, H-1′A), 2.62–2.69 (m, 1H, H-1′B), 3.10–3.20 (buried m, 1H, H-6), 3.40–3.60 (buried m, 1H, H-6B), 3.92–3.95 (m, 1H, H-2), 4.05–4.10 (q, J=6.8 Hz, 2H, OCH_2CH_3), 4.40–4.42 (buried m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (C-3′), 18.1 (C-4), 21.4 (OCH_2CH_3), 24.4 (C-5), 28.3 (C-3), 38.1 (C-1′), 38.3 (C-6), 46.1 (C-2), 60.7 (OCH_2CH_3), 62.3 (C-2′) 156.1 (NCO).

*4.3.23. Ethyl (2S)-2-[(2R)-2-hydroxypropyl]piperidine-1-carboxylate (**27c**).* Following the general procedures IIIa–c, reduction of **18c** (0.23 g, 1.0 mmol) gave **27c** (0.23 g, 95%) as a thick liquid (yield after separation of the diastereomers as mentioned in the general procedure **IIIa–c**); $[\alpha]_D^{28}$ −56.8 (c 0.2, $CHCl_3$); IR (neat) 3510, 2994, 1680, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22–1.67 (m, 12H, H-3′, H-4, H-5, H-3, OCH_2CH_3), 1.84–1.87 (m, 1H, –OH), 2.15–2.35 (m, 2H, H-1′), 2.84–2.91 (m, 1H, H-6A), 3.81–3.86 (m, 1H, H-6B), 4.00–4.03 (m, 1H, H-2), 4.13 (m, 2H, OCH_2CH_3), 4.38–4.39 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (C-3′), 17.9 (C-6), 25.4 (OCH_2CH_3), 25.4 (C-5), 29.0 (C-3) 39.2 (C-1′), 39.5 (C-6), 49.5 (C-2), 61.3 (OCH_2CH_3), 65.1 (C-2′), 155.0 (NCO).

*4.3.24. 1-[(2S)-Piperidin-2-yl]acetone (**3**).* Compound **18a** (0.28 g, 1.0 mmol) was dissolved in EtOH and hydrogenated over Pd/C (1 atm) at rt for 6 h. The reaction mixture was then filtered and concentrated under reduced pressure to give **3** as a colourless thick liquid. It was then treated with 5 N HCl (2 mL) in chloroform (10 mL) for 2 h at rt and dried under reduced pressure. The crude mass was subjected to column chromatography (SiO_2, chloroform/methanol, 9:1) to give **3**·HCl (0.13 g, 70%) as a pale yellow thick liquid; IR (neat) 3310, 1710 cm^{-1}; $[\alpha]_D^{28}$ −16.2 (c 0.05, EtOH) {lit.[27k] $[\alpha]_D^{23}$ −9.2 (c 1.2, EtOH)}; ee 99%; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41–1.90 (m, 6H, H-5, H-5, H-3), 2.15 (s, 3H, H-3′), 2.70–2.90 (m, 2H, H-1′), 3.21–3.27 (m, 1H, H-6A), 3.35–3.45 (m, 2H, H-6B, H-5);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.3 (C-4), 25.4 (C-5), 30.6 (C-3′), 31.9 (C-3), 46.4 (C-1′), 49.9 (C-6), 52.37 (C-2), 208.4 (CO).

*4.3.25. 1-[(2S)-1-Methylpiperidin-2-yl]acetone (**4**).* Following the similar procedure as described for compound **1**, compound **18c** (0.22 g, 1.0 mmol) gave compound **4**·HCl (0.09 g, 60%) as a pale yellow thick liquid (SiO_2, $CHCl_3$/MeOH, 9:1); $[\alpha]_D^{28}$ −25.0 (*c* 0.2, H_2O); IR (neat) 3390, 2920, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20–1.70 (m, 6H), 1.94 (s, 3H, H-3′), 2.32 (s, 3H, NC*H*$_3$), 2.32–2.51 (m, 2H, H-1′), 2.80–2.95 (buried m, 1H, H-6A), 3.03–3.08 (m, 2H, H-6B and H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.1 (C-4), 24.2 (C-5), 29.6 (C-3), 29.8 (C-3′), 42.0 (C-2), 44.5 (C-1′), 55.0 (C-6), 59.0 (NCH_3), 205.5 (CO).

*4.3.26. (2S)-1-[(2S)-Piperidin-2-yl]propan-2-ol (**7**).* Compound **30a** (0.25 g, 0.9 mmol) was dissolved in EtOH and directly hydrogenated (1 atm) over Pd/C (0.025 g) for 6 h at rt. The reaction mixture was then filtered and dried under reduced pressure to give the product **7** (0.12 g, 95%) as colourless crystalline compound turning viscous on exposure to atmosphere; $[\alpha]_D^{28}$ +27.5 (*c* 0.07, EtOH) {lit.[35l] $[\alpha]_D^{25}$ +28.4 (*c* 1.13, EtOH)}; ee 99%; IR (neat) 3375, 2960, 1418 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (d, *J*=7.2 Hz, 3H, H-3′), 1.28–1.78 (m, 8H, H-4, H-5, H-3, H-1′), 1.50–1.60 (m, 3H), 2.50–2.57 (m, 1H, H-6A), 2.85–2.89 (m, 1H, H-6B), 3.03–3.05 (m, 1H, H-2), 3.50 (br s, 2H, OH and NH), 4.02–4.10 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-3′), 24.4 (C-4), 25.4 (C-5), 30.9 (C-3), 43.3 (C-1′), 46.6 (C-6), 54.8 (C-2), 64.8 (C-2′).

*4.3.27. (2R)-1-[(2S)-Piperidin-2-yl]propan-2-ol (**8**).* Following the same procedure as for (*SS*)-isomer compound **27a** (0.25 g, 0.9 mmol) on hydrogenation gave **8** (0.12 g, 95%) as a pale yellow crystalline solid becoming viscous on exposure to atmosphere; $[\alpha]_D^{28}$ −15.6 (*c* 0.05, EtOH) {lit.[35l] $[\alpha]_D^{23}$ −16.2 (*c* 1.5, MeOH)}; ee 99%; IR (neat) 3350, 2924 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (d, *J*=6 Hz, 3H, H-3′), 1.18–1.78 (m, 8H, H-4, H-5, H-3, H-1′), 2.49–2.69 (m, 1H, H-6A), 2.96–3.01 (m, 1H, H-6B), 3.30 (br s, 2H, NH and OH), 3.91–3.95 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.9 (C-3′), 24.4 (C-4), 27.0 (C-5), 34.1 (C-3), 44.1 (C-1′), 45.9 (C-6), 58.3 (C-2), 69.1 (C-2′).

*4.3.28. (2S)-1-[(2S)-1-Methylpiperidin-2-yl]propan-2-ol (**9**).* Following the similar procedure as for compound **5**, compound **30c** (0.1 g, 0.5 mmol) gave **9** (0.06 g, 90%) as a pale yellow thick liquid; $[\alpha]_D^{28}$ −35.0 (*c* 0.06, EtOH) {lit.[35j] $[\alpha]_D$ +34.5 (*c* 0.85, EtOH) for (*RR*)-isomer}; ee 99%; IR (neat) 3380, 2967, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (d, *J*=6 Hz, 3H, H-3′), 1.20–1.82 (m, 8H, H-4, H-5, H-3, H-1′), 2.35 (s, 3H, NC*H*$_3$), 2.39–2.42 (m, 1H, H-6A), 2.57–2.60 (m, 1H, H-6B), 2.90–2.95 (m, 1H, H-2), 3.60 (br s, 1H, OH), 3.75–3.91 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 22.6, 24.1, 26.2, 30.0, 39.1, 39.3, 50.2, 60.8, 62.5, 68.0.[35j]

*4.3.29. (2R)-1-[(2S)-1-Methylpiperidin-2-yl]propan-2-ol (**10**).* Similar procedure followed as for compound **5**, compound **27c** (0.1 g, 0.5 mmol) furnished the product **10** (0.06 g, 90%) as a thick colourless liquid; $[\alpha]_D^{28}$ −70.0 (*c* 0.05, EtOH) {lit.[35j] $[\alpha]_D$ +67.5 (*c* 0.65, EtOH) for (*SR*)-isomer}; ee 99%; IR (neat) 3362, 2964, 1418 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (d, *J*=6.4 Hz, 3H, H-3′), 1.14–1.82 (m, 8H, H-4, H-5, H-3, H-1′), 2.35 (s, 3H, NC*H*$_3$), 2.38–2.44 (m, 1H, H-6A), 2.55–2.58 (m, 1H, H-6B), 2.90–2.95 (m, 1H, H-2), 3.85–3.93 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (C-4), 22.6 (C-5), 24.1 (C-3′), 26.1 (C-3), 39.2 (C-1′), 39.2 (C-2), 51.8 (C-6), 60.8 (C-2′), 68.1 (NCH_3).

*4.3.30. Benzyl (2R)-2-[(1Z)-2-nitrobut-1-en-1-yl]piperidine-1-carboxylate (**22a**).* Following the general procedure I, Henry-olefination of compound **24a** (0.25 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the product **22a** (0.24 g, 80% for two steps) as a pale yellow thick liquid; R_f=0.40 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −39.1 (*c* 0.14, $CHCl_3$); IR (neat) 3100, 2989, 2934, 2800,1690, 1520 and 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90–1.81 (m, 9H, H-4, H-5, H-3, H-4′), 2.48–2.62 (m, 2H, H-3′), 2.89–2.96 (m, 1H, H-6A), 4.03–4.06 (m, 1H, H-6B), 5.00–5.08 (m, 3H, H-2, C*H*$_2$Ph), 7.18–7.31 (m, 6H, H-1′, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.6 (C-4′), 19.4 (C-4), 20.2 (C-5), 24.9 (C-3), 29.9 (C-3′), 40.3 (C-6), 48.5 (C-2), 67.6 (*C*H$_2$Ph), 127.9 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.6 (PhCH), 128.7 (PhCH), 130.9 (C-1′), 136.3 (PhC), 155.7 (C-2′), 155.8 (NCO); HRMS: *m*/*z* calcd for $C_{17}H_{22}N_2O_4Na$ $[M+Na]^+$: 341.1477; found: 341.1478.

*4.3.31. tert-Butyl (2R)-2-[(1Z)-2-nitrobut-1-en-1-yl]piperidine-1-carboxylate (**22b**).* Following the general procedure I, Henry-olefination of compound **24b** (0.22 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the product **22b** (0.24 g, 85% for two steps) as a pale yellow thick liquid; R_f=0.45 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −46.8 (*c* 0.05, $CHCl_3$); IR (neat) 2964, 2900, 1690, 1520 and 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.06 (t, *J*=7.2 Hz, 3H, H-4′), 1.38 (s, 9H, ^{t}Bu*H*), 1.41–1.80 (m, 6H, H-4, H-5, H-3), 2.58–2.68 (m, 2H, C-3′), 2.80–2.87 (m, 1H, H-6A), 3.94–3.97 (m, 1H, H-6B), 4.90–4.98 (buried m, 1H, H-2), 7.20 (d, *J*=3.2 Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-4′), 19.6 (C-4), 20.2 (C-5), 25.1 (C-3), 28.4 (OC(*C*H$_3$)$_3$), 30.0 (C-3′), 40.1 (C-6), 48.1 (C-2), 80.3 (O*C*(CH$_3$)$_3$), 131.7 (C-1′), 154.4 (C-2′), 154.5 (NCO); HRMS: *m*/*z* calcd for $C_{14}H_{24}N_2O_4Na$ $[M+Na]^+$: 307.1634; found: 307.1637.

*4.3.32. Ethyl (2R)-2-[(1Z)-2-nitrobut-1-en-1-yl]piperidine-1-carboxylate (**22c**).* Following the general procedure I, Henry-olefination of compound **24c** (0.18 g, 1.0 mmol) with nitroethane (0.83 mL, 11.0 mmol) gave the product **22c** (0.20 g, 80% for two steps) as a colourless thick liquid; R_f=0.35 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −50.9 (*c* 0.04, $CHCl_3$); IR (neat) 2960, 1690, 1550 and 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07 (t, *J*=6 Hz, 3H, H-4′), 1.89 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.37–1.82 (m, 6H, H-4, H-5, H-3), 2.57–2.72 (m, 2H, H-3′), 2.86–2.93 (m, 1H, H-6A), 4.00–4.09 (m, 2H, H-6B, O*C*H$_2$CH$_3$), 4.95–5.01 (buried m, 1H, H-2), 7.19 (d, *J*=2.4 Hz, 1H, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (C-4′), 14.6 (OCH$_2$*C*H$_3$), 19.5 (C-4), 20.2 (C-5), 24.9 (C-3), 29.9 (C-3′), 40.1 (C-6), 48.3 (C-2), 61.2 (O*C*H$_2$CH$_3$), 131.1 (C-1′), 154.2 (C-2′), 155.5 (NCO); HRMS: *m*/*z* calcd for $C_{12}H_{20}N_2O_4Na$ $[M+Na]^+$: 279.1321; found: 279.1321.

*4.3.33. Benzyl (2R)-2-(2-oxobutyl)piperidine-1-carboxylate (**19a**).* Following the general procedure II, Nef reaction on **22a** (0.32 g, 1.0 mmol) gave **19a** (0.22 g, 75%) as a thick liquid; $[\alpha]_D^{26}$ −10.1 (*c* 0.32, $CHCl_3$); IR (neat) 2974, 1710, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, *J*=7.2 Hz, 3H, H-4′), 1.35–1.61 (m, 6H, H-4, H-5, H-3), 2.34–2.42 (m, 2H, H-3′), 2.53–2.65 (m, 2H, H-1′), 2.76–2.82 (m, 1H, H-6A), 3.96–3.99 (m, 1H, H-6B), 4.71–4.72 (m, 1H, H-2), 5.04 (s, 2H, PhC*H*$_2$), 7.21–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.6 (C-4′), 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 39.8 (C-3′), 42.9 (C-1′), 47.6 (C-2), 67.1 (Ph*C*H$_2$), 126.9 (PhCH), 127.8 (PhCH), 127.9 (PhCH), 128.4 (PhCH), 128.5 (PhCH), 136.8 (PhC), 155.3 (NCO), 209.5 (C-2′).

*4.3.34. tert-Butyl (2R)-2-(2-oxobutyl)piperidine-1-carboxylate (**19b**).* Following the general procedure II, Nef reaction on **22b** (0.28 g, 1.0 mmol) gave **19b** (0.18 g, 70%) as a thick liquid; R_f=0.25 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −10.5 (*c* 0.18, $CHCl_3$); IR (neat) 2994, 1711, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, *J*=7.2 Hz, 3H, H-4′), 1.37 (s, 9H, ^{t}Bu*H*), 1.30–1.55 (m, 6H, H-4, H-5, H-3), 2.33–2.57 (m, 4H, H-1′, H-3′), 2.69–2.75 (m, 1H, H-6A), 3.89–3.99 (buried m, 1H, H-6B), 4.60–4.64 (buried m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.6 (C-4′), 18.9 (C-4), 25.3 (C-5), 28.38 (OC(*C*H$_3$)$_3$), 28.5

(C-3), 36.1 (C-3′), 39.3 (C-1′), 42.9 (C-6), 47.4 (C-2), 79.6 (OC(CH$_3$)$_3$), 154.7 (NCO), 209.7 (CO); HRMS: *m*/*z* calcd for $C_{14}H_{25}NO_3Na$ [M+Na]$^+$: 278.1732; found: 278.1735.

*4.3.35. Ethyl (2R)-2-(2-oxobutyl)piperidine-1-carboxylate (**19c**).* Following the general procedure II, Nef reaction on **22c** (0.32 g, 1.0 mmol) gave **19c** (0.15 g, 60%) as a thick liquid; R_f=0.20 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −10.1 (*c* 0.05, $CHCl_3$); IR (neat) 2990, 1718, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.96 (t, *J*=7.2 Hz, 3H, H-4′), 1.17 (t, *J*=6.8 Hz, 3H, OCH$_2$*C*H$_3$), 1.31–1.62 (m, 6H, H-4, H-5, H-3), 2.34–2.49 (m, 2H, H-3′), 2.53–2.65 (m, 2H, H-1′), 2.73–2.79 (m, 1H, H-6A), 3.93–3.95 (m, 1H, H-6B), 4.03 (q, *J*=7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.67–4.68 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.7 (C-4′), 14.6 (OCH$_2$*C*H$_3$), 18.8 (C-4), 25.2 (C-5), 28.3 (C-3), 36.1 (C-3′), 39.5 (C-1′), 42.9 (C-6), 47.4 (C-2), 61.3 (O*C*H$_2$CH$_3$), 115.5 (NCO), 209.6 (C-2′); HRMS: *m*/*z* calcd for $C_{12}H_{21}NO_3Na$ [M+Na]$^+$: 250.1419; found: 250.1418.

*4.3.36. Benzyl (2S)-2-[(2S)-2-hydroxybutyl]piperidine-1-carboxylate (**31a**).* Following the general procedures IIIa–c, compound **19a** (0.29 g, 1.0 mmol) gave **31a** (0.27 g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ −27.9 (*c* 0.08, $CHCl_3$); IR (neat) 3430, 2990, 1680, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.70–0.90 (3H, m, H-4′), 1.10–1.97 (m, 10H, H-4, H-5, H-3, H-1′, H-3′), 2.59–2.71 (m, 2H, H-6A, OH), 3.10–3.20 (buried m, 1H, H-6B), 3.96–3.99 (m, 1H, H-2′), 4.42–4.47 (m, 1H, H-2′), 5.02–5.13 (m, 2H, PhC*H*$_2$), 7.25–7.30 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.5 (C-4′), 19.2 (C-4), 25.5 (C-5), 29.2 (C-3), 29.4 (C-3′), 37.1 (C-1′), 39.3 (C-6), 47.3 (C-2), 67.5 (O*C*H$_2$Ph), 68.6 (C-2′), 127.9 (PhCH), 128.1 (PhCH), 128.4 (PhCH), 128.5 (PhCH), 136.6 (PhC), 156.8 (NCO).

*4.3.37. Benzyl (2S)-2-[(2R)-2-hydroxybutyl]piperidine-1-carboxylate (**28a**).* Following the general procedures IIIa–c, compound **19a** (0.29 g, 1.0 mmol) gave **28a** (0.27 g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ −46.8 (*c* 0.13, $CHCl_3$); IR (neat) 3400, 2995, 1680, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.70–0.84 (buried m, 3H, H-4′), 1.32–1.70 (m, 10H, H-4, H-5, H-3, H-3′, H-1′), 2.79–2.85 (m, 1H, H-6A), 3.40–3.45 (buried m, 1H, H-6B), 3.95–3.97 (m, 1H, H-2), 4.36–4.37 (m, 1H, H-2′), 5.01–5.08 (m, 2H, C*H*$_2$Ph), 7.20–7.28 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.0 (C-4′), 18.9 (C-4), 25.5 (C-5), 29.2 (C-3), 30.3 (C-3′), 37.6 (C-1′), 39.6 (C-6), 48.9 (C-2), 67.1 (*C*H$_2$Ph), 71.4 (C-2′), 127.9 (PhCH), 128.0 (PhCH), 128.1 (PhCH), 128.2 (PhCH), 128.3 (PhCH), 136.8 (PhC), 155.9 (NCO).

*4.3.38. (2S)-1-[(2S)-Piperidin-2-yl]butan-2-ol (**11**).* Following the similar procedure as for compound **2**, compound **31a** (0.29 g, 1.0 mmol) gave **11** (0.15 g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ +18.6 (*c* 0.05, EtOH) {lit.[35j] $[\alpha]_D$ +17.5 (c, 0.80, EtOH)}; ee 99%; IR (neat) 3370, 2970 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (t, *J*=7.2 Hz, 3H, H-4′), 1.17–1.93 (m, 10H, H-4, H-5, H-3, H-3′, H-1′), 2.80–2.83 (m, 1H, H-6A), 3.23–3.24 (m, 1H, H-6B), 3.40–3.43 (m, 1H, H-2), 3.56–3.67 (m, 1H, H-2′ and NH), 3.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.1 (C-4′), 22.1 (C-4), 22.6 (C-5), 28.8 (C-3), 30.2 (C-3′), 39.3 (C-1′), 45.1 (C-6), 54.7 (C-2), 67.9 (C-2′).

*4.3.39. (2R)-1-[(2S)-Piperidin-2-yl]butan-2-ol (**12**).* Similar procedure was followed as for compound **2**, compound **28a** (0.29 g, 1.0 mmol) gave **12** (0.15 g, 95%) as a colourless thick liquid; $[\alpha]_D^{26}$ −7.6 (*c* 0.06, EtOH) {lit.[35j] $[\alpha]_D$ −6.6 (*c* 0.80, EtOH)}; ee 99%; IR (neat) 3370, 2980, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, *J*=7.2 Hz, 3H, H-4′), 1.31–1.79 (10H, H-4, H-5, H-3, H-3′, H-1′), 2.62–2.68 (m, 1H, H-6A), 2.82–2.87 (m, 1H, H-6B), 3.12–3.15 (m, 1H, H-2), 3.68–3.74 (m, 1H, H-2′), 4.60 (br s, 2H, OH and NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 9.9 (C-4′), 23.6 (C-4), 25.0 (C-5), 31.0 (C-3), 32.4 (C-3′), 40.9 (C-1′), 45.4 (C-6), 58.2 (C-2), 73.7 (C-2′).

*4.3.40. Benzyl (2S)-2-[(E)-2-nitrovinyl]pyrrolidine-1-carboxylate (**44a**).* Following the general procedure I, Henry-olefination of compound **23a** (0.23 g, 1.0 mmol) with nitromethane (0.66 mL, 11.0 mmol) gave **44a** (0.24 g, 90% for two steps) as a pale yellow thick liquid; R_f=0.55 (hexane/EtOAc, 8:2); IR (neat) 2989, 2934, 2800,1690, 1520 and 1350 cm^{-1}; $[\alpha]_D^{26}$ −76.1 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76–2.11 (m, 4H, H-4, H-3), 3.39–3.45 (m, 2H, H-5), 4.46–4.54 (m, 1H, H-2), 4.49–5.09 (m, 2H, OC*H*$_2$Ph), 6.76–6.95 (m, 1H, H-2′), 7.00–7.04 (m, 1H, H-1′), 7.21–7.28 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (C-4), 31.2 (C-3), 46.7 (C-5), 55.2 (C-2), 67.3 (PhC*H*$_2$), 127.9 (PhCH), 128.2 (PhCH), 128.3 (PhCH), 128.6 (PhCH), 136.0 (PhC), 140.0 (C-1′), 141.4 (C-2′), 154.6 (NCO); HRMS: *m*/*z* calcd for $C_{14}H_{16}N_2O_4Na$ [M+Na]$^+$: 299.1008; found: 299.1004.

*4.3.41. Benzyl (2S)-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (**38a**).* To a solution of ammonium acetate (4.0 g, 52 mmol) in MeOH/H_2O (4:3, 16 mL) was added 15% aq $TiCl_3$ (3.6 mL, 3.5 mmol) followed by a solution of **44a** (0.28 g, 1.0 mmol) in MeOH (5 mL) at 0 °C. After stirring for 3 h at rt, the mixture was extracted with ether (20 mL×3). The ether layer was washed with saturated aq $NaHCO_3$ (15 mL×4) and saturated aq NaCl (20 mL×2), dried over anhyd Na_2SO_4 and concentrated under reduced pressure. The crude product was immediately treated with $NaBH_4$ (0.37 g, 1.0 mmol) in 10 mL MeOH. After 1 h stirred at rt, the reaction mixture was concentrated and diluted with ethyl acetate (30 mL), washed with dil HCl (10 mL×3). The crude mixture was column chromatographed (SiO_2, hexane/EtOAc/7:3) to give the title compound **38a** (0.14 g, 55%) as a colourless thick liquid; $[\alpha]_D^{26}$ −7.0 (*c* 0.04, $CHCl_3$) {lit.[41a] $[\alpha]_D$ −7.6 (*c* 1.1, $CHCl_3$)}; IR (neat) 3400, 2900, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52–2.05 (m, 6H, H-4, H-3, H-1′), 3.41–3.45 (m, 2H, H-2′), 3.55–3.61 (m, 2H, H-5), 4.18–4.26 (m, 1H, H-2), 5.15–5.16 (m, 2H, PhC*H*$_2$), 7.33–7.38 (m, 5H, PhCH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6 (C-4), 31.1 (C-3), 38.2 (C-1′), 46.3 (C-5), 54.3 (C-2), 59.0 (C-2′), 67.1 (Ph*C*H$_2$), 126.8 (PhCH), 127.0 (PhCH), 127.5 (PhCH), 135.6 (PhC), 155.7 (NCO).

*4.3.42. Benzyl (2S)-2-[(E)-2-nitrovinyl]piperidine-1-carboxylate (**44b**).* Following the general procedure I, Henry-olefination of compound **24a** (0.25 g, 1.0 mmol) with nitromethane (0.66 mL, 11.0 mmol) gave the product **44b** (0.26 g, 90% for two steps) as a pale yellow thick liquid; R_f=0.65 (hexane/EtOAc, 8:2); $[\alpha]_D^{26}$ −64.0 (*c* 0.05, $CHCl_3$); IR (neat) 2900, 2800,1690, 1520, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34–1.67 (m, 4H, H-4, H-5), 1.76–1.77 (m, 2H, H-3), 2.78–2.84 (m, 1H, H-6A), 4.00–4.06 (m, 1H, H-6B), 5.04–5.11 (m, 3H, H-2, PhC*H*$_2$), 6.86 (d, *J*=13.2 Hz, 1H, H-2′), 7.14–7.19 (dd, *J*=8.8 and 4.8 Hz, 1H, H-1′), 7.26–7.32 (m, 5H, Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.7 (C-4), 24.9 (C-5), 28.8 (C-3), 40.6 (C-6), 49.6 (C-2), 67.7 (PhC*H*$_2$), 128.0 (PhCH), 128.3 (PhCH), 128.6 (PhCH), 136.2 (PhC), 140.6 (C-1′), 140.9 (C-2′), 155.3 (NCO); HRMS: *m*/*z* calcd for $C_{14}H_{16}N_2O_4Na$ [M+Na]$^+$: 313.1164; found: 313.1163.

*4.3.43. Benzyl (2S)-2-(2-hydroxyethyl)piperidine-1-carboxylate (**38b**).* Following the similar procedure as for compound **38a**, compound **44b** (0.29 g, 1.0 mmol) gave **38b** (0.15 g, 55%) as a pale yellow thick liquid; $[\alpha]_D^{26}$ −20.2 (*c* 0.06, $CHCl_3$) {lit.[41d] $[\alpha]_D^{25}$ −18.5 (*c* 1.0, $CHCl_3$)}; IR (neat) 3400, 2900, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35–1.92 (m, 8H, H-4, H-5, H-3, H-1′), 2.65–2.71 (m, 2H, H-2′), 3.20–3.30 (m, 1H, H-6A), 3.51–3.54 (m, 1H, H-6B), 3.97–4.00 (m, 1H, H-2), 4.40–4.41 (m, 1H, O*H*), 5.03–5.06 (m, 2H, PhC*H*$_2$), 7.23–7.28 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (C-4), 25.2 (C-5), 29.2 (C-3), 32.3 (C-1′), 39.3 (C-6), 46.9 (C-2), 58.5

(C-2′), 67.4 ($PhCH_2$), 127.8 (PhCH), 127.9 (PhCH), 128.0 (PhCH), 128.1 (PhCH), 128.5 (PhCH), 136.5 (PhC), 156.7 (NCO).

Acknowledgements

We acknowledge IISc, Bangalore, for ^{1}H NMR and HRMS facilities and DST, New Delhi, for financial assistance. We also thank NIO, Goa for optical activity measurements. One of authors (C.B.) is thankful to CSIR, New Delhi, for awarding Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.055.

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