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PAPER

Diastereoselective construction of *syn*-α-oxyamines *via* three-component α-oxyaldehyde–dibenzylamine–alkyne coupling reaction: application in the synthesis of (+)-β-conhydrine and its analogues†

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A Cu(I)-catalyzed α-oxyaldehyde–dibenzylamine–alkyne coupling reaction was delineated for the construction of α-oxyamines with excellent yields and diastereoselectivity. Crystal structure analysis and theoretical calculations were also supportive of the formation of *syn*-α-oxyamines as the major products. Application of the methodology addresses the synthesis of (+)-β-conhydrine along with analogs having two different diversity features. A ring size variation allows construction of piperidine and pyrrolidine rings while a variation of side arm functionality is achieved by complete regioselective opening of epoxide by different organocopper ylides (Gilman reagents). A lactam–Cu(I) complexation motif is proposed which allows an intramolecular attack of ylides at the terminal epoxy carbon *via* the six-membered cyclic transition state. The present work features the synthesis of (+)-β-conhydrine over eight steps in 26% yield and its seven analogs in 21–28% yields.

Introduction

In recent years, the scaffolds of natural products have inspired the synthesis of focused compound libraries in drug discovery research.[1] Due to their diverse biological activities, substituted piperidines and pyrrolidines have been the target of considerable synthetic efforts.[2] Critical analyses of large number of piperidine and pyrrolidine based natural product structures have led to the identification of a few privileged skeletal fragments.[3] Among these, 2-(hydroxyalkyl)-piperidine and 2-(hydroxyalkyl)-pyrrolidine (Fig. 1) are two privileged subunits, which have aroused widespread synthetic interest because of their frequent appearance in many biologically active alkaloids[3b] and interesting stereochemical feature present around the α-oxyamine moiety. Nojirimycin **1**[4] and (+)-α-conhydrine **2**[5] are examples of natural products with a 2-(hydroxyalkyl)-piperidine moiety present in their structures. On the other hand, a 2-(hydroxyalkyl)-pyrrolidine nucleus can be found in 1,4-dideoxy-1,4-imino hexitol **3**,[6] uniflorine A,[7] casuarine,[8] australine, *etc.* (−)-Swainsonine **4**[9] and (−)-erycibelline **5**[10] are indolizidine and nortropane alkaloids respectively, in which fused scaffolds of 2-(hydroxyalkyl)-piperidine and 2-(hydroxyalkyl)-pyrrolidine can be identified. These natural products have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic, and antiobesity drugs.[11] As a result, these natural products and their analogs have been attractive and important synthetic targets.

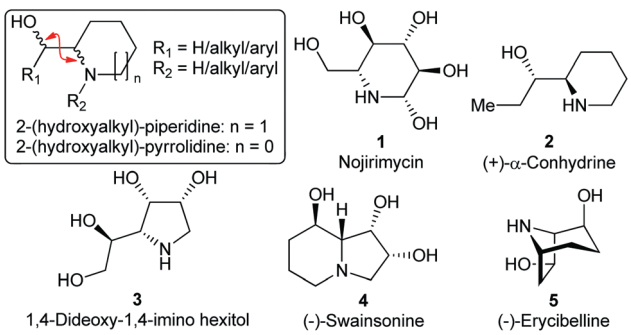

Fig. 1 Structures of natural products having 2-(hydroxyalkyl)-piperidine and 2-(hydroxyalkyl)-pyrrolidine skeletal fragments.

In the scientific literature, synthesis of natural product analogs is commonly focused towards either enantiomers or diastereomers. An alternate approach is also frequently executed by introducing various functional groups on an important synthetic intermediate to create a diverse molecular library.[12] However, the manipulation of the ring size, which is frequently executed in medicinal chemistry research[13] for the generation of analogs, is less reflected in the synthesis of natural product analogs.[14]

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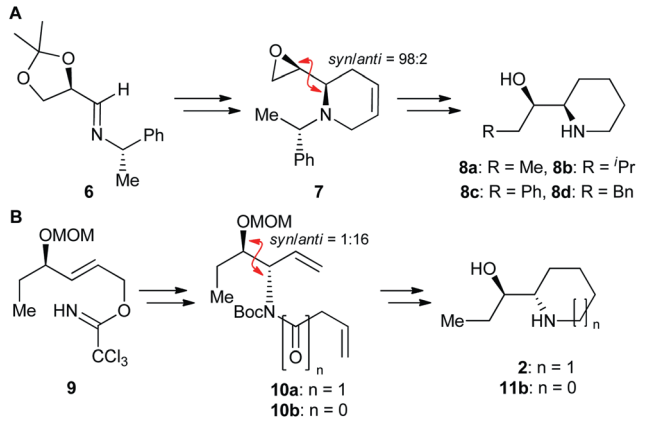


Scheme 1 Synthetic approaches to diastereoselective construction of α-oxyamines for the synthesis of conhydrine and its analogs. (**A**) Synthesis of (+)-β-conhydrine and its analogs **8a–8d** *via* diastereoselective addition of allylmagnesium bromide to *N*-benzylimine **6** followed by epoxide opening with different R–, (**B**) Palladium-catalyzed diastereoselective aza-Claisen rearrangement of allylic trichloroacetimidate **9** followed by RCM cyclization for the synthesis of (+)-α-conhydrine **2** and its pyrrolidine analog **11**.

Considering (+)-α-conhydrine **2** as an example, various synthetic methods are reported for the natural product, its enantiomer and diastereomers.[15] Each of these strategies feature new synthesis aimed at the 2-(hydroxymethyl)-piperidine moiety with stereoselective construction of the α-oxyamine moiety. One of these design principles is associated with the diastereoselective construction of a α-oxyamine followed by the formation of the piperidine ring. Following this strategy, Gálvez and co-workers have reported a diastereoselective Grignard reaction (*syn–anti* = 98 : 2) on the imine **6** to obtain the *syn*-α-oxyamine stereochemistry followed by a ring-closure metathesis (RCM) approach to build the piperidine ring (Scheme 1A).[16] Subsequently, the acetonide protected dihydroxy moiety was converted to an epoxide ring forming the intermediate **7**. They further extended the methodology for the synthesis of (+)-β-conhydrine **8a** (over 7-steps in 21% overall yield) and its analogues **8b–8d** having various side arms by the opening of the epoxide ring of **7** by different carbon nucleophiles. In 2007, Sutherland and co-workers adapted a Pd(II)-catalyzed [3,3]-sigmatropic (Overman reaction) approach to construct *anti*-α-oxyamine with high diastereoselectivity (*syn–anti* = 1 : 16).[17] Subsequent attachment of linkers of different lengths provided intermediates **10a** and **10b**, respectively. Further, a RCM strategy was applied to synthesize (+)-α-conhydrine **2** (over 13-steps in 4% overall yield) and **11** as the first ring-contracted pyrrolidine analog of **2**.

Results and discussion

We set the challenge to develop a new strategy to synthesize conhydrine and its analogs by simultaneously addressing the variation (i) in ring size and (ii) side arm functionality. We decided to rely on the principle of diastereoselective construction of the α-oxyamine followed by the formation of either a piperidine or a pyrrolidine ring. In this regard, we realized the importance of the metal catalyzed α-oxyaldehyde–amine–alkyne (three-component) coupling reaction reported by Huang *et al*. for the diastereoselective construction of *syn*-α-oxyamine[18] which can be applied in the synthesis of (+)-β-conhydrine. Starting from the optically pure acetonide protected glyceraldehyde **12**, piperidine and phenylacetylene an AuI catalyzed (5 mol%) three-component reaction in water at room temperature was successful in constructing the corresponding *syn*-α-oxyamine product in 65% yield and with a *syn* to *anti* ratio up to 82 : 18. We realized that simple alteration of the alkyne and the amine components would be necessary for further construction of piperidine and pyrrolidine rings. On the other hand, the acetonide protected 1,2-diol moiety would also be helpful for accessing analogs of conhydrine having varied side arm functionality. We realized that the three-component coupling (A^3-coupling) reaction would also be significant providing a shorter synthetic route. However, a further improvement of diastereoselectivity during the three-component coupling (A^3-coupling) reaction described by Huang *et al*.[18] was necessary to establish the novelty of our strategy.

Therefore, we decided to introduce a di-substituted amine with bulkier substituents which can also be removed easily whenever necessary. A terminal alkyne, substituted with a protecting group, orthogonal to that of amine was thought to be ideal for chain elongation for further construction of either piperidine or pyrrolidine ring. Our judgment led to the selection of the dibenzylamine **13** anticipating the role of benzyl group for driving the diastereoselectivity. Additionally, the hydrogenolysis conditions for removing this protecting group are also suitable for complete reduction of the alkyne C≡C bond. We also decided to replace AuI with CuBr due to the established importance of the Cu(I) salt in the three-component aldehyde–amine–alkyne coupling reaction.[19] Also, the ready availability, low toxicity, insensitivity to air, and cheaper price led us to explore the methodology with a Cu(I)halide.

Applicability of the methodology in the diastereoselective construction of the amino group was evaluated by the reaction of aldehyde **12** and di-benzylamine **13** with various terminal alkynes in the presence of CuBr as catalyst in toluene as solvent (Fig. 2A).[19a] The substitution pattern of the terminal alkynes was varied from **14a** to **14g** (Fig. 2B). The three-component reaction of **12**, di-benzylamine **13** and phenyl acetylene **14a** (R = –Ph) resulted in the formation of the major *syn*-diastereomer **15a** in 68% yield and with *syn–anti* = 78 : 22 (Fig. 2C). When cyclohexenyl acetylene **14b**, was introduced, a significant enhancement in diastereoselectivity, *syn–anti* = 91 : 9 was achieved for the *syn*-α-oxyamine **15b** with 65% yield. Introduction of terminal alkyne **14c** with aliphatic side chain R = –^{t}Bu resulted in formation of **15c** in 73% yield and an excellent *syn* to *anti* ratio of >99% was observed. Similarly, the reactions of the alkyne **14d** (R = –CH_2OCH_3) under comparable conditions provided aminoalkyne **15d** as a single diastereomer with 88% yield. The complete diastereoselectivities were also maintained when alkynes **14e–14g** (R = –CH_2OTBDPS, –CH_2NHBoc, and –TMS) were subjected to the copper(I) catalyzed three component reaction. In these cases, the yields of the reactions were calculated to be 70%, 76% and 84%, respectively.

The *syn*-stereochemistry of the three-component reaction product was convincingly confirmed by the crystal structure of the α-oxyamine **15c** (Fig. 3A). The relative stereochemistry of

the acetonide protected secondary hydroxyl group and the di-benzyl protected amino group in **15c** matched the stereochemistry present in the unnatural (+)-β-conhydrine. Excellent diastereoselectivity observed in each of these multi-component reactions was further rationalized by the geometry optimization study of the intermediate iminium cation **16** (Fig. 3B). Interestingly, the computational gas-phase modelling at 0 K by the DFT-B3LYP/6-311G(d,p) method[20] using Gaussian 03[21] confirmed the presence of a sterically crowded *si* face (Fig. 3C and 3D) allowing attack of the alkynide anion preferentially from the more accessible *re* face. We believe that π-stacking interactions between the phenyl groups of the iminium cation **16** and phenyl acetylene **14a** allow the approach of the alkyne from the *si*-face although steric crowding governs the formation of the *syn*-product **15a** (Fig. 2). As a result, the *anti*-addition product was also formed as the minor isomer reducing the diastereoselectivity during the aldehyde–amine–alkyne coupling reaction.

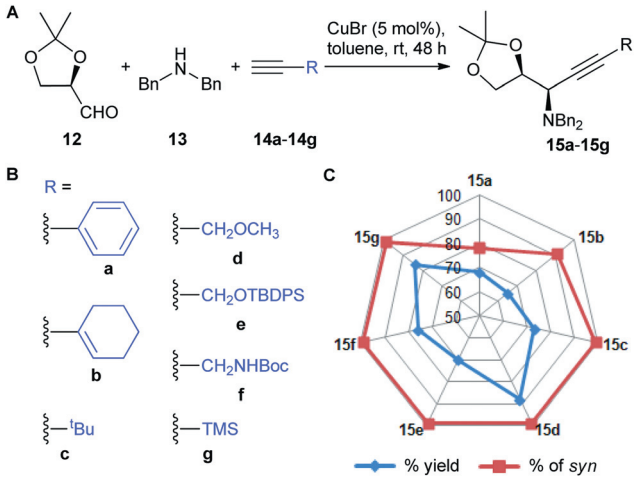


Fig. 2 Cu(I) catalyzed three component reaction of acetonide protected D-glyceraldehyde **12** and di-benzylamine **13** with various terminal alkynes **14a–14g**.

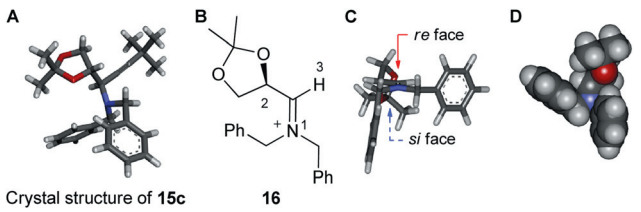
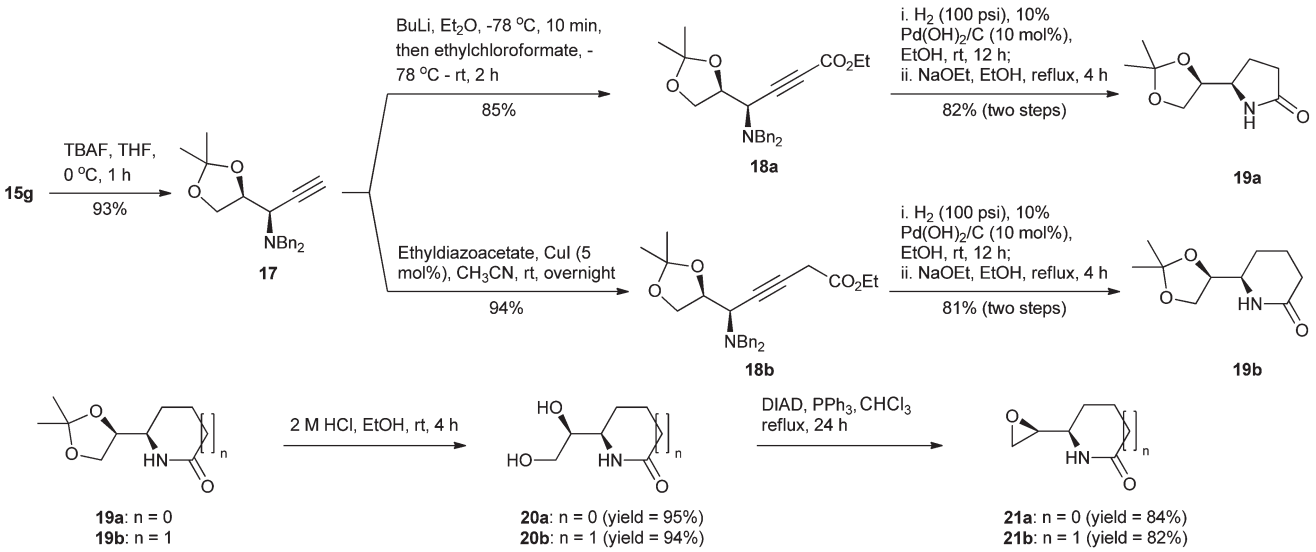


Fig. 3 X-ray crystal structure of **15c** (**A**); representation of the of the iminium cation **16** (**B**); side view of the DFT-B3LYP/6-311G(d,p) geometry optimized structure of **16** (**C**) and the space filling model of optimized structure of **16** from the more hindered *si* face (**D**).

After confirming the stereochemistry of the three-component reaction product, the TMS-protected aminoalkyne **15g** was engaged for the next stages to construct the pyrrolidine and piperidine cores for generating analogues of (+)-β-conhydrine. Deprotection of the trimethylsilyl group of **15g** under TBAF conditions afforded the terminal alkyne **17** in 93% yield (Scheme 2). The terminal alkyne **17** was then treated with ethyl chloroformate in the presence of BuLi following the methodology described by Knochel and co-worker to introduce the ester moiety of **18a** with 85% yield.[19a] The ester **18a** then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond occurred. The crude reaction mixture was then subjected to cyclization using NaOEt to provide the γ-lactam **19a** in 82% yield over two steps. Further deprotection of ketal group of **19a** was carried out by ethanolic HCl to afford the diol **20a** in 95% yield. The diol **20a** was then converted to the epoxy-γ-lactam intermediate **21a** in 84% yield by reacting with DIAD in presence of PPh_3 (Mitsunobu conditions).[22]

A similar strategy was also employed to construct the piperidine core required to synthesize (+)-β-conhydrine analogues (Scheme 2). The terminal alkyne **17** when treated with ethyl diazoacetate under 5 mol% CuI conditions following the

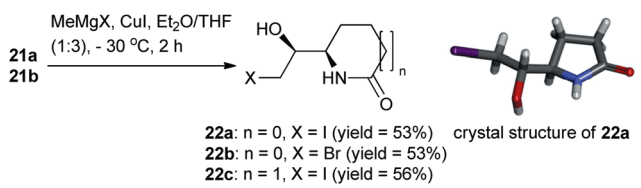


Scheme 2 Synthesis of the epoxy-γ- and epoxy-δ-lactam **21a** and **21b**, respectively.

methodology described by Fu and Suarez,[23] the 3-alkynoate compound **18b** was formed in 94% yield. However, the 3-alkynoate **18b** was isolated as an inseparable mixture with the corresponding allene isomer in 87 : 13 ratio which was determined from the ^{1}H-NMR data. This observation was not surprising considering the literature report by Fu and co-worker. No further purification was attempted as complete hydrogenation of these unsaturated moieties would lead to a single product. When the alkyne **18b** along with its allene isomer was treated with 10% $Pd(OH)_2/C$ (10 mol%) under hydrogen atmosphere (100 psi), complete hydrogenolysis of benzyl groups along with complete reduction of alkyne and allene occurred. The crude amino ester was then converted to the δ-lactam **19b** using NaOEt with 81% yield over two steps. In the next step, the deprotection of the ketal moiety of **19b** was carried out by ethanolic HCl to afford the diol **20b** in 94% yield. The diol **20b** was then converted to the epoxide.

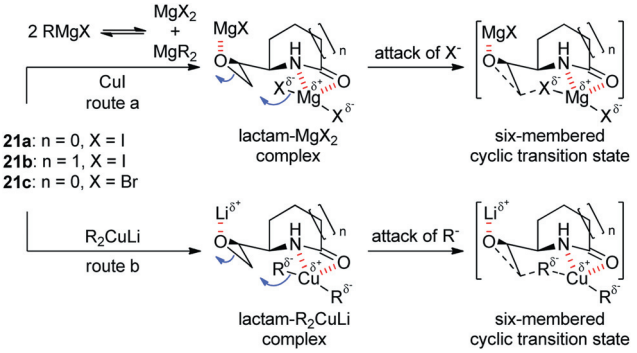
With the crucial epoxy-γ- and epoxy-δ-lactam intermediates **21a** and **21b** in hand, we next investigated the scope of the strategy to synthesize (+)-β-conhydrine and its analogues. Following the methodology described by Fray *et al.*,[24] treatment of the epoxide **21a** with methylmagnesium iodide in presence of 20 mol% CuI resulted in the exclusive formation of an unexpected iodohydrin **22a** in 53% yield (Scheme 3). The change of the Grignard reagent to methylmagnesium bromide also resulted in the corresponding bromo derivative **22b** in 53% yield. A similar iodide mediated epoxide opening product **22c** was also formed in 56% yield during the reaction of **21b** with methylmagnesium iodide in presence of 20 mol% CuI. The structure of the undesired **22a** was confirmed by X-ray crystallography (Scheme 3).

Exclusive formation of halohydrins **22a–22c** indicate that the halide (X^- = I^- and Br^-) from the Grignard reagent is acting as the better nucleophile compared to the alkyl anion (R^-). These observations can be explained by the Schlenk equilibrium of the Grignard reagent that resulted in the formation of MgX_2 and X^- acted as the better nucleophile compared to Me^-.[25] A chelation motif of MgX_2 with the lactam further supported the regioselective attack of X^- to the terminal epoxy-carbon *via* the 6-membered cyclic transition state (Scheme 3, route a).[26] We believed that the lactam–Mg^{2+} complexation-motif if it exists, can be turned into advantage by altering the nucleophile. Therefore, we decided to employ organocopper based ylides (*i.e.* Gilman reagent) for achieving regioselective intramolecular attack of R^- taking advantage of the better nucleophilicity of R^- in the Gilman reagent and a lactam–Cu^+ complexation (Scheme 4, route b).[27]



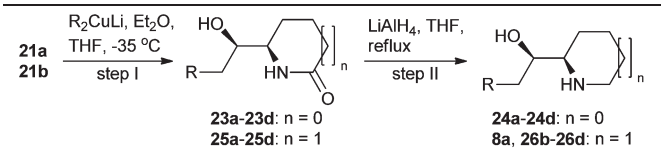
Scheme 3 Formation of halohydrins **22a–22c** from epoxylactams in the presence of Grignard conditions. X-ray crystal structure of **22a**.

Therefore, the treatment of Me_2CuLi with the epoxide **21a** in Et_2O–THF provided the desired hydroxy-γ-lactam **23a** as a single regioisomer in 77% yield (Table 1, entry 1, step I). Finally, the γ-lactam **23a** was reduced by $LiAlH_4$ in THF under refluxing conditions to furnish **24a** as the pyrrolidine analogue of (+)-β-conhydrine in 81% yield (Table 1, entry 1, step II). The epoxy group of **21a** was also opened with other Gilman reagents (R = Bu, ^{t}Bu and Ph) to obtain hydroxy-γ-lactams **23b–23d** with 76%, 72% and 68% yields, respectively. Formation of the single regioisomeric products **23a–23d** during each of the epoxide opening reactions supported our hypothesis of the intramolecular attack by R^- as a result of lactam–Cu^+ complexation. Synthesized hydroxy-γ-lactams **23b–23d** were then converted to corresponding pyrrolidine analogues **24b–24d** with 86%, 84% and 72% yields, respectively (Table 1, entries 2–4).



Scheme 4 Proposed regioselective pathways for intramolecular epoxide ring-opening by X^- (route a) and R^- (route b).

Table 1 Synthesis of β-(+)-conhydrine **8a** and its analogues **24a–24d**, **26b–26d**



			Step I		Step II	
Entry	Epoxide	R	Product[a]	% Yield	Product	% Yield
1	**21a**	—Me	**23a**	77	**24a**	81
2	**21a**	—Bu	**23b**	76	**24b**	86
3	**21a**	—^{t}Bu	**23c**	72	**24c**	84
4	**21a**	—Ph	**23d**	68	**24d**	72
5	**21b**	—Me	**25a**	73	**8a**	78
6	**21b**	—Bu	**25b**	73	**26b**	73
7	**21b**	—^{t}Bu	**25c**	75	**26c**	77
8	**21b**	—Ph	**25d**	77	**26d**	78

[a] Confirmed by ^{1}H NMR analysis of products isolated in each reaction. No regioisomer corresponding to primary hydroxyl group was detected.

Fig. 4 X-ray crystal structures of hydroxy-γ-lactam **23d** (**A**) and hydroxy-δ-lactam **25b** (**B**).

In order to synthesize the (+)-β-conhydrine, the epoxy-δ-lactam intermediate **21b** was treated with Me_2CuLi to furnish the single regioisomeric hydroxy-δ-lactam **25a** in 73% yield. The LAH reduction of **25a** provided (+)-β-conhydrine **8a** with 78% yield. Starting from acetonide protected D-glyceraldehyde **12**, synthesis of the natural product was achieved in 8-steps in 26% overall yield. The structure of the $LiAlH_4$ reduction product was confirmed by comparing the recorded NMR (^{1}H- and ^{13}C-) spectral and specific rotation data (observed: +7.1 in EtOH, reported +7.9 in EtOH) with the data available in the literature.[28] We also synthesized (+)-β-conhydrine analogues **26b**, **26c** and **8c** (R = Bu, ^{t}Bu and Ph) following the epoxide opening followed by lactam reduction strategy (Table 1, entries 6–8) in 21–28% yields.

The crystal structure of the hydroxy-γ-lactam **23d** (Fig. 4A) and that of hydroxy-δ-lactam **25b** (Fig. 4B) also corroborated with the desired stereochemistry present in (+)-β-conhydrine. Examination of the crystal structures of **23d** and **25b** reveal significant similarity in their solid state packing. From the crystal structures of **23d** and **25b**, it is evident that each molecule forms an intermolecular H-bond through –OH, and –NH with the free C═O oxygen atom of the next one, resulting in the formation of 1D hydrogen bonded extended sheet type assembly (Fig. S6.A and S6.B†). Each of these hydrogen bonded 1D networks are further linked *via* hydrophobic interactions to provide the 3D packing in the solid state.

Conclusions

In conclusion, a Cu(I) catalyzed three-component coupling reaction strategy was efficiently employed for the diastereoselective construction of *syn*-α-oxyamines which was confirmed by a single-crystal X-ray diffraction study and theoretical calculation. The methodology was further applied in the synthesis of (+)-β-conhydrine and its analogs having various ring size and side arm functionality. Ring size variation was addressed by the construction of piperidine and pyrrolidine rings. On the other hand, side arm variation was implemented by regioselective opening of epoxides by Gilman reagents. A lactam–Cu(I) complexation motif was proposed indicating an intramolecular attack of the R^- on the terminal epoxide carbon *via* a six-membered transition state. Single-crystal X-ray diffraction studies allowed the confirmation of the stereochemistry of the epoxide opened products which were finally converted to (+)-β-conhydrine and its analogs. The present work reports the synthesis of (+)-β-conhydrine over eight-steps in 26% overall yield along with its seven analogs over same number of steps in 21–28% yields.

Although, the present work covered the synthesis of piperidine and pyrrolidine analogues, the methodology is also amenable for further variation in the ring size and with a broader prospect of employing a wide range of side arm functionality. The synthesized (+)-β-conhydrine analogues deserve to be evaluated for their biological activity and elaborated to other structurally diverse analogues for structure activity relation (SAR) studies. Efforts along these lines are in progress.

Experimental section

General methods

The acetonide protected D-glyceraldehyde was prepared from D-mannitol according to the published methods.[29] Other substrates and reagents were purchased from common commercial sources and used without additional purification. THF and diethyl ether were pre-dried over Na wire. Then the solvent was refluxed over Na (1%, w/v) and benzophenone (0.2%, w/v) under an inert atmosphere until the blue color of the benzophenone ketyl radical anion persists. All reactions were conducted under a nitrogen atmosphere. Solvents: petroleum ether and ethyl acetate (EtOAc) were distilled prior to thin layer and column chromatography. Reactions were controlled using TLC on silica. Column chromatography was performed on silica gel (100–200 mesh).

General copper(I) catalyzed aldehyde–amine–alkyne reaction procedure

Method A. To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **12** (1.0 mmol) in dry toluene (2.0 mL) were added dibenzylamine **13** (1.0 mmol), 4 Å molecular sieves (500 mg), CuBr (0.05 mmol), and alkyne **14a–14g** (1.0 mmol). The reaction mixture was stirred at room temperature for 48 h. After completion, the reaction mixture was filtered through celite bed and washed with Et_2O (2 × 10 mL). The combined filtrate was concentrated under reduced pressure to obtain a liquid which was further purified by column chromatography over silica gel (*Eluent*: 0–5% EtOAc in petroleum ether) to furnish the corresponding multi-component reaction product **15a–15g**.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylprop-2-yn-1-amine 15a ($C_{28}H_{29}NO_2$). Following Method A, reaction of **12** (300 mg, 2.30 mmol) with **13** (456 g, 2.31 mmol) and alkyne **14a** (0.250 g, 2.44 mmol) in dry toluene (5 mL) in the presence of CuBr (18 mg, 0.13 mmol), 4 Å molecular sieves (1.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **15a** (644 mg, 68%) as colorless oil. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25} = -70.30$ (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49–7.45 (m, 6H), 7.35–7.32 (m, 3H), 7.30 (t, J = 7.3 Hz, 4H), 7.22 (t, J = 7.3 Hz, 2H), 4.36 (q, J = 6.4 Hz, 1H), 4.06 (dd, J = 8.4, 6.4 Hz, 1H), 3.97–3.90 (m, 3H), 3.80 (d, J = 7.4 Hz, 1H), 3.55 (d, J = 13.9 Hz, 2H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 132.0 (2C), 129.1 (4C), 128.5 (2C), 128.3, 128.4 (4C), 127.1 (2C), 123.0, 109.8, 86.9, 84.4, 76.5, 67.5, 56.2, 55.6 (2C), 26.7, 25.7; HRMS (ESI) Calcd for $C_{28}H_{30}NO_2$ $[M + H]^+$ 412.2277, found 412.2281.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-doxolan-4-yl)-3-(trimethylsilyl)prop-2-yn-1-amine 15g ($C_{25}H_{33}NO_2Si$). Following Method A, reaction of **12** (5.00 g, 38.4 mmol) with **13** (6.91 g, 34.9 mmol) and alkyne **14g** (3.46 g, 34.9 mmol) in dry toluene (75 mL) in the presence of CuBr (275 mg, 1.92 mmol), 4 Å molecular sieves (190.10 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **15g** (11.95 g, 84%) as colorless oil. IR (KBr) ν (cm^{-1}): 2986, 2161, 1647, 1495, 1370, 1250, 1074, 1001; $[\alpha]_D^{20} = -113.5$ (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 7.2 Hz, 4H), 7.30 (t, J = 7.4 Hz, 4H), 7.21 (t, J = 7.3 Hz, 2H), 4.25 (q, J = 6.4 Hz, 1H), 4.01 (dd, J = 8.2, 6.4 Hz, 1H), 3.88 (dd, J = 8.2, 6.4 Hz, 1H), 3.83 (d, J = 14.2 Hz, 2H), 3.61 (d, J = 7.4 Hz, 1H), 3.43 (d, J = 14.2 Hz, 2H), 1.22 (s, 3H), 1.34 (m, 3H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 129.1 (4C), 128.3 (4C), 127.1 (2C), 109.7, 100.7, 91.7, 76.2, 67.5, 56.5 (2C), 55.5, 26.7, 25.8, 0.4 (3C); HRMS (ESI) Calcd for $C_{25}H_{34}NO_2Si$ 408.2359 $[M + H]^+$, found 408.2355.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-prop-2-yn-1-amine 17 ($C_{22}H_{25}NO_2$)

To a solution of TMS-alkyne **15g** (7 g, 17.2 mmol) in dry THF (40 mL) placed at 0 °C, TBAF (2.25 g, 8.6 mmol, 1 M in THF) was added drop wise and the mixture was stirred at this temperature for 1 h. The reaction mixture was diluted by adding H_2O (50 mL) followed by the extraction of the product in Et_2O (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to afford **7** (5.37 g, 93%) as colorless oil. IR (KBr) ν (cm^{-1}): 3289, 3027, 2986, 2805, 1715, 1602, 1370, 1257, 1150, 1074, 1027; $[\alpha]_D^{25} = -99.1$ (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, J = 7.3 Hz, 4H), 7.31 (t, J = 7.6 Hz, 4H), 7.23 (t, J = 7.3 Hz, 2H), 4.29 (q, J = 6.2 Hz, 1H), 4.01 (dd, J = 8.4, 6.6 Hz, 1H), 3.91 (dd, J = 8.2, 6.6 Hz, 1H), 3.89 (d, J = 14.2 Hz, 2H), 3.57 (d, J = 7.3 Hz, 1H), 3.46 (d, J = 13.7 Hz, 2H), 2.37 (s, 1H), 1.33 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4 (2C), 129.0 (4C), 128.4 (4C), 127.2 (2C), 109.8, 78.7, 76.4, 74.5, 67.2, 55.5 (2C), 55.1, 26.6, 25.5; HRMS (ESI) Calcd for $C_{22}H_{26}NO_2$ 336.1966 $[M + H]^+$, found 336.1965.

Synthesis of (*R*)-ethyl 4-(dibenzylamino)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ynoate 18a ($C_{25}H_{29}NO_4$)

To a solution of **17** (4.00 g, 11.90 mmol) in dry Et_2O (40 mL) cooled at −78 °C was added dropwise *n*-BuLi (8.2 mL, 13.10 mmol, 1.6 M in hexane). The reaction mixture was stirred at the same temperature for 30 min followed by addition of ethyl chloroformate (2.58 g, 23.80 mmol). The reaction mixture was allowed to come to room temperature and stirred for 2 h. The reaction mixture was quenched with water (20 mL) and the product was extracted with Et_2O (2 × 30 mL), dried over Na_2SO_4. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **18a** (4.12 g, 85%) as colorless oil. IR (KBr) ν (cm^{-1}): 2986, 2220, 1713, 1495, 1454, 1370, 1243, 1148, 1074; $[\alpha]_D^{25} = -123.9$ (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 7.3 Hz, 4H), 7.31 (t, J = 7.3 Hz, 4H), 7.28–7.20 (t, J = 7.3 Hz, 2H), 4.32 (q, J = 6.5 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.03 (dd, J = 8.5, 6.6 Hz, 1H), 3.93 (d, J = 14.3 Hz, 2H), 3.90 (dd, J = 8.5, 5.9 Hz, 1H), 3.70 (d, J = 7.1 Hz, 1H), 3.48 (d, J = 13.8 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.5, 138.8 (2C), 129.0 (4C), 128.4 (4C), 127.3 (2C), 110.1, 83.1,78.7, 75.8, 67.1, 62.3, 55.7 (2C), 55.2, 26.5, 25.4, 14.2; HRMS (ESI) Calcd for $C_{25}H_{30}NO_4$ 408.2175 $[M + H]^+$, found 408.2184.

Synthesis of (*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidin-2-one 19a ($C_9H_{15}NO_3$)

To a solution of **18a** (10.00 g, 24.54 mmol) in EtOH (100 mL) was added 10% $Pd(OH)_2/C$ (2.45 g, 2.45 mmol) and the reaction mixture was stirred at room temperature under 100 psi pressure of hydrogen for 24 h. The reaction mixture was filtered through celite and the celite bed was washed with EtOH (2 × 20 mL). To the combined solution was added NaOEt (1.67 g, 24.54 mmol) and refluxed for 2 h. The reaction mixture was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to furnish the pure **19a** (3.73 g, 82% over 2 steps) as colourless oil. IR (KBr) ν (cm^{-1}): 3261, 2987, 2894, 1631, 1456, 1381, 1328, 1292, 1217, 1074; $[\alpha]_D^{25} = -47.2$ (c = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.14 (br s, 1H), 4.04 (dd, J = 8.4, 6.4 Hz, 1H), 3.96 (dd, J = 7.2, 5.4 Hz, 1H), 3.66 (dd, J = 8.5, 5.4 Hz, 1H), 3.61 (q, J = 6.8 Hz, 1H), 2.36–2.31 (m, 2H), 2.20–2.11 (m, 1H), 1.73–1.66 (m, 1H), 1.33 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.0, 110.1, 79.3, 66.2, 67.1, 29.8, 26.8, 25.3, 23.1; HRMS (ESI) Calcd for $C_9H_{15}NO_3Na$ 208.0949 $[M + Na]^+$, found 208.0949.

Synthesis of (*R*)-5-((*S*)-1,2-dihydroxyethyl)pyrrolidin-2-one 20a ($C_6H_{11}NO_3$)

To a solution of **19a** (2.12 g, 11.5 mmol) in EtOH (20 mL) was added 2 M HCl (6 mL) and the mixture was stirred at room temperature for 2 h. After completion of the reaction, the solution was neutralized with solid K_2CO_3 and reaction mixture was concentrated under reduced pressure. The crude product was subjected to column chromatography over silica gel (*Eluent*: 20% MeOH in $CHCl_3$) to furnish the pure **20a** (1.58 g, 95%) as white solid. Mp. 94–96 °C; IR (KBr) ν (cm^{-1}): 3229, 2927, 1651, 1416, 1393, 1269, 1106, 1085, 1039, 1008; $[\alpha]_D^{25} = -11.6$ (c = 0.5, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.40 (br s, 1H), 4.76 (d, J = 4.6 Hz, 1H), 4.53 (t, J = 5.0 Hz, 1H), 3.56–3.52 (m, 1H), 3.35–3.32 (m, 2H), 3.31–3.25 (m, 1H), 2.16–1.96 (m, 3H), 1.84–1.75 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 177.2, 74.2, 62.9, 55.3, 30.1, 23.3; HRMS (ESI) Calcd for $C_6H_{11}NO_3Na$ 168.0637 $[M + Na]^+$, found 168.0634.

Synthesis of (*R*)-5-((*S*)-oxiran-2-yl)pyrrolidin-2-one 21a ($C_6H_9NO_2$)

To a solution of **20a** (1.20 g, 8.27 mmol) in anhydrous $CHCl_3$ (80 mL) were added PPh_3 (3.26 g, 12.41 mmol) and DIAD

(2.51 g, 12.41 mmol). The reaction mixture was refluxed for 36 h and then allowed to come to room temperature. The reaction mixture was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish the pure **21a** (884 mg, 84%) as colorless oil. IR (KBr) ν (cm^{-1}): 2948, 1682, 1462, 1437, 1279, 1255, 1108, 877; $[\alpha]_D^{25} = -55.3$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.60 (br s, 1H), 3.46 (q, J = 6.3 Hz, 1H), 2.96 (ddd, J = 6.2, 3.7, 2.5 Hz, 1H), 2.82 (t, J = 4.6 Hz, 1H), 2.63 (dd, J = 4.6, 2.7 Hz, 1H), 2.48–2.25 (m, 3H), 2.10–1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.6, 56.0, 54.7, 44.9, 29.7, 23.8; HRMS (MALDI): Calcd for $C_6H_{11}KNO_3$ 184.0371 $[M + H_2O + K]^+$, found 184.0469.

Synthesis of (*R*)-ethyl 5-(dibenzylamino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-ynoate 18b ($C_{26}H_{31}NO_4$)

To a solution of **17** (4 g, 11.9 mmol) in CH_3CN (40 mL) were added ethyl diazoacetate (1.62 g, 14.2 mmol) and CuI (112 mg, 0.59 mmol, 5 mol%). The reaction mixture was stirred for 12 h at room temperature. Then the crude reaction mixture was concentrated *in vacuo* and subsequently filtered through a short pad of silica by eluting with Et_2O. The filtrate was further concentrated *in vacuo*. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% EtOAc in petroleum ether) to furnish **18b** (4.72 g, 94%) as pale yellow oil. IR (KBr) ν (cm^{-1}): 2984, 17.44, 1560, 1495, 1370, 1258, 1072, 1028; $[\alpha]_D^{25} = -70.50$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 7.3 Hz, 4H), 7.28 (t, J = 7.6 Hz, 4H), 7.20 (t, J = 8.0 Hz, 2H), 4.28–4.19 (m, 3H), 4.00 (dd, J = 8.2, 6.4 Hz, 1H), 3.89–3.84 (m, 3H), 3.58 (dt, J = 7.3, 2.3 Hz, 1H), 3.47 (d, J = 13.7 Hz, 2H), 3.35 (d, J = 2.3 Hz, 2H), 1.34–1.21 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 139.6 (2C), 128.9 (4C), 128.3 (4C), 127.0 (2C), 109.8, 78.4, 78.3, 76.4, 67.4, 61.7, 55.5 (3C), 26.6, 26.3, 25.6, 14.3; HRMS (ESI) Calcd for $C_{26}H_{31}NO_4Na$, 444.2151 $[M + Na]^+$, found 444.2150.

Synthesis of (*R*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one 19b ($C_{10}H_{17}NO_3$)

To a solution of **18b** (6.30 g, 14.9 mmol) in ethanol (60 mL) placed in a Parr apparatus was added 10% $Pd(OH)_2/C$ (2.09 g, 1.49 mmol) and subsequently stirred under 100 psi H_2 pressure at room temperature for 24 h. The reaction mixture was filtered through a small celite pad. To the resulting filtrate was added NaOEt (1.01 g, 14.9 mmol) and refluxed for 2 h. The reaction mixture was dried under reduced pressure and re-dissolved in EtOAc (30 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to afford **19b** (2.36 g, 81% over 2 steps) as yellow oil. IR (KBr) ν (cm^{-1}): 3322, 2994, 2858, 1659, 1463, 1378, 1292, 1221, 1160, 1085, 1031; $[\alpha]_D^{25} = -14.4$ (c = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.20 (br s, 1H), 4.04 (dd, J = 8.6, 6.4 Hz, 1H), 3.85–3.89 (m, 1H), 3.66 (dd, J = 8.6, 5.5 Hz, 1H), 3.32–3.29 (td, J = 9.2, 4.6 Hz, 1H), 2.45–2.38 (m, 1H), 2.30–2.27 (m, 1H), 1.94–1.91 (m, 1H), 1.76–1.68 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.33–1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.7, 109.9, 79.2, 66.3, 56.3, 31.4, 26.9, 25.4, 24.9, 19.8; HRMS (ESI) Calcd for $C_{10}H_{17}NO_3Na$ 222.1106 $[M + Na]^+$, found 222.1106.

Synthesis of (*R*)-6-((*S*)-1,2-dihydroxyethyl)piperidin-2-one 20b ($C_7H_{13}NO_3$)

To a solution of **19b** (2.10 g, 199.08 mmol) in EtOH (20 mL) was added 2 M HCl (5 mL) and the mixture was stirred for 2 h at room temperature. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 20% MeOH in $CHCl_3$) to afford **20b** (1.58 g, 94%) as colorless oil. IR (KBr) ν (cm^{-1}): 3291, 3205, 2911, 1646, 1473, 1404, 1309, 1167, 1028, 955; $[\alpha]_D^{25}$ = +4.40 (c = 0.4, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 6.62 (br s, 1H), 4.88 (d, J = 5.3 Hz, 1H), 4.56 (t, J = 5.5 Hz, 1H), 3.44–3.40 (m, 1H), 3.36–3.31 (m, 1H), 3.24–3.19 (m, 2H), 2.09–2.00 (m, 2H), 1.72 (t, J = 5.4 Hz, 1H), 1.55–1.44 (m, 1H), 1.35–1.28 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 171.1, 74.4, 63.4, 55.0, 31.7, 25.1, 20.2; HRMS (ESI) Calcd for $C_7H_{13}NO_3Na$ 182.0793 $[M + Na]^+$, found 182.0797.

Synthesis of (*R*)-6-((*S*)-oxiran-2-yl)piperidin-2-one 21b ($C_7H_{11}NO_2$)

To a solution of **20b** (830 mg, 5.22 mmol) in anhydrous $CHCl_3$ (20 mL) were added PPh_3 (1.51 g, 5.74 mmol) and DIAD (diisopropyl azodicarboxylate) (1.16 g, 5.74 mmol). The reaction mixture was refluxed for 24 h. The reaction mixture was allowed to come to the room temperature and solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to afford **21b** (604 mg, 82%) as colorless oil. IR (KBr) ν (cm^{-1}): 2950, 1645, 1473, 1395, 1302, 1175, 919; $[\alpha]_D^{25} = -30.80$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.50 (br s, 1H), 3.08–3.03 (m, 1H), 2.94–2.91 (m, 1H), 2.82 (t, J = 4.6 Hz, 1H), 2.62 (dd, J = 4.6, 2.3 Hz, 1H), 2.43–2.27 (m, 2H), 1.98–1.88 (m, 2H), 1.76–1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.1, 55.8, 55.1, 45.2, 31.4, 25.1, 19.5; HRMS (ESI) Calcd for $C_7H_{11}NO_2Na$ 164.0687 $[M + Na]^+$, found 164.0685.

General procedure for opening of epoxide Gilman reagent

Method B. To a suspension of CuI (5.00 mmol) in dry Et_2O (20 mL) placed at −35 °C, was added dropwise BuLi (10.00 mmol, 1.6 M in hexane). To the suspension was added dropwise a solution of either of the epoxides **21a** and **21b** (1.00 mmol) in dry THF (4.5 mL) and the mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was carefully quenched at −35 °C with saturated NH_4Cl (15 mL). The reaction mixture was allowed to come to room temperature with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 25 mL).

The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The dried mass was subjected to column chromatography over silica gel to furnish the pure lactam **23a–23d**, **25a–25d**.

(*R*)-6-((*R*)-1-Hydroxypropyl)piperidin-2-one 25a ($C_8H_{15}NO_2$). Following Method B, the Gilman reagent was prepared by adding MeLi (1.6 M) in pentane (11 mL, 17.7 mmol) to a suspension of CuI (1.68 g, 8.85 mmol) in dry Et_2O (40 mL) at −35 °C. Opening of the epoxide was carried out by adding a solution of **21b** (250 mg, 1.77 mmol) in dry THF (7 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **25a** (203 mg, 73%) as colorless oil. IR (KBr) ν (cm^{-1}): 3384, 2958, 1645, 1487, 1416, 1323, 1166, 1090; $[\alpha]_D^{25}$ = +3.8 (c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 6.76 (s, 1H), 4.88 (d, J = 5.5 Hz, 1H), 3.18–3.09 (m, 2H), 2.16–2.03 (m, 2H), 1.82–1.76 (m, 2H), 1.59–1.45 (m, 2H), 1.28–1.20 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 170.9, 74.9, 57.4, 31.7, 25.5, 24.6, 20.1,10.4; HRMS (ESI) Calcd for $[C_8H_{15}NO_2Na]^+$ 180.1000 $[M + Na]^+$, found 180.1004.

General procedure for reduction of lactam by $LiAlH_4$

Method C. To a suspension of $LiAlH_4$ (3.00 mmol) in dry THF (10 mL) placed at 0 °C was added a solution of one of the lactams **23a–23d**, **25a–25d** (1.00 mmol) in THF (5 mL) and the resulting mixture was stirred at reflux for 8 h. After cooling to 0 °C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (8 mL). The crude product was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The dried mass was subjected to column chromatography over silica gel to furnish the pure lactam **24a–24d**, **8a**, **26b–26d**.

Synthesis of (+)-β-conhydrine (8a). Following Method C, reaction of **25a** (150 mg, 0.95 mmol) with $LiAlH_4$ (108 mg, 2.86 mmol) followed by purification by column chromatography over silica gel (*Eluent*: 30% MeOH in $CHCl_3$) provided (+)-β-conhydrine **8a** (107 mg, 78%) as colorless oil. IR (KBr) ν (cm^{-1}): 3447, 3326, 2965, 2855, 1467, 1392, 1128, 1030; $[\alpha]_D^{25}$ = +7.1 (c = 0.6, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.24–3.20 (m, 1H), 3.11–3.07 (m, 2H), 2.57 (t, J = 10.3 Hz, 1H), 2.36 (t, J = 7.5 Hz, 1H), 1.78–1.76 (m, 1H), 1.65–1.52 (m, 3H), 1.39–1.29 (m, 3H), 1.78–1.09 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 72.6, 62.9, 45.4, 26.5, 25.4, 22.6, 22.3, 9.8; HRMS (ESI) Calcd for $C_8H_{18}NO$ 144.1388 $[M + H]^+$, found 144.1380.

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Notes and references

1 (*a*) L. A. Marcaurelle and C. W. Johannes, *Prog. Drug Res.*, 2008, **66**, 189; (*b*) J. W. H. Li and J. C. Vederas, *Science*, 2009, **325**, 161; (*c*) T. F. Molinski, D. S. Dalisay, S. L. Lievens and J. P. Saludes, *Nat. Rev. Drug Discovery*, 2009, **8**, 69.
2 D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.
3 (*a*) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347; (*b*) M. A. Wijdeven, J. Willemsen and F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, 2010, 2831.
4 S. Inouye, T. Tsuruoka and T. Niida, *J. Antibiot. Ser. A*, 1966, **19**, 288.
5 (*a*) T. Wertheim, *Justus Liebigs Ann. Chem.*, 1856, **100**, 328; (*b*) J. Vetter, *Food Chem. Toxicol.*, 2004, **42**, 1373; (*c*) E. Späth and E. Adler, *Monatsh. Chem.*, 1933, **63**, 127.
6 A. T. Carmona, J. Fuentes, I. Robina, R. Garcia Eliazar, R. Demange, P. Vogel and L. Winters Ana, *J. Org. Chem.*, 2003, **68**, 3874.
7 T. Matsumura, M. Kasai, T. Hayashi, M. Arisawa, Y. Momose, I. Arai, S. Amagaya and Y. Komatsu, *Pharm. Biol.*, 2000, **38**, 302.
8 R. J. Nash, P. I. Thomas, R. D. Waigh, G. W. J. Fleet, M. R. Wormald, P. M. d. Q. Lilley and D. J. Watkin, *Tetrahedron Lett.*, 1994, **35**, 7849.
9 (*a*) M. J. Schneider, F. S. Ungemach, H. P. Broquist and T. M. Harris, *Tetrahedron*, 1983, **39**, 29; (*b*) P. R. Dorling, C. R. Huxtable and S. M. Colegate, *Biochem. J.*, 1980, **191**, 649.
10 Y. Lu, T. Yao and Z. Chen, *Yaoxue Xuebao*, 1986, **21**, 829.
11 N. Asano, in *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*, ed. E. Fattorusso and O. Tagialatela-Scafati, Wiley-VCH Verlag, Weinheim, Germany, 2008, pp. 111–138.
12 Y.-F. Chang, C.-W. Guo, T.-H. Chan, Y.-W. Pan, E.-L. Tsou and W.-C. Cheng, *Mol. Diversity*, 2011, **15**, 203.
13 L. Guandalini, E. Martini, L. Di Cesare Mannelli, S. Dei, D. Manetti, S. Scapecchi, E. Teodori, C. Ghelardini and M. N. Romanelli, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1936.
14 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608.
15 (*a*) F. Galiovsky and H. Mulley, *Monatsh. Chem.*, 1948, **79**, 426; (*b*) V. Ratovelomanana, J. Royer and H. P. Husson, *Tetrahedron Lett.*, 1985, **26**, 3803; (*c*) P. Guerreiro, V. Ratovelomanana-Vidal and J.-P. Genet, *Chirality*, 2000, **12**, 408; (*d*) D. L. Comins and A. L. Williams, *Tetrahedron Lett.*, 2000, **41**, 2839; (*e*) C. Agami, F. Couty and N. Rabasso, *Tetrahedron Lett.*, 2000, **41**, 4113; (*f*) C. Agami, F. Couty and N. Rabasso, *Tetrahedron*, 2001, **57**, 5393; (*g*) S. K. Pandey and P. Kumar, *Tetrahedron Lett.*, 2005, **46**, 4091; (*h*) D. Enders, B. Nolte, G. Raabe and J. Runsink, *Tetrahedron: Asymmetry*, 2002, **13**, 285; (*i*) S. R. V. Kandula and P. Kumar, *Tetrahedron: Asymmetry*, 2005, **16**, 3268; (*j*) S. V. Kandula and P. Kumar, *Tetrahedron Lett.*, 2003, **44**, 1957; (*k*) A. Voituriez, F. Ferreira and F. Chemla, *J. Org. Chem.*, 2007, **72**, 5358.
16 J. A. Gálvez, M. D. Diaz de Villegas, R. Badorrey and P. López-Ram-de-Víu, *Org. Biomol. Chem.*, 2011, **9**, 8155.
17 A. G. Jamieson and A. Sutherland, *Org. Lett.*, 2007, **9**, 1609.
18 B. Huang, X. Yao and C.-J. Li, *Adv. Synth. Catal.*, 2006, **348**, 1528.
19 (*a*) N. Gommermann and P. Knochel, *Tetrahedron*, 2005, **61**, 11418; (*b*) N. Gommermann and P. Knochel, *Chem. Commun.*, 2005, 4175; (*c*) N. Gommermann, C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5763.
20 (*a*) P. Hohenberg and W. Kohn, *Phys. Rev.*, 1964, **136**, B864; (*b*) W. Kohn and L. Sham, *Phys. Rev.*, 1965, **140**, A1133; (*c*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*d*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
21 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill,

B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision C.02)*, 2003.
22 A. Pico, A. Moyano and M. A. Pericas, *J. Org. Chem.*, 2003, **68**, 5075.
23 A. Suarez and G. C. Fu, *Angew. Chem., Int. Ed.*, 2004, **43**, 3580.
24 M. J. Fray, E. J. Thomas and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1983, 395.
25 C. Bonini, R. Di Fabio, G. Sotgiu and S. Cavagnero, *Tetrahedron*, 1989, **45**, 2895.
26 G. Righi, G. Pescatore, F. Bonadies and C. Bonini, *Tetrahedron*, 2001, **57**, 5649.
27 (*a*) S. Mori and E. Nakamura, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley-VCH, Weinheim, Germany, 2002, pp. 315–346; (*b*) G. Schroeder, W. Wysocka, B. Leska, R. Kolanos, K. Eitner and J. K. Przybylak, *J. Mol. Struct.*, 2002, **616**, 193.
28 S. Lebrun, A. Couture, E. Deniau and P. Grandclaudon, *Tetrahedron: Asymmetry*, 2008, **19**, 1245.
29 (*a*) J. Kang Eun, J. Cho Eun, K. Ji Mi, E. Lee Young, M. Shin Dong, Y. Choi Soo, K. Chung Young, J.-S. Kim, H.-J. Kim, S.-G. Lee, S. Lah Myoung and E. Lee, *J. Org. Chem.*, 2005, **70**, 6321; (*b*) C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear and C. S. Vianco, *J. Org. Chem.*, 1991, **56**, 4056.

