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Alpha-amination of labdane-type diterpenes by organocatalysis

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ABSTRACT:

The first electrophilic α -amination reaction of labdane-type diterpene (-)-(5*S*,9*S*,10*S*,13*S*)-labd-7-en-15-oic acid and (+)-(5*S*,8*R*,9*R*,10*S*,13*R*)-8-hydroxyabdan-15-oic acid, isolated from aerial parts of *Ageratina jocotepecana* is presented. In the presence of dibenzylazodicarboxylate and proline followed by an *in situ* reduction, the corresponding hydrazino alcohols were obtained. It is demonstrated that the first diterpene moiety had no influence in the diastereoselectivity that is then controlled by the catalyst used, at the opposite to the second diterpene that mainly control the diastereochemistry of the product.

Keywords: *Ageratina jocotepecana*, cativic acid, 13-*epi*-labdanolic acid, amination, organocatalysis, diastereomers.

Introduction

Terpenes are a class of chemical compounds widely distributed in nature as bioactive compounds; these terpenoids have been identified as high value chemicals in food, cosmetic, pharmaceutical and biomaterials.¹⁻⁴

Therefore, the chemical derivatization from natural products has received more extensive attention, as obtained structures may led to interesting biological activities. In particular the labdane-type diterpenes have shown different biological activities such as antibacterial, antifungal, anti-inflammatory or anticancer properties.^{5,6} Caticvic acid (**1**) is a labdane-type diterpene isolated firstly by Kalman in 1938 from *Prioria copaifera*, known locally as “Cativa” tree.⁷ Our team reported in a previous work the isolation of caticvic acid (**1**) and 13-*epi*-labdanolic acid (**2**) from *Ageratina jocotepecana* and the determination of their absolute configuration (Fig. 1).⁸

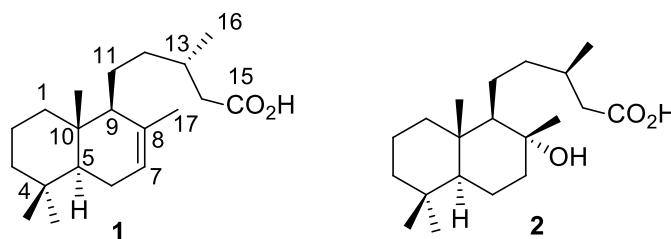


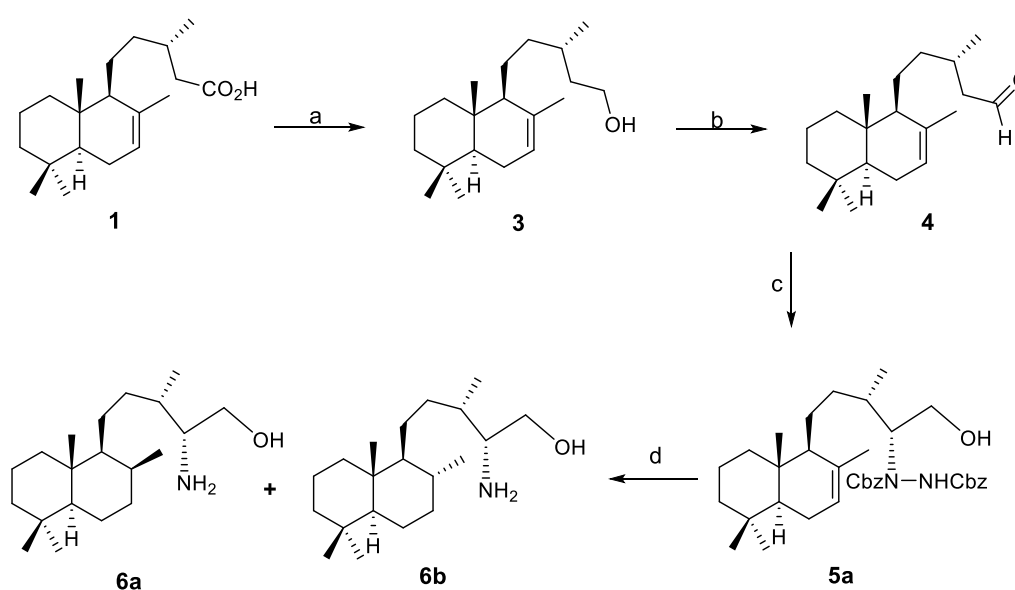
Fig 1. Structures of caticvic acid (**1**) and 13-*epi*-labdanolic acid (**2**).

Notably structures bearing α -amine substitution are widely distributed such bioactive compounds, additionally amines are important building blocks structures in chemistry and provide many functionalities in natural products.⁹ The use of electrophilic α -amination reaction is now a well-known method to generate C-N bonds in organic structures.¹⁰ In particular the use of chiral amines in reactions have received wide attention in recent years because of their diverse applications as organocatalysts^{11,12} since the concomitant description by the teams of Jorgensen¹³ and List¹⁴ then Zhong¹⁵ of the use of proline as a catalyst in the enantioselective direct α -amination of aldehydes

using azodicarboxylate esters as electrophiles. The enantioselectivity was explained by an enamine transition state formed during the mechanism, where the carboxylic acid proton of proline catalyst directs the approach by hydrogen-bonding of one face of the prochiral enamine with the incoming nitrogen atom of the electrophile.¹⁶ MacMillan and co-workers reported the use of proline methyl and other secondary amines like organocatalyst in very good enantioselectivities and yield.¹⁷ Liu reported the first enantioselective α -amination of aromatic ketones catalyzed by chiral primary amines derived from cinchona alkaloids, showing the diastereoselectivity employing cinchonine derivatives.^{18–20} Herein we have evaluated the organocatalytic α -amination of derivatives of **1** and **2** using dibenzyl azodicarboxylate (DBAD) as the electrophile.

Results and discussion

At first the carboxylic acid **1** was treated with LiAlH_4 to provide the primary alcohol **3** in 94% that was oxidized with pyridinium chlorochromate (PCC) to give the aldehyde **4** in 93% (scheme 1). The organocatalyzed α -amination reaction was done using DBAD as the electrophile.



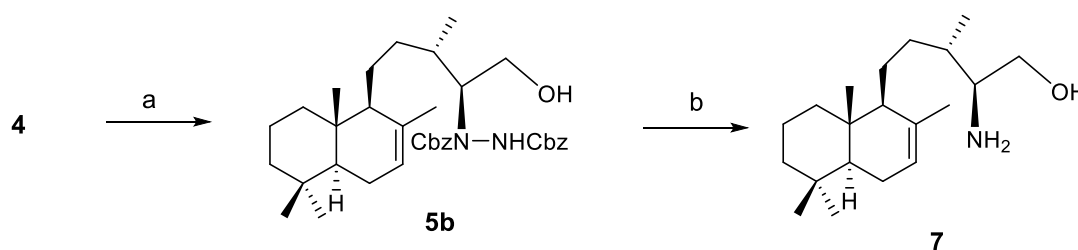
Scheme 1. Reagents and conditions: (a) LiAlH₄, THF, 4 h, 94%; (b) PCC, MgSO₄, CH₂Cl₂, 5 h, 93%; (c) (i) *L*-Proline, DBAD, CHCl₃, 24 h, R.T.; (ii) NaBH₄, MeOH, 2 h; 76% in 2 steps, *d.e.* 52%; (d) (i) H₂, Pd/C and/or Pt, EtOAc, 24 h, (ii) Nickel Raney, 63% in two steps.

The influence of the chirality of proline has been first tested, as the substrate itself could influence in the diastereoselectivity of the final product. Then the reaction of **4** in acetonitrile was first investigated in the presence of the racemic proline catalyst at R.T. for 24 h, followed by an *in situ* reduction of the aldehyde (Table 1, entry 1). A mixture of the expected hydrazino alcohols **5a** and its epimer **5b** were obtained with the medium yield of 61% after purification. The zero value of the diastereomeric excess of the mixture suggested that the configuration of the starting material **1** was not involved in the diastereoselectivity of the α -amination of **5a** and **5b**. The same result was noticed in chloroform (entry 4).

The use of *L*- and *D*-proline respectively led to the diastereomers **5a** and **5b** with similar medium yield and low *d.e.* of 17% and 14% (entries 2 and 3). The reactions in chloroform gave better results with yields of 76% and 74% for **5a** and **5b** respectively and diastereomeric excesses of 52% and 58% (entries 5-6).

Additionally to increase the diastereomeric excesses we tried with the catalyst (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol, but the reaction was not efficient with this substrate, then the use of 9-amino-(9-deoxy)-*epi*-quinine and 9-amino-(9-deoxy)-*epi*-cinchonidine were tested, the results were interesting for the global yield up to 70%, but did not increase the *d.e.* with 0% and 16% respectively (entries 7 and 8). The configurations of products **5a** and **5b** were determined according to the mechanism of the catalyst. Then the use of the catalyst *L*-proline should lead mostly to the compound **5a**, whereas its enantiomer would give **5b**. The α -hydrazino compound **5a** has been hydrogenolized with H₂, Pd/C then Nickel Raney in *one pot* to obtain the corresponding free amino alcohol. In particular, the conditions of the first step could allow the control

of the hydrogenation. Then the hydrogenation reaction of diastereomer **5a** employing palladium and platinum catalysts to afford the free hydrazine intermediate, which was hydrolyzed with Nickel Raney in *one pot* reaction to afford an inseparable mixture of the reduced products **6a** and **6b** in 63% of yield and a proportion 6a/6b of 35/65, where can be noticed the reduction of the double bond. The compound was corroborated by the mass spectroscopy confirming the molecular ion $[M + H]^+$ at m/z 310.3115, which was in agreement with the formula $C_{20}H_{40}NO$. The hydrogenation reaction only with the palladium catalyst further Nickel Raney treatment of **5b** provided the product **7** with the yield of 80% (scheme 2). The spectrum data of 1H NMR showed one signal that we attributed to the vinyl proton **7** at δ 5.37, and the mass spectrum showed the molecular ion $[M + H]^+$ at m/z 308.2946, corresponding with formula $C_{20}H_{38}NO$ where the double bond was conserved. The results suggested that platinum catalyst was the responsible to make the reduction of the double bond giving a mixture of products with the CH₃-17 in alpha and beta position.

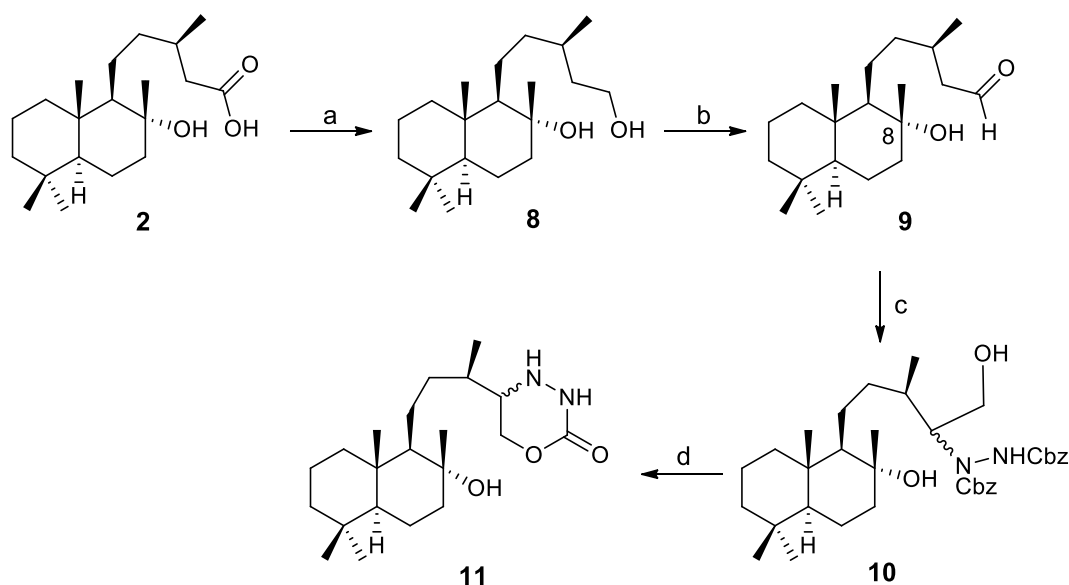


Scheme 2. Reagents and conditions: (a) (i) *D*-Proline, DBAD, $CHCl_3$, 24 h, R.T.; (ii) $NaBH_4$, MeOH, 2 h; 74% in 2 steps, *d.e.* 58%; (b) (i) H_2 , Pd/C, EtOAc, 24 h, (ii) Nickel Raney, 80% in two steps.

The carboxylic acid **2** previously isolated with a yield of 10-15% from leaves of *Ageratina jocosotepenaca*, was introduced in a similar way (scheme 3). The reduction reaction of **2** with $LiAlH_4$ provided the alcohol **8** in 94%, and further oxidation with PCC gave the aldehyde **9** in 80% yield. The α -amination reaction in chloroform and DBAD as electrophile using racemic proline as catalyst followed by the reduction *in*

situ with NaBH₄/methanol procedure was done. It is interesting to notice than in this case, the chirality of the initial **9** influenced the stereoselectivity of the reaction, as the expected hydrazine alcohol **10** was obtained with a yield of 33% and a *d.e.* of 44% in the presence of racemic proline (Table 1, entry 9).

The use of chiral proline (entries 10 and 11 respectively with *L*- and *D*-proline) led to the same diastereomer as major product with similar yields and *d.e.* up to 60%. These results could be explained by the presence of the hydroxyl group of **9** at position C-8, by hydrogen binding with the DBAD directing the attack to one favored face of the enamine. The hydrogenation reaction with Pd/C further Raney nickel treatment afforded the corresponding product with the amine free, which cyclisation led to the product **11** with a yield of 93%. Similar cyclisations have been reported by Bräse in 2007.²¹ Then the hydroxyl group in position C-15 induced an internal cyclisation with the carbonyl of Cbz affording the new six members ring of 1,3,4-oxadiazinane moiety. The ¹³C NMR spectrum showed a signal at δ 159.8 ppm that we attributed to a carbonyl group obtained from the Cbz group, the spectrum of IR ν_{\max} also showed the signal at 1746 cm⁻¹, the mass spectrum showed the molecular ion [M - OH]⁺ at *m/z* 349.2854 corresponding with formula C₂₁H₃₇N₂O₂.



Scheme 3. Reagents and conditions: (a) LiAlH₄, THF, 4 h, 94%; (b) PCC, MgSO₄, CH₂Cl₂, 5 h, 80%; (c) (i) *L*-Proline, DBAD, CHCl₃, 48 h, R.T.; (ii) NaBH₄, MeOH, 2 h, 36%; (d) (i) H₂, Pd/C, EtOAc, 24 h, (ii) Nickel Raney 3 h, 93% in 2 steps.

Molecular modeling of enamine structures **4a**, **4b**, **9a** and **9b** with *L*- and *D*-proline (Supporting Information) were carried out to explain the major stereoisomer for this reaction (Fig 2). The carboxylic group in the proline-enamine-involving transition state favor an intramolecular hydrogen bond which lead the attack of the azodicarboxylate. The global minimum energy conformers of the *E*-enamine for **4** showed that the N-H hydrogen bond with the carboxyl group of proline gave the opposite attack face of the enamine formed (C-14–C-15), the approach furnished for DBAD for an *anti* orientation with a *Re* face when *L*-proline is used (**4a-1**), giving a product with *R* configuration in C-14, the population calculated from free energies afforded the 37.47% for **4a-1**, in the other hand the *syn* orientation with a *Si* face was observed when *D*-proline is used with a population 52.49% for **4b-1**, affording the product with the opposite configuration, the observed stereochemistry is consistent with the demonstrated by Jorgensen¹³ and List¹⁴ with the use of *L*-proline. In case of global minimum energy conformer for the *E*-enamine formed with aldehyde **9** and *L*-proline (**9a-1**), the orientation of N-H hydrogen bond was observed for the *Si* face and an *anti* orientation, where the population of global minimum conformer is 87.53% for **9a-1**, giving an *S* configuration of the final product, finally the global minimum energy conformer of **9b-1** with 29.44% of population was observed with an *syn* orientation and N-H hydrogen bond led to *Re* face of the enamine, giving the *R* product, encourage by these results the presence of the inversion of configuration in C-13 for **9** respect to **4** could provide a steric effect with methyl group which change the orientation of the mechanism of *L*-proline, additionally the presence of hydroxyl group of **9** at position C-8 showed an hydrogen bond with the

OH of carboxyl of proline **9a-8** (Supporting Information), this conformation was only notice when *L*-proline was used, nevertheless the population contribution was less than 1% of total conformers.

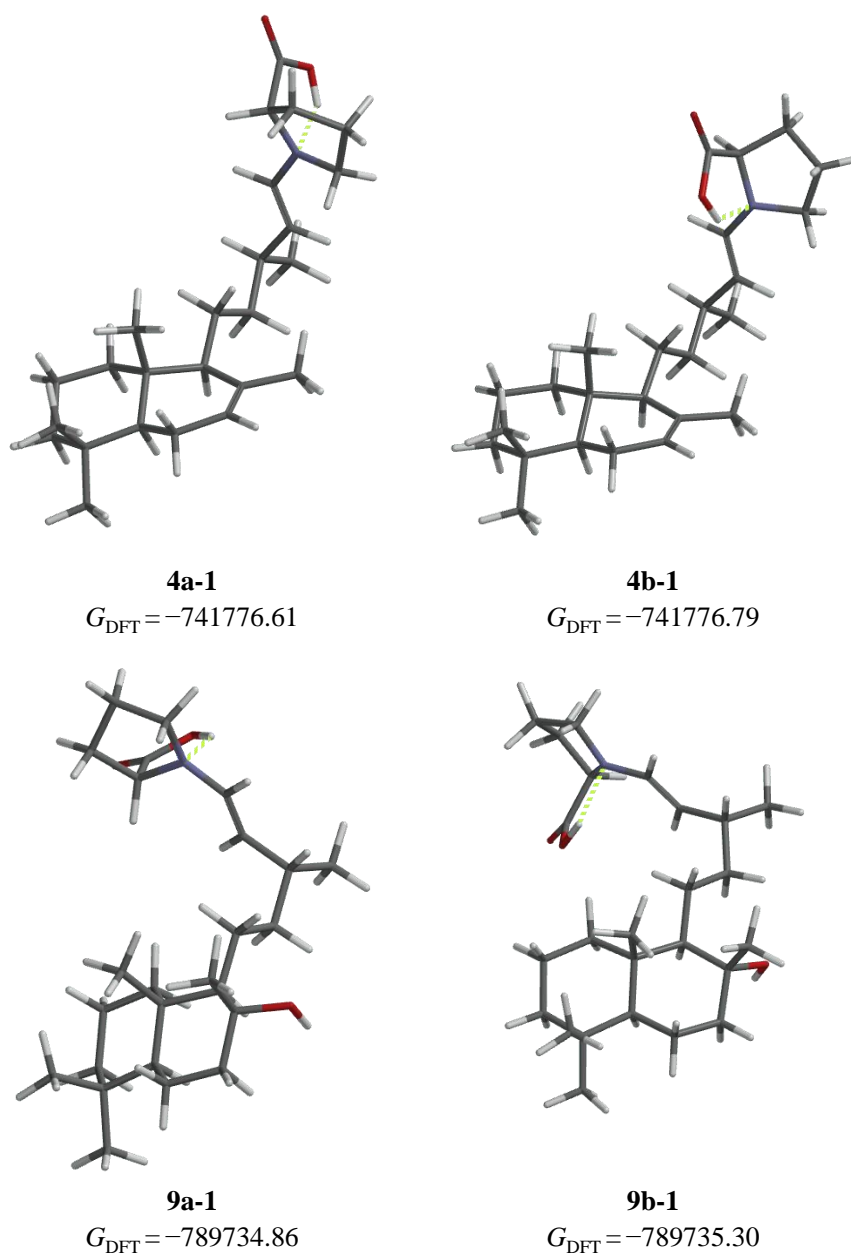


Fig 2. Enamine structures by *L*- and *D*-proline catalyst activation of **4** and **9**, global minimum energy conformers for **4a-1**, **4b-1**, **9a-1** and **9b-1** in kcal/mol.

Conclusion

We presented new derivatives of the natural cativic acid (**1**) and 13-*epi*-labdanolic acid (**2**). In particular, the influence of the structure in the diastereoselectivity of the reaction of electrophilic organocatalyzed amination was demonstrated. The reaction was not influenced by the decalin core, unless it was bearing an hydroxyl group at C-8.

Experimental part

General

The commercially available laboratory grade chemicals were used. The NMR 1D and 2D spectra were performed on Bruker AVANCE1 300MHz spectrometer. Chemical shift values (δ) were referenced with TMS as reference solvent and reported in ppm, coupling constants (J) in Hz. Silica gel Merck 60 (230–400 mesh) was used for column chromatography and reactions were monitored by thin layer chromatography. HRESIMS were measured on Xevo Q-ToF WATERS Quadrupole Hybrid Time-of-Flight Mass Spectrometer, Versailles France. Melting points were determined on a Buchi apparatus (Schemelzpunktbestimmungs-Apparat nach Dr.Tottoli) and values are not corrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. The infrared spectra were recorded on a Nicolet 6700 FTIR - CsI spectrometer.

All new compounds **3-11** are fully described in the supporting information.

General reduction methodology with LiAlH₄:

To cativic acid (**1**, 102.9 mg) or 13-*epi*-labdanolic acid (**2**, 97.8 mg.), 1 eq dissolved in THF anhydrous (5 mL) under argon atmosphere, LiAlH₄ (16.57 mg to **1** or 14.87 mg to **2**, 1.3 eq) was added in one portion. After 4 h (monitored by TLC) the reaction was quenched with HCl 10% (1 mL), extracted with ethyl acetate (25 mL) and washed with

H₂O distilled (40 mL), solution saturated of NaHCO₃ (60 mL), H₂O distilled (60 mL), the organic layer was dried over MgSO₄ and concentrated under vacuum to afford pure compound **3** (92.5 mg, 94%) or **8** (88 mg, 94%).

(-)-(5S,9S,10S,13S)-labd-7-en-15-ol (3).

Colorless oil; $[\alpha]_D -1$ (*c* 1, CHCl₃); IR ν_{\max} 3338, 2920, 1457, 1378, 1055, 620 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (1H, br s, H-7), 3.67 (2H, m, H-15), 1.97 (1H, m, H-6a), 1.84 (1H, m, H-1a), 1.79 (1H, m, H-6b), 1.66 (3H, s, H-17), 1.62 (1H, m, H-12a), 1.54 (1H, m, H-2a), 1.54 (1H, m, H-9), 1.53 (1H, m, H-13), 1.51 (1H, m, H-14a), 1.45 (1H, m, H-11a), 1.40 (1H, m, H-3a), 1.39 (1H, m, H-2b), 1.37 (1H, m, H-12b), 1.15 (1H, m, H-5), 1.13 (1H, m, H-3b), 1.13 (1H, m, H-14b), 1.12 (1H, m, H-11b), 0.92 (3H, d, *J* = 6.1 Hz, H-16), 0.90 (1H, m, H-1b), 0.87 (3H, s, H-19), 0.84 (3H, s, H-18), 0.75 (3H, s, H-20); ¹³C NMR (75 MHz, CDCl₃) δ 135.7 (C-8), 122.2 (C-7), 61.4 (C-15), 55.5 (C-9), 50.3 (C-5), 42.5 (C-3), 40.1 (C-14), 39.7 (C-12), 39.3 (C-1), 37.0 (C-10), 33.3 (C-18), 33.1 (C-4), 30.6 (C-13), 24.5 (C-11), 24.0 (C-6), 22.3 (C-17), 22.0 (C-19), 19.9 (C-16), 19.0 (C-2), 13.7 (C-20); HRESIMS *m/z* 293.2847 (calcd for C₂₀H₃₆O + H⁺, 293.2844).

General oxidation reaction methodology with PCC:

Compound **3** (143 mg) or **8** (76.5 mg), 1 eq was stirred in CH₂Cl₂ (5 mL) with MgSO₄ (44.13 mg to **3** or 22.24 mg to **8**, 0.75 eq), PCC (158.07 mg to **3** or 79.66 mg to **8**, 1.5 eq) was added and stirred for 5 h. At the end of the reaction (monitored by TLC) the solvent was evaporated carefully and pentane (20 mL) was added; the solvent was filtered over celite and washed with pentane. The solvent was evaporated to afford pure compound **4** (132 mg, 93%) or **9** (60.4 mg, 80%).

(-)-(5S,9S,10S,13S)-labd-7-en-15-al (4):

Yellow oil; $[\alpha]_D -7$ (c 1, CHCl_3); IR ν_{max} 2921, 1725, 1458, 1380, 1044 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 9.76 (1H, br s, H-15), 5.37 (1H, br s, H-7), 2.44 (1H, dd, $J = 16.0$, 5.5 Hz, H-14a), 2.22 (1H, dd, $J = 16.0$, 8.0 Hz, H-14b), 2.05 (1H, m, H-13), 1.92 (1H, m, H-6a), 1.83 (1H, m, H-1a), 1.82 (1H, m, H-6b), 1.65 (3H, s, H-17), 1.57 (1H, m, H-9), 1.50 (1H, m, H-11a), 1.50 (1H, m, H-12a), 1.42 (2H, m, H-2a and H-2b), 1.42 (1H, m, H-3a), 1.17 (1H, m, H-5), 1.17 (1H, m, H-12b), 1.13 (1H, m, H-3b), 1.10 (1H, m, H-11b), 0.98 (3H, d, $J = 6.7$ Hz, H-16), 0.95 (1H, m, H-1b), 0.87 (3H, s, H-19), 0.85 (3H, s, H-18), 0.75 (3H, s, H-20); ^{13}C NMR (75 MHz, CDCl_3) δ 203.12 (C-15), 135.3 (C-8), 122.5 (C-7), 55.3 (C-9), 50.3 (C-5), 42.4 (C-3), 50.9 (C-14), 39.7 (C-12), 39.3 (C-1), 37.0 (C-10), 33.3 (C-18), 33.1 (C-4), 29.2 (C-13), 24.6 (C-11), 23.9 (C-6), 22.3 (C-17), 22.0 (C-19), 20.3 (C-16), 18.9 (C-2), 13.7 (C-20).

General alpha-amination and reduction *in situ* reaction methodology:

Aldehyde **4** (20.5 mg to obtain **5a** or 19 mg to obtain **5b**) or **9** (24 mg), 1 eq was stirred in chloroform (2 mL) with proline (3.25 mg to obtain **5a** or 3.01 mg to obtain **5b** and 3.58 mg to **9**, 40%) at R.T. for 10 minutes. DBAD (23.16 mg to obtain **5a** or 21.46 mg to obtain **5b** and 25.53 mg to **9**, 1.1 eq) was added, reaction was monitored by TLC until complete. The reduction *in situ* with NaBH_4 (4 mg to obtain **5a** or 3.71 to obtain **5b** and 4.41 mg to **9**, 1.5 eq) in methanol (2 mL) was done. After 2-3 h the reaction was quenched with a saturated solution of NaHCO_3 (10 mL) and extracted with ethyl acetate (25 mL). The organic layer was washed with H_2O distilled (60 mL) and dried over MgSO_4 , the solvent was evaporated under vacuum and the crude was purified by column chromatography with pentane-ethyl acetate mixtures as eluent, to afforded **5a**

(31.5 mg, 76%, 52% *d.e.*), **5b** (28.4 mg, 74%, 58% *d.e.*) or **10** (17 mg, 36%) from **4** or **9** respectively and depending on the proline used.

(-)-(5S,9S,10S,13S,14R)-labd-7-en-14-[N,N'-(dibenzyl carbonyl)hydrazino]-15-ol (5a):

Solid white; m. p. 139-141 °C; $[\alpha]_D -4$ (*c* 1, CHCl₃); IR ν_{\max} 3341, 3202, 2916, 1720, 1410, 1312, 1271, 742, 694 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35 (10H, m, Ar), 6.41 (1H, s, NH), 5.36 (1H, br s, H-7), 5.18 (4H, m, CH₂Ph), 4.16 (1H, m, H-14), 3.70 (1H, m, H-15a), 3.45 (1H, m, H-15b), 1.92 (1H, m, H-6a), 1.85 (1H, m, H-11a), 1.82 (1H, m, H-6b), 1.79 (1H, m, H-1a), 1.62 (3H, s, H-17), 1.55 (1H, m, H-12a), 1.51 (1H, m, H-13), 1.47 (1H, m, H-9), 1.47 (1H, m, H-11b), 1.45 (1H, m, H-2a), 1.43 (1H, m, H-3a), 1.13 (1H, m, H-5), 1.12 (1H, m, H-3b), 1.11 (1H, m, H-2b), 1.06 (1H, m, H-12b), 0.91 (1H, m, H-1b), 0.87 (3H, s, H-19), 0.85 (3H, s, H-18), 0.82 (3H, d, *J* = 6.5 Hz, H-16), 0.71 (3H, s, H-20); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 157.5 (CO), 135.9- 127.4 (Ar), 135.1 (C-8), 122.7 (C-7), 68.7 (CH₂Ph), 65.6 (C-14), 60.6 (C-15), 55.4 (C-9), 50.3 (C-5), 42.4 (C-3), 39.3 (C-1), 37.0 (C-10), 35.8 (C-12), 33.4 (C-13), 33.1 (C-18), 33.1 (C-4), 23.9 (C-11), 23.7 (C-6), 22.2 (C-17), 22.0 (C-19), 18.9 (C-2), 16.7 (C-16), 13.7 (C-20); HRESIMS *m/z* 591.3807 (calcd for C₃₆H₅₀N₂O₅ + H⁺, 591.3798).

General hydrogenation reaction methodology:

Derivative **5a** (28.4 mg), **5b** (39.7 mg) or **10** (31.4 mg), 1 eq was stirred in ethyl acetate (2 mL) with the catalyst Pd/C (5.68 mg to **5a**, 7.94 mg to **5b** or 4.71 mg to **10**) and/or Pt (5.68 mg to **5a**) with H₂. The reaction was monitored by TLC until the reaction was completed (24 h), then *in situ* Raney nickel (5.68 mg to **5a**, 7.94 mg to **5b** or 4.71 mg to **10**) reactive was added. After 3 h the reaction was filtered over celite to afford an

unseparable mixture of **6a** and **6b** (9.3 mg, 63%) or the products **7** (16.5 mg, 80%) or **11** (17.6 mg, 93%) respectively from **5a**, **5b** or **10**.

(5S,9S,10S,13S,14S)-labd-7-en-14-amino-15-ol (7):

Colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 5.37 (1H, br s, H-7), 3.66 (2H, m, H-15a and H-15b), 3.60 (1H, m, H-14), 1.97 (1H, m, H-6a), 1.94 (2H, m, H-11a and H-11b), 1.86 (1H, m, H-6b), 1.83 (1H, m, H-1a), 1.65 (2H, m, H-12a and H-12b), 1.64 (3H, s, H-17), 1.62 (1H, m, H-13), 1.53 (1H, m, H-9), 1.44 (2H, m, H-2a and H-2b), 1.37 (1H, m, H-3a), 1.13 (1H, m, H-5), 1.08 (1H, m, H-3b), 0.91 (3H, m, H-16), 0.90 (1H, m, H-1b), 0.86 (3H, s, H-19), 0.83 (3H, s, H-18), 0.73 (3H, s, H-20); ^{13}C NMR (75 MHz, CDCl_3) δ 135.7 (C-8), 122.2 (C-7), 61.4 (C-15), 55.5 (C-9), 51.8 (C-14), 50.3 (C-5), 42.5 (C-3), 39.8 (C-12), 39.3 (C-1), 37.0 (C-10), 33.3 (C-4), 33.1 (C-18), 29.8 (C-13), 24.5 (C-6), 24.0 (C-11), 22.3 (C-17), 22.0 (C-19), 19.0 (C-2), 14.3 (C-16), 13.7 (C-20); HRESIMS m/z 308.2946 (calcd for $\text{C}_{20}\text{H}_{37}\text{NO} + \text{H}^+$, 308.2953).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supporting Information

Full experimental data detailed description of the procedure ^1H and ^{13}C NMR, optical rotation, IR, mass spectra data for compounds associated with this article can be found online via the “Supplementary Content” section of this article’s webpage.’

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Table 1. The α -amination/reduction of the aldehydes **4** and **9**.

Entry ^a	Conditions	Solvent	Major product	Yield ^b (%)	<i>d.e.</i> ^c of 5a/5b (%)
1	4 , racemic proline	CH ₃ CN	5a and 5b	61	0
2	4 , <i>L</i> -proline	CH ₃ CN	5a	53	17
3	4 , <i>D</i> -proline	CH ₃ CN	5b	54	14
4	4 , racemic proline	CHCl ₃	5a and 5b	65	0
5	4 , <i>L</i> -proline	CHCl ₃	5a	76	52
6	4 , <i>D</i> -proline	CHCl ₃	5b	74	58
7	4 , 9-amino-(9-deoxy)- <i>epi</i> -quinine	CHCl ₃	5a and 5b	83	0
8	4 , 9-amino-(9-deoxy)- <i>epi</i> -cinchonidine	CHCl ₃	5a	72	16
9	9 , racemic proline	CHCl ₃	10	33	44
10	9 , <i>L</i> -proline	CHCl ₃	10	36	70
11	9 , <i>D</i> -proline	CHCl ₃	10	26	62

^a Reaction purified after *in situ* reduction.

^b Isolated yield after purification over column chromatography.

^c *d.e.* determined after purification over column chromatography.