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Asymmetric synthesis of (−)-α-conhydrine

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Abstract—The enantioselective synthesis of (−)-α-conhydrine has been achieved by two different synthetic routes. The key steps include Sharpless asymmetric dihydroxylation, regioselective opening of a cyclic sulfate and Wittig olefination.

1. Introduction

Alkaloid mimics with a nitrogen in the ring, especially those α-substituted by a 1-hydroxyalkyl side chain, constitute a framework frequently encountered in natural alkaloids.[1] This pattern is found in many biologically active alkaloids such as conhydrine **1**, (−)-castanospermine **2**, (−)-slaframine **3**, and (−)-swainsonine **4** (Fig. 1).[2] Conhydrine is one of the alkaloids of the hemlock, isolated from the seeds and leaves of the poisonous alkaloids plant *Conium maculatum*, whose extracts were used in the ancient Greece for the execution of criminals.[3] Various asymmetric syntheses of α- and β-conhydrine have been documented.[4] While a number of auxiliary-supported syntheses or chiral pool approaches have been reported for unnatural β-conhydrine,[4] less attention has been paid to the enantioselective synthesis of (−)-α-conhydrine.[5] In connection with our studies on the enantioselective synthesis of naturally occurring lactones[6] and amino alcohols,[7] we became interested in developing a simple and feasible route to (−)-α-conhydrine. Herein, we report a new and highly enantioselective synthesis of (−)-α-conhydrine by two different strategies employing AD, regioselective opening of a cyclic sulfate and Wittig olefination as the key steps.

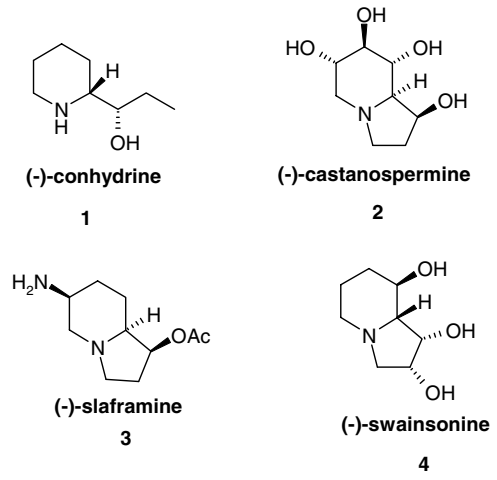

Figure 1.

2. Results and discussion

The synthesis of target molecule (−)-α-conhydrine **1** involves the preparation of enantiomerically pure diols **7** and **19** by employing the AD reaction and their subsequent synthetic manipulations. As shown in Scheme 1,[5b] the commercially available propionaldehyde **5** was treated with (methoxycarbonylmethylene)triphenylphosphorane in benzene under reflux to give the Wittig product *trans*-**6** in 85% yield. Subsequently, olefin **6** was subjected to a Sharpless asymmetric dihydroxylation[8] using osmium tetroxide as oxidant, potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand to afford **7** in excellent yield and with 95% ee.[9] Diol **7** was then treated with thionyl chloride and triethyl amine to give the cyclic sulfite, which was oxidized using $RuCl_3/NaIO_4$ to furnish the corresponding cyclic sulfate **8**[10] in 88% yield. The essential feature of our synthetic strategy was based on the presumption that the nucleophilic opening of cyclic sulfate **8** would occur in a regioselective manner at the α-carbon atom. Thus, when cyclic sulfate **8** was reacted with NaN_3, it

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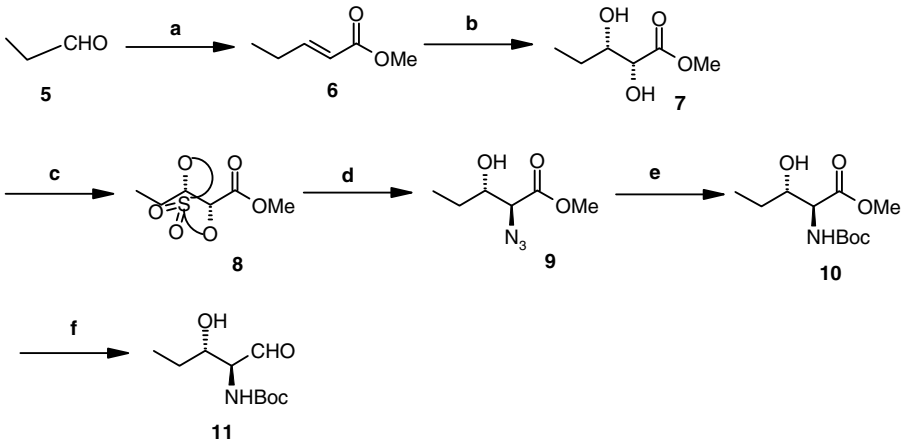


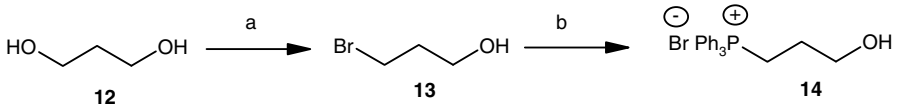
Scheme 1. Reaction conditions: (a) $Ph_3P{=}CHCOOMe$, benzene, reflux, 2 h, 85%; (b) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0 °C, 88%; (c) (i) $SOCl_2$, Et_3N, dry DCM, 20 min; (ii) $RuCl_3/NaIO_4$, 1 h, 88%; (d) NaN_3, acetone, 1 h; 20% aq H_2SO_4, ether, 12 h, 78%; (e) Boc_2O, Pd/C, H_2, EtOAc, 6 h, 98%; (f) DIBAL-H, −78 °C, 1 h.

furnished azido alcohol **9** with an apparent complete selectivity for an attack at the C-2, α-position. The carbonyl group must be responsible for the increased reactivity of the α-position.[11] Subsequently, azide **9** was reduced to an amine using 10% Pd/C under hydrogenation conditions, followed by protection of the amine with $(Boc)_2O$ to give **10**, which on reduction with DIBAL-H afforded the corresponding aldehyde **11** in good yield.

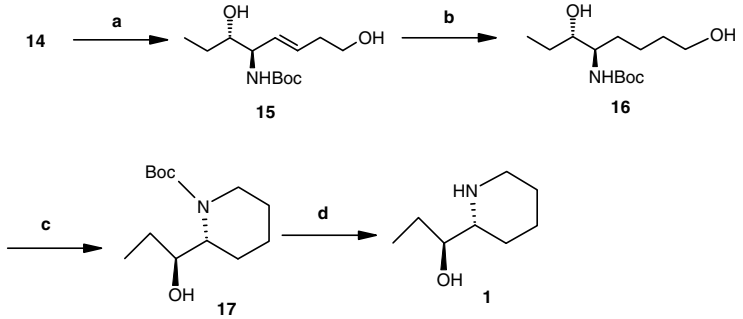
It was now possible to reach the target molecule by a three carbon chain elongation and subsequent cyclization.

To this end, we first synthesized the phosphonium salt **14**,[12] as shown in Scheme 2. Monobromination of 1,3-propanediol **12** with 48% aq HBr using Dean–Stark water-separator gave the bromo alcohol **13**, which was treated with triphenylphosphine in the presence of potassium carbonate to furnish **14** as a white crystalline solid (Scheme 2).[5b] With the phosphonium salt **14** in hand, we then proceeded to carry out the Wittig olefination. The ylide prepared from the reaction of *n*-BuLi and phosphonium salt **14**, was reacted with aldehyde **11** to afford olefin **15** in moderate yield (Scheme 3).[5b] The olefin reduction by hydrogenation using Pd/C gave **16**, which was subjected to cyclization using methanesulfonyl chloride and triethyl amine followed by deprotection of the Boc group to furnish (−)-α-conhydrine **1**.[5b] The physical and spectroscopic data of **1** were in full agreement with the literature data.[5a]

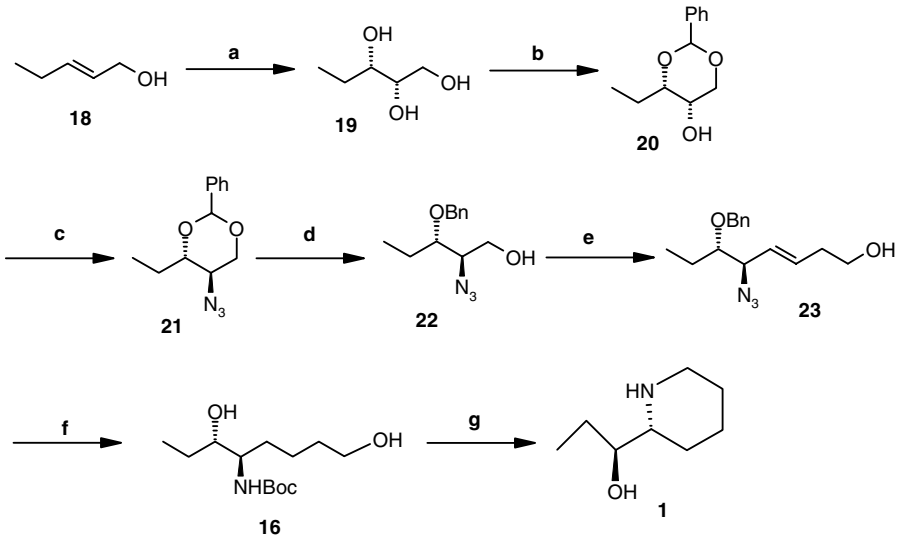
Although we successfully achieved the synthesis of target molecule **1** in high ee, the yield obtained at the Wittig step was not very satisfactory. Therefore, we looked into an alternative synthetic strategy with an aim to synthesize the target molecule in high yield and good enantiomeric excess. As illustrated in Scheme 4,



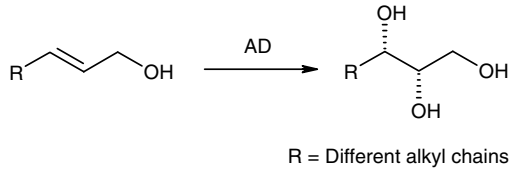
Scheme 2. Reaction conditions: (a) 48% aq HBr, benzene, 28 h, 79%; (b) PPh_3, K_2CO_3, dry acetonitrile, reflux, 7 h, 26%.



Scheme 3. Reaction conditions: (a) *n*-BuLi, THF, 0 °C, 30 min then **11**, rt, 12 h, 40%; (b) Pd/C, H_2, MeOH, 4 h, 95%; (c) MsCl, Et_3N, dry DCM, −78 °C, 1 h, 84%; (d) CF_3COOH, CH_2Cl_2, 12 h, rt, 74%.



Scheme 4. Reaction conditions: (a) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_2CO_3, *t*-BuOH/H_2O (1:1), 24 h, 0 °C; 75%; (b) $C_6H_5CH(OMe)_2$, dry CH_2Cl_2, *p*-TSA, rt, 12 h, 74%; (c) (i) CH_3SO_2Cl, dry CH_2Cl_2, rt, 6 h; (ii) NaN_3, dry DMF, 80 °C, 24 h, 86%; (d) DIBAL-H, −78 °C to room temperature, dry CH_2Cl_2, overnight, 90%; (e) (i) PCC, anhyd CH_3COONa, celite; (ii) salt **14**, *n*-BuLi, dry THF, 0 °C–rt, 74%; (f) 10% Pd/C, H_2, Boc_2O, EtOAc, 24 h, 86%; (g) steps c and d (Scheme 3).



Scheme 5.

the commercially available *trans*-2-pentenol was subjected to asymmetric dihydroxylation[8] using osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand to give (2*S*,3*S*)-triol **19** in excellent yield. Sharpless asymmetric dihydroxylation (AD) on allylic alcohols presented in Scheme 5, with different alkyl chains was reported to give the two stereogenic centers in 95–97% enantiomeric excess.[13] Thus, by analogy, triol **19** prepared was assumed to be enantiomerically pure. Furthermore, in order to achieve the synthesis of (−)-conhydrine **1** from **19**, we required the transformation of a hydroxyl group into an azido one, with concomitant reversal of stereochemistry at the 2-position. To this end, the protection of **19** as a benzylidene derivative was effected, using benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TSA to afford a mixture of 1,3-and 1,2-benzylidene compounds in a 9:1 ratio. The desired major 1,3-benzylidene compound **20** was separated by silica gel column chromatography. Our initial attempt to introduce the azido functionality under Mitsunobu conditions using Ph_3P/DEAD and freshly prepared hydrazoic acid was unsuccessful. Therefore we proceeded with a two-step reaction sequence. Thus, compound **20** was treated with methanesulfonyl chloride and triethylamine to give *O*-mesylate derivative, which on reaction with sodium azide in DMF afforded **21** with the desired stereochemistry at the 5-position. The smooth cleavage of benzylidene protecting group was achieved under reductive conditions using DIBAL-H at −78 °C to room temperature to afford **22** in 90% yield. PCC oxidation of alcohol **22** followed by a Wittig reaction using salt **14** gave the required olefin **23** in 75% yield. Reduction of the olefin and azide with concomitant benzyl deprotection using 10% Pd/C under hydrogenation conditions in the presence of Boc_2O gave the Boc protected amino alcohol **16**. Subsequent conversion into target compound **1** was carried out following the same reaction sequence as described in Scheme 3.

3. Conclusion

In conclusion, we have accomplished the enantioselective synthesis of (−)-α-conhydrine by two different synthetic strategies employing Sharpless asymmetric dihydroxylation, regioselective opening of a cyclic sulfate and Wittig olefination as the key steps. The merits of this synthesis are high enantioselectivity and various possibilities available for structural modifications. The other enantiomer can be synthesized by β-dihydroxylation of olefin **6** and **18** and following the reaction sequence as shown above.

4. Experimental section

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Optical rotations were measured using a sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on a Perkin–Elmer model 683 grating infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on Brucker AC-200 spectrometer in $CDCl_3$ solution with residual $CHCl_3$ as the internal

standard. Enantiomeric excess was measured using either the chiral HPLC or by comparison with the specific rotation. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer.

4.1.1. Methyl-*trans*-pent-2-enoate 6. To a solution of (methoxycarbonylmethylene)triphenylphosphorane (63.46 g, 0.19 mol) in benzene (200 mL) was added propionaldehyde **5** (10 g, 0.172 mol). The reaction mixture was refluxed for 2 h and the solvent concentrated to near dryness. Column chromatography on silica gel using EtOAc/pet ether (0.2:9.8) as eluent gave the Wittig product **6** (16.72 g) as a colorless oil. Yield: 85%; IR (neat, cm^{-1}): ν_{max} 1617, 1722; ^1H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, $J = 8$ Hz, 3H), 2.08–2.18 (m, 2H), 3.64 (s, 3H), 5.74 (d, $J = 16$ Hz, 1H), 6.87–6.98 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 25.1, 53.8, 122.2, 135.5, 174.2.

4.1.2. Methyl (2*S*,3*S*)-2,3-dihydroxypentanoate 7. To a mixture of $K_3Fe(CN)_6$ (42.80 g, 0.13 mol), K_2CO_3 (17.96 g, 0.13 mol), $(DHQ)_2PHAL$ (341 mg, 1 mol %) in *t*-BuOH/H_2O (1:1) were added osmium tetroxide (1.75 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (4.16 g, 43.80 mol). After stirring for 5 min at 0 °C, olefin **6** (5 g, 43.80 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2.5 g). The stirring was continued for an additional 45 min and then, the solution extracted with ethyl acetate (5 × 100 mL). The combined organic phases were washed with 10% aq KOH, brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (4:6) as eluent gave **7** (5.71 g) as a viscous liquid. Yield: 88%; $[\alpha]_D^{25} = -5.5$ (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3562, 1722; ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, $J = 6$ Hz, 3H), 1.57–1.72 (m, 2H), 2.05 (br s, 2H), 3.73–3.78 (m, 1H), 3.83 (s, 3H), 4.14 (d, $J = 4$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 26.0, 53.3, 72.8, 73.8, 173.4. Anal. Calcd for $C_6H_{12}O_4$ (148.16): C, 48.64; H, 8.16. Found: C, 48.52; H, 8.09.

4.1.3. (2*S*,3*S*)-5-Ethyl-2,2-dioxo-[1,3,2]dioxathiolane-4-carboxylic acid methyl ester 8. To a solution of diol **7** (2 g, 13.49 mmol) in dry CH_2Cl_2 (12 mL) was added Et_3N (5.46 g, 7.52 mL, 53.99 mmol). The mixture was cooled in an ice bath and thionyl chloride (2.4 g, 1.47 mL, 20.17 mmol) added dropwise. The reaction mixture was stirred for 20 min and then quenched by adding water (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Then the solution was cooled with an ice-water bath and diluted with CH_3CN (32 mL) and CCl_4 (32 mL). $RuCl_3 \cdot H_2O$ (15 mg, 0.072 mmol) and $NaIO_4$ (6.16 g, 28.83 mmol) were added followed by water (47 mL). The resulting orange mixture was stirred at room temperature for 1 h. The mixture was then diluted with ether (50 mL), and the two phases separated. The organic layer was washed with water (40 mL), saturated aq $NaHCO_3$ (30 mL), brine, dried Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (2:8) as eluent gave **8** (2.5 g) as a colorless liquid. Yield: 88%; $[\alpha]_D^{25} = -15.6$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3142, 3022, 2914, 1722; ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, $J = 7.4$ Hz, 3H), 1.97–2.09 (m, 2H), 3.89 (s, 3H), 4.89–4.93 (m, 1H), 5.30–5.32 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.5, 25.8, 52.7, 79.3, 85.2, 164.4. Anal. Calcd for $C_6H_{10}SO_6$ (210.21): C, 34.28; H, 4.80. Found: C, 34.16; H, 4.72.

4.1.4. Methyl (2*R*,3*S*)-2-azido-3-hydroxypentanoate 9. To a solution of cyclic sulfate **8** (2.5 g, 11.89 mmol) in acetone (15 mL) cooled to 0 °C was added NaN_3 (3.86 g, 59.46 mmol) and the resulting mixture stirred for 1 h at room temperature until no cyclic sulfate remained as indicated by TLC. The solution was then concentrated, and the residue stirred with 20% aq H_2SO_4 and ether (5 mL of each phase/mmol substrate) for 12 h. The resultant solution was then extracted with ether. The combined organic phases were washed with water, brine dried Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (1:9) as eluent furnished **9** (1.60 g) as a colorless liquid. Yield: 78%; $[\alpha]_D^{25} = -4.7$ (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3429, 2112, 1744; ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, $J = 7.4$ Hz, 3H), 1.50–1.69 (m, 2H), 2.33 (br s, 1H, OH), 3.83 (s, 3H), 3.87–3.91 (m, 1H), 3.97 (d, $J = 5.9$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5, 25.6, 51.7, 61.0, 73.0, 168.9. Anal. Calcd for $C_6H_{11}N_3O_3$ (173.17): C, 41.61; H, 6.40; N, 24.27. Found: C, 41.59; H, 6.36; N, 24.25.

4.1.5. Methyl (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-hydroxypentanoate 10. To a solution of azide **9** (2.0 g, 11.54 mmol) in ethyl acetate (10 mL) was added 10% Pd/C (75 mg) and Boc_2O (3.97 mL, 17.32 mmol). The resulting solution was stirred under a hydrogen atmosphere at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave **10** (2.8 g) as a liquid. Yield: 98%; $[\alpha]_D^{25} = -6.9$ (*c* 2.0, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3522, 3342, 1719; ^1H NMR (200 MHz, $CDCl_3$): δ 0.99 (t, $J = 8$ Hz, 3H), 1.44 (s, 9H), 1.52–1.63 (m, 2H), 2.54 (br s, OH, 1H), 3.62 (s, 3H), 3.83–3.86 (m, 1H), 4.38–4.40 (m, 1H), 5.54 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.1, 26.3, 28.1, 52.3, 58.0, 74.3, 80.3, 155.8, 171.2. Anal. Calcd for $C_{11}H_{21}NO_5$ (247.29): C, 53.43; H, 8.56; N, 5.66. Found: C, 53.40; H, 8.52; N, 5.64.

4.1.6. 3-Bromopropanol 13. To a stirred solution of 1,3-propanediol **12** (5 g, 65.70 mmol) in benzene (100 mL) was added 48% aq HBr (12.7 mL, 78.84 mmol) and the mixture stirred under reflux for 28 h while trapping the water formed using a Dean–Stark water separator. The mixture was washed with 6 M NaOH solution (50 mL), 10% HCl (50 mL), water (2 × 100 mL), and brine (75 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to near dryness. The crude product was purified by silica gel column chroma-

tography using EtOAc/pet ether (1:9) to give **13** (7.2 g) as a colorless oil. Yield: 79%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05–2.25 (m, 2H), 2.55 (br s, 1H), 3.54 (t, $J = 6$ Hz, 2H), 3.78 (t, $J = 8$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.1, 34.6, 59.5.

4.1.7. (3-Hydroxypropyl)-triphenylphosphonium bromide 14. A solution of 3-bromopropanol **13** (5 g, 35.97 mmol), triphenylphosphine (9.43 g, 35.97 mmol), and K_2CO_3 (4.97 g, 35.97 mmol) in dry CH_3CN (50 mL) was heated at reflux under nitrogen for 7 h. K_2CO_3 was filtered off and the filtrate diluted with ether and the solution allowed to stand, during which, product **14** was precipitated out as white crystals. (3.8 g, 26%). Mp 226–227 °C [lit.[12] Mp 226–229 °C]; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88–1.92 (m, 2H), 3.70–3.85 (m, 3H), 4.60–4.66 (m, 2H), 7.71–7.79 (m, 15H).

4.1.8. [5-Hydroxy-1-(1-hydroxypropyl)-pent-2-enyl]-carbamic acid *tert*-butyl ester 15. To a solution of **10** (0.3 g, 1.21 mmol) dissolved in dry DCM (5 mL) was added DIBAL-H (0.48 mL, 1.21 mmol, 2.5 M solution of DIBAL-H in toluene) dropwise at −78 °C. The reaction mixture was stirred for 1 h until the disappearance of the starting material as indicated by TLC and then quenched with saturated sodium potassium tartrate. The precipitate obtained was filtered off and the combined organic layers dried over Na_2SO_4 and concentrated to near dryness, which was used as such in the next step without further purification.

To a suspension of Wittig salt **14** (0.4 g, 1.01 mmol) in dry THF (5 mL) was added *n*-BuLi (1.1 mL, 2.3 mmol) at 0 °C and stirred for 30 min. To this solution the above crude aldehyde was added and stirred at rt for 12 h, and then quenched with satd aq NH_4Cl. The aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel column chromatography using EtOAc/pet ether (6:4) as eluent gave **15** (0.127 g) as a colorless oil. Yield: 40%; $[\alpha]_D^{25} = -10.3$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3511, 3328, 1609; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, $J = 10$ Hz, 3H), 1.25–1.36 (m, 2H), 1.47 (s, 9H), 2.1 (br s, 2H), 2.15–2.30 (m, 2H), 2.89–2.97 (m, 2H), 4.20 (q, $J = 6$ Hz, 1H), 4.30 (t, $J = 6$ Hz, 1H), 5.42 (br s, 1H), 5.98–5.99 (m, 1H), 6.53 (t, $J = 6$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.6, 21.6, 28.0, 30.5, 61.0, 64.9, 71.2, 80.1, 128.5, 132.0, 153.2. Anal. Calcd for $C_{13}H_{25}NO_4$ (259.34): C, 60.21; H, 9.72; N, 5.40. Found: C, 60.18; H, 9.71; N, 5.38.

4.1.9. [5-Hydroxy-1-(1-hydroxypropyl)-pentyl]-carbamic acid *tert*-butyl ester 16. To a solution of **15** (0.50 g, 1.93 mmol) in methanol (10 mL) was added Pd/C (50 mg) under a hydrogen atmosphere and mixture stirred for 4 h. After completion of the reaction, the mixture was filtered through a celite pad, and concentrated to near dryness. The crude product was purified by silica gel column chromatography using EtOAc/pet ether (6:4) as eluent to give **16** (0.478 g) as a liquid. Yield: 95%; $[\alpha]_D^{25} = -9.8$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3520, 3318; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (t, $J = 10$ Hz, 3H), 1.23–1.25 (m, 2H), 1.43 (s, 9H), 1.46–1.49 (m, 4H), 1.55–1.62 (m, 2H), 2.01 (br s, 2H), 3.52 (t, $J = 8$ Hz, 2H), 3.66–3.83 (m, 2H), 5.56 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.2, 19.0, 22.7, 25.6, 28.0, 31.7, 56.2, 62.2, 64.9, 77.8, 153.2. Anal. Calcd for $C_{13}H_{27}NO_4$ (261.36): C, 59.74; H, 10.41; N, 5.36. Found: C, 59.72; H, 10.38; N, 5.33.

4.1.10. 2-(1-Hydroxypropyl)-piperidine-1-carboxylic acid-*tert*-butyl ester 17. To a stirred solution of compound **16** (0.4 g, 1.53 mmol) in dry CH_2Cl_2 (6 mL) was added methanesulfonyl chloride (0.14 mL, 1.83 mmol) at −78 °C and then triethyl amine (0.25 mL, 1.83 mmol) was added dropwise. After the mixture was stirred at −78 °C for 1 h, aqueous ammonium chloride (3 mL) was added. The mixture was warmed to room temperature and diluted with CH_2Cl_2 (5 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed, and the residue purified by flash chromatography using EtOAc/pet ether (4:6) to give **17** as a colorless liquid (0.31 g). Yield: 84%; $[\alpha]_D^{25} = -12.2$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3422, 1688; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, $J = 6$ Hz, 3H), 1.32–1.45 (m, 6H), 1.45 (s, 9H), 1.52–1.63 (m, 2H), 2.02 (t, $J = 8$ Hz, 2H), 2.96 (br s, 1H), 3.32–4.32 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 23.3, 24.4, 25.3, 26.2, 27.3, 53.2, 60.2, 70.9, 75.5, 164.9. Anal. Calcd for $C_{13}H_{25}NO_3$ (243.18): C, 64.16; H, 10.36; N, 5.76. Found: C, 64.12; H, 10.33; N, 5.72.

4.1.11. Synthesis of (−)-α- conhydrine 1. To an ice-bath solution of **17** (23 mg, 0.095 mmol) in dry CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.2 mL, 0.095 mmol). The reaction mixture was stirred at room temperature for 12 h and then saturated aq $NaHCO_3$ added and the mixture extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (4:6) as eluent to give **1** (12 mg) as a solid. Yield: 74%; $[\alpha]_D^{25} = -8.9$ (*c* 1.0, ethanol). {lit.[5a] $[\alpha]_D^{25} = -8.6$ (ethanol)}]. The physical and spectroscopic data of **1** were in full agreement with the literature data.[5a]

4.1.12. (2*S*,3*S*)-Pent-1,2,3-triol 19. To a mixture of $K_3Fe(CN)_6$ (55.97 g, 0.17 mmol), K_2CO_3 (23.49 g, 0.17 mmol), and $(DHQ)_2PHAL$ (452 mg, 1 mol %) in *t*-BuOH–H_2O (1:1) cooled at 0 °C was added osmium tetroxide (2.3 mL, 0.1 M solution in toluene, 0.4 M mol %) followed by methanesulfonamide (5.5 g, 58.09 mmol). After stirring for 5 min at 0 °C, olefin **18** (5 g, 58.09 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite. Stirring was continued for an additional 45 min and then the solution extracted with ethyl acetate (5 × 100 mL). The combined organic phases were washed with 10% aq KOH, brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using EtOAc/pet ether (6:4) as eluent gave **19** (5.21 g) as a viscous liquid. Yield: 75%; $[\alpha]_D^{25} = -6.7$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}):

ν_{max} 3400–3200, 2919, 2851, 1455, 1375, 1074; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.9 (t, $J = 6$ Hz, 3H), 1.42–1.56 (m, 2H), 2.11 (br s, 2H), 3.51–3.59 (m, 2H), 3.67–3.73 (m, 3H). Anal. Calcd for $C_5H_{12}O_3$ (120.15): C, 49.98; H, 10.07. Found: C, 49.96; H, 10.02.

4.1.13. (2*S*,3*S*)-1,3-*O*-Benzylidenepentane-1,2,3-triol 20. To a solution of **19** (3 g, 24.96 mmol) in dry CH_2Cl_2 (40 mL) were added *p*-TsOH (80 mg) and benzaldehyde dimethyl acetal (4.56 g, 4.49 mL, 29.96 mmol). The reaction mixture was stirred at room temperature for 12 h. Subsequently, it was neutralized with saturated aq $NaHCO_3$. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were washed with aq $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Column chromatography over silica gel using EtOAc/pet ether (1:9) as eluent furnished the major product **20** (3.82 g) as a colorless liquid. Yield: 74%; $[\alpha]_D^{25} = -11.5$ (*c* 0.48, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3512, 2922, 2849, 1451, 1377, 1276, 1215; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.0 (t, $J = 7.4$ Hz, 3H), 1.69–1.87 (m, 2H), 2.52 (br s, 1H, OH), 3.45–3.74 (m, 1H), 3.63–3.72 (m, 1H), 3.93 (dd, $J = 2$, 12 Hz, 2H), 5.58 (s, 1H), 7.37–7.58 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.2, 24.0, 72.7, 79.8, 81.5, 101.3, 125.8, 128.1, 134.3, 137.9. Anal. Calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.21; H, 7.74. Found: C, 69.18; H, 7.71.

4.1.14. (2*R*,3*S*)-2-Azido-1,3-*O*-benzylidenepentane-1,3-diol 21. To a solution of **20** (2 g, 9.6 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (1.65 g, 1.1 mL, 14.40 mmol), Et_3N (2.27 mL, 16.32 mmol), and DMAP (cat). The reaction mixture was stirred at room temperature for 6 h and then poured into Et_2O–H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with water, brine, dried over Na_2SO_4, and concentrated to a white solid, which was dissolved in dry DMF (20 mL). Sodium azide (3.4 g, 48.01 mmol) was added and the reaction mixture stirred at 80 °C for 24 h. It was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine, dried over Na_2SO_4, and concentrated. Column chromatography on silica gel using EtOAc/pet ether (0.7:9.3) as eluent gave **21** (1.92 g) as a colorless liquid. Yield: 86%; $[\alpha]_D^{25} = -8.8$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 2122, 2752, 1432, 1327, 1256, 1225; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, $J = 4$ Hz, 3H), 1.62–1.76 (m, 2H), 3.50–3.62 (m, 2H), 3.99–4.01 (m, 2H), 5.97 (s, 1H), 7.39–7.53 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 25.4, 51.7, 69.0, 80.0, 103.2, 126.4, 128.4, 129.2, 137.3. Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.27): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.76; H, 6.44; N, 17.98.

4.1.15. (2*R*,3*S*)-2-Azido-3-benzyloxypentan-1-ol 22. To a solution of **21** (0.4 g, 1.71 mmol), in dry CH_2Cl_2 (10 mL) was added dropwise DIBAL-H (2.57 mL, 2 M solution in toluene, 5.14 mmol) at −78 °C under an argon atmosphere. The mixture was gradually allowed to warm to room temperature and the stirring continued overnight. The reaction mixture was cooled to 0 °C and to this was added successively saturated NH_4Cl (3 mL) and ethyl acetate (5 mL). After being stirred for 1 h at room temperature, the mixture was filtered through a celite pad. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using EtOAc/pet ether (1:9) as eluent to give **22** (0.36 g) as a colorless oil. Yield: 90%; $[\alpha]_D^{25} = -12.2$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3433, 2126, 1322, 1216, 1156, 1025; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, $J = 6.8$ Hz, 3H), 1.29–1.41 (m, 2H), 2.08 (br s, 1H), 2.11–2.14 (m, 1H), 3.37–3.43 (m, 1H), 3.60 (d, $J = 5.9$ Hz, 2H), 4.69 (s, 2H), 7.33–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.3, 24.4, 59.6, 61.2, 74.2, 76.3, 127.6, 128.3, 129.6, 137.4. Anal. Calcd for $C_{12}H_{17}N_3O_2$ (235.28): C, 61.26; H, 7.28; N, 17.86. Found: C, 61.22; H, 7.25; N, 17.85.

4.1.16. (5*R*,6*S*)-5-Azido-6-benzyloxyoct-3-ene-1-ol 23. To a stirred solution of PCC (0.68 g, 3.19 mmol), anhydrous sodium acetate (0.26 g, 3.19 mmol), and celite in dry CH_2Cl_2 (5 mL) at 0 °C was added alcohol **22** (0.5 g, 2.12 mmol) in dry CH_2Cl_2 (3 mL) under an argon atmosphere and stirring was continued for 4 h at room temperature until the completion of reaction as indicated by TLC. The reaction mixture was washed thoroughly with diethyl ether and concentrated to give an aldehyde, which was used immediately in the next step without further purification.

To a stirred solution of salt **14** (1.70 g, 4.25 mmol) in dry THF (20 mL) was added *n*-BuLi (2.12 mL, 2 M solution in hexane, 4.25 mmol) at 0 °C and stirring continued for further 30 min. The above aldehyde was added to the reaction mixture and stirred for 12 h at ambient temperature and quenched with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, and concentrated to near dryness. Purification by silica gel column chromatography using EtOAc/pet ether (7:3) as eluent gave **23** (0.35 g) as a viscous liquid. Yield: 74%; $[\alpha]_D^{25} = -19.3$ (*c* 0.52, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3429, 2133, 1616, 1221, 1156, 1025; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, $J = 6.0$ Hz, 3H), 1.32–1.46 (m, 2H), 2.02 (s, 1H), 2.15–2.23 (m, 2H), 2.62–2.66 (m, 1H), 3.01 (q, $J = 8.2$ Hz, 1H), 3.62 (t, $J = 10.5$ Hz, 2H), 4.69 (s, 2H), 5.48 (t, $J = 12.6$ Hz, 1H), 5.55 (q, $J = 12.6$ Hz, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.4, 24.6, 36.5, 62.2, 64.6, 73.9, 81.2, 126.4, 127.6, 128.4, 129.3, 132.6, 137.5. Anal. Calcd for $C_{15}H_{21}N_3O_2$ (275.35): C, 65.43; H, 7.69; N, 15.26. Found: C, 65.40; H, 7.63; N, 15.21.

4.1.17. [5-Hydroxy-1-(1-hydroxypropyl)-pentyl]-carbamic acid *tert*-butyl ester 16. To a solution of azide **23** (0.3 g, 1.09 mmol) in ethyl acetate was added 10% Pd/C (75 mg) and Boc_2O (0.3 mL, 1.3 mmol). The resulting solution was stirred under a hydrogen atmosphere for 24 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet

ether (3:7) as eluent gave **16** (0.24 g) as a colorless liquid. yield: 86%; $[\alpha]_D^{25} = -8.9$ (*c* 0.86, $CHCl_3$). The physical and spectroscopic data were in accord with those described in Section 4.1.9. The transformation of **16** to the target compound **1** is already described in Sections 4.1.10 and 4.1.11.

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