Malaysian Journal of Chemistry, 2022, Vol. 24(2), 223-227
(Special Issue: International Conference on Synthesis Chemistry-ICOSC2022, Universiti Teknologi MARA)

Asymmetric Synthesis of Hydroxy *N,O*-Heterobicyclic Octanes

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A new asymmetric synthesis of several hydroxy *N,O*-heterobicyclic octanes is described in this paper. The synthesis employed Salen catalysed epoxide ring opening of the starting material *meso*-cyclohexene followed by the azide reduction and NBoc protection of (1*S*,6*S*)-6-azido-3-cyclohexenol, allylic hydroxylation and lactonization with final carbonyl reduction to produce hydroxy *N,O*-heterobicyclic octane.

Key words: *N,O*-heterobicyclic octane: anticancer; retronecine; cis-butyrolactone

Received: March 2022 ; Accepted: March 2022

Pyrrolizidine alkaloids (PAs) have potent hepatotoxic, genotoxic, cytotoxic, tumorigenic, and neurotoxic activities, which pose major threats to human health, [1]. Pyrrolizidine alkaloids (Figure 1) containing retronecines as necine bases have been shown to be hepatotoxic and in some cases, carcinogenic [2]. Retronecine is a crystalline amino dihydroxy bicyclic alcohol $C_8H_{13}NO_2$ formed by hydrolysis of different alkaloids and derived from pyrroles (such as senecionine or monocrotaline). The most toxic PAs belong to the retronecine-type, which include mono- or diesters at C7 and C9 positions. Retronecine-type and otonecine-type PAs, which have a C1−C2 double bond in their unsaturated necine base, are hepatotoxic, [3].

Considering the focal role of retronecine or its derivatives in alkaloid synthesis, considerable efforts have been invested to synthesise this type of molecule with excellent enantioselectivity. Previous studies on the synthesis of retronecine bases have been accomplished from N-alkylated Geissman-Waiss lactone [4], pyrrolizidine [5], nitrones [6], (*S*)-3-acetotyssuccinimide [7], 1-(2,4,6-triisopropylphenyl) ethanol [8] and chiral pool [7, 9, 10].

In light of the purported potential of hydroxy *N,O*-heterobicyclic octane as precursor for the synthesis of retronecine and as part of our continued interest in hydroxy *N,O*-heterobicyclic octanes derived from cis-γ-butyrolactone [11-13] we hereby report a concise synthesis strategy for hydroxy *N,O*-heterobicyclic octane in this paper.

In this study, hydroxy *N,O*-heterobicyclic octanes were synthesised from meso-cyclohexene via epoxide ring opening catalysed by Salen complex followed by azide reduction and NBoc protection of (1*S*,6*S*)-6-azido-3-cyclohexenol, then allylic hydroxylation, and lactonization with final carbonyl reduction reaction.

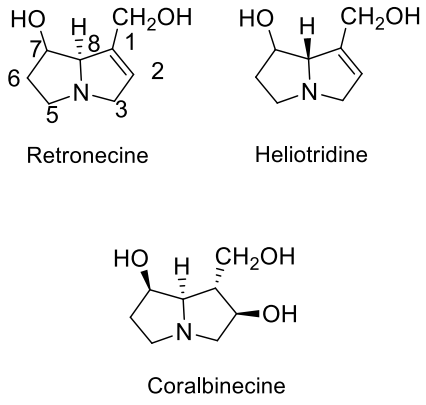


Figure 1. Some examples of pyrrolizidine alkaloids.

†Paper presented at the International Conference on Synthesis Chemistry-ICOSC2022, Universiti Teknologi MARA

EXPERIMENTAL

1. Reagents and Instrumentations

All chemicals and solvents utilised in this study were of reagent grade, and no further purification was done unless specified. Ethanol was stored under N_2 over 4°A molecular sieves. The thin layer chromatography (TLC) packed with silica gel 60 F254 (Merck KGaA) and visualised under UV light (λ = 254 nm) were performed to monitor all the reactions. Melting point were determined with a Buchi SMP 20. Nuclear magnetic resonance (NMR) spectra for ^1H and ^{13}C were acquired with a Bruker Ultra Shield 400 MHz spectrometer at 300 K using tetramethylsilane (TMS) as an internal standard in chloroform solvent ($CDCl_3$) at ambient temperature. Parts per million (ppm, units) were recorded to express chemical shifts. The coupling constants were recorded in hertz (Hz). The multiplicity of the signals for the ^1H NMR spectra is indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Fourier transformed infrared (FT-IR) spectra were obtained from an FT-IR spectrophotometer 1700X (Perkin Elmer, Waltham, MA) with neat or KBr pellets and wavenumber (ν) in cm^{-1}. MS spectra were recorded by Agilent GC–7890A MS 5975. The concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at a reduced pressure.

2. Synthesis of ((1*S*,6*S*)-(6-Azidocyclohex-3-en-1- y l) oxy)-trimethylsilane (2)

To a mixture of epoxide **1** (610 mg, 6.32 mmol, 1 equiv.) in 2.1 mL of diethyl ether was added Salen catalyst complex (88 mg, 0.12 mmol, 2 mol %). The mixture was stirred for 15 min, and trimethylsilylazide (0.88 mL, 6.63 mmol, 1.05 equiv.) was added slowly and stirred for 46 h at room temperature. Then the yellowish crude product was purified by column chromatography on a silica gel (hexanes/ EtOAc, 9:1) to yield **2** (840 mg, 63%) as a yellowish oil. R*f* = 0.83 (SiO_2, hexanes/EtOAc 9:1); 63% , 85% ee. IR (film-KBr): ν = 2957, 2905, 2107, 1438, 1250, 1140, 881, 840, 748, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.48−5.61 (m, 2H), 3.73−3.84 (m, 1H), 3.49−3.59 (m, 1H), 2.32−2.48 (m, 2H), 2.08−2.20 (m, 1H), 1.90−2.03 (m, 1H), 1.98 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 124.6, 123.9, 71.9, 62.9, 34.7, 30.9. MS [CI, NH_3]: m/z (%) = 212.1 (11) [M + H]+, 184.1 (29.9) [(M + H)+ − N_2].

3. Synthesis of *tert*-butyl (1*S*, 6*S*)-6 (hydroxy) cyclohex-3-enylcarbamate (Compound (3)

To a solution of compound **2** (0.21 g, 1.02 mmol, 1 equiv.) in ethanol (4 mL), di-*tert*-butyldicarbonate reagent (BOC_2O; 0.45 g, 2.04 mmol, 2 equiv.) was added followed by 20% $Pd(OH)_2/C$ (10.2 mg) at room temperature. The reaction proceeded with the addition of triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.). After stirring for 24 h, the resulting mixture was filtered through Celite. After complete removal of ethanol, the filtrate was purified using column chromatography (pet ether/ethyl acetate =15: 0.5) to give compound **3** (0.18 g,78%) as a white solid. R_f = 0.25 (SiO_2, hexanes: ethyl acetate 21:7); M.p. 76-78 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 5.50-5.60 (m, 2H), 4.90 (brs, 1H), 3.60-3.70 (m, 1H), 3.20-3.30 (m, 1H), 2.30-2.50 (m, 1H), 2.00-2.10 (m, 1H), 1.80-1.90 (m, 1H), 1.60-1.70 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 124.9 (2C), 124.5 (2C), 80.1, 70.8, 52.4, 33.9, 31.6, 28.4 (3C); IR (Film-KBr): ν = 3362, 2928, 2854, 1679, 1524, 1445, 1303, 1237, 1167, 1057, 1011, 878 cm^{-1}. MS [CI, NH_3] m/z (%) = 213.1 (100) [M^+]; Calculated for [$C_{11}H_{19}NO_3$]: 213.14.

4. Synthesis of Tert-butyl ((1*S*,6*R*)-5,6-dihydro xycyclohex-3-en-1-yl)carbamate (4)

Grounded selenium dioxide (SeO_2, 0.078 g, 1.41 mmol, 1 equiv.) was added to 3 mL dry ethanol containing compound **3** (0.10 g, 0.47 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 5 min. Then, *tert*- butylhydroperoxide (TBHP, 0.18 mL, 1.89 mmol, 2 equiv.) was added to the reaction mixture, and refluxed for 24 h. The resultant products were concentrated under reduced pressure and purified using column chromatography on silica gel with hexane : ethyl acetate (21:7) to yield 0.05 g (46%) compound **4** as a yellowish solid. R_f = 0.4 (SiO_2, hexane: ethyl acetate 21: 7); melting point 73-75°C, ^1H NMR (400 MHz, $CDCl_3$): δ 5.40-5.50 (m, 2H), 4.43-4.60 (brs, IH), 3.66-3.75 (m, 2H), 3.25-3.44 (m, 1H), 2.45-2.63 (d, 1H, *J* = 15.6), 2.15-2.25 (d, 1H, *J* = 12), 1.46 (s, 9H); 13C NMR (75 MHz, $CDCl_3$): δ 156.8, 124.5 (2C), 124.4 (2C), 79.3, 69.4, 56.4, 52.1, 31.3, 28.3 (2C); IR (film-KBr): ν = 3601, 3552, 2979, 2933, 1713, 1505, 1453, 1367, 1279, 1253, 1158, 985, 862, 791. MS [CI, NH_3] *m/z* (%) = 253.01 (75) [M + H^+ + Na^+], 252.9 (10) [M + Na^+]; calculated for $C_{11}H_{19}NO_4$: 229.1314 [M + Na]$^+$, found 252.1207 [M + Na]$^+$.

5. Synthesis of (3a*S*,6*S*,6a*R*)-*tert*-butyl 6-hydroxy -2,5-dioxotetrahydro-2H-furo[3,2-b]pyrrole -4(5H)-carboxylate (5)

Ruthenium (III) chloride trihydrate ($RuCl_3.3H_2O$, 0.0019 g, 0.00913 mmol, 8.3% mole equiv.) was added to a stirred solution of compound **4** (0.025 g, 0.11 mmol, 1 equiv.) in 3 mL of biphasic solution of CCl_4: CH_3CN: H_2O 1:1:2. The reaction mixture was stirred at 0°C for 5 min then grounded sodium metaperiodate ($NaIO_4$, 0.096 g, 0.45 mmol, 4.1 equiv.) was added portion wise to the reaction mixture and stirred for 24 hours at 0°C. The solvent was removed

under reduced pressure to obtain a yellow crude compound, which was purified using the column chromatography on silica gel with the mobile phase methanol: ethyl acetate (0.5:9.5) to give the compound **5** in 0.018 g with 63% yield. R_f = 0.4 (SiO_2, methanol: ethyl acetate 0.5:9.5); melting point 162-164°C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99-5.13 (m, 1H), 4.71-4.84 (m, 1H), 3.50 -3.59 (dd, *J* = 4.2, 7.2, 1H), 2.93-3.02 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 169.5, 149.4, 84.6, 73.5, 68.7, 58.3, 38.6, 28.4. IR (film-KBr): ν = 3421, 2978, 2935, 1755, 1722, 1616, 1366, 1330, 1254, 1164, 1052, 803. MS [CI, NH_3] *m/z* (%) = 281.1 [M + H^+ + Na^+]; calculated for $C_{11}H_{15}NO_6$: 257.08.

6. Synthesis of (3a*S*,6*S*,6a*R*)-*tert*-butyl 6-hydroxy-2-oxotetrahydro-2H-furo[3,2-*b*]pyrrole-4(5H)-carboxylate (6)

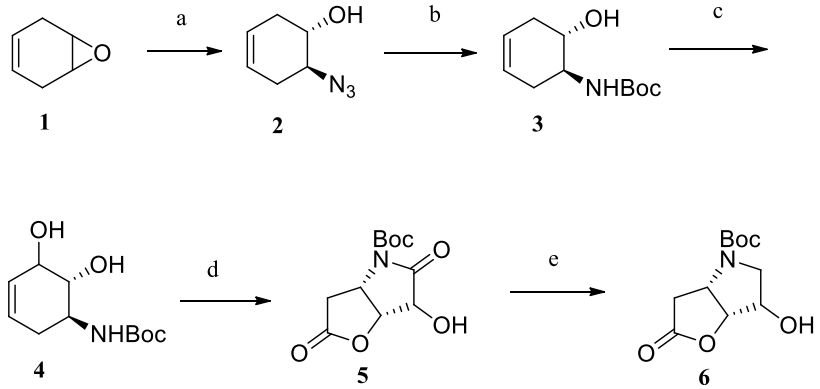
Borane DMS (0.016 mL, 0.17 mmol, 3 equiv.) was added dropwise to a stirred solution of compound 5 (0.015 g, 0.058 mmol, 1 equiv.) in 5 mL of dry THF at 0℃, then the mixture was left for 2 days under N_2 atmosphere. 2 mL MeOH was added until no evolution of gas, then the solvent was removed by rotary evaporator and this process was repeated three times. The resultant products were concentrated under a reduced pressure and purified using the column chromatography on silica gel with methanol: ethyl acetate (0.5: 9.5) to give compound **6** as a yellowish product. R_f = 0.9 (SiO_2, methanol: ethyl acetate 0.5:9.5), ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90-5.01 (m, 1H), 4.50-4.55 (m, 1H), 3.90-3.98 (m, 1H), 3.70-3.79 (m, 1H), 3.29-3.31 (m, 1H), 2.28-2.4 (m, 1H), 2.04-2.15 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 156.1, 83.2, 79.9, 63.2, 57.5, 44.1, 37.0, 28.3. IR (film): ν = IR (film): ν = 3399, 2918, 2850, 1771, 1732, 1462, 1261, 1097, 1023, 802. MS [CI, NH3] *m/z* (%) = 281.0 [M + 2NH_4^+ + 2H^+]; calculated for $C_{11}H_{17}NO_5$: 243.11.

RESULTS AND DISCUSSION

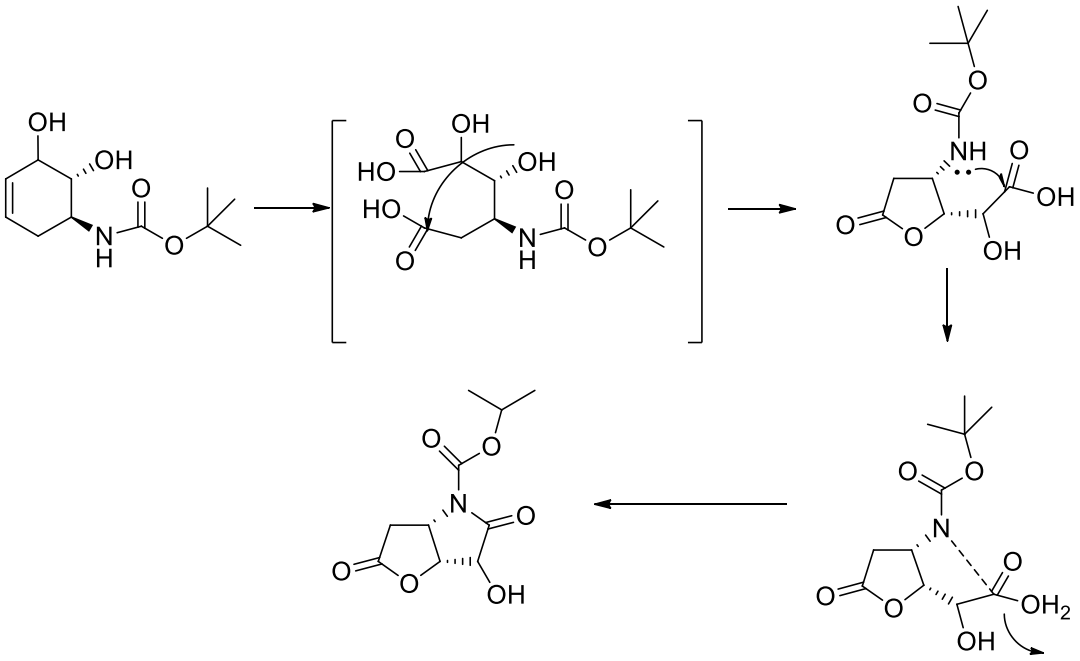
Scheme 1 shows the synthesis of compound **6** with epoxide ring opening of the starting material cyclohexdiene epoxide **1** via treatment with $TMSN_3$ in the presence of Salen complex catalyst to give 85% yield of **2** (1*S*,6*S*)-6-azido-3-cyclohexenol. Mesoepoxides are attractive starting materials for the synthesis of enantiopure chemical products. The azide functionility of (1*S*,6*S*)-6-azido-3-cyclohexenol **2** was reduced next using Pd/$(OH)_2$/C in the presence of triethylsilane, and the amine was then protected with di*tert*-butyldicarbonate to afford 78% of **3**.

The preparation of *tert*-butyl ((1*S*,6*S*)-5,6-dihydroxycyclohex-3-en-1-yl) carbamate **4** from *tert*-butyl ((1*S*,6*S*)-6-hydroxycyclohex-3-en-1-yl) carbamate **3** was carried out next via allylic hydroxylation with 46% yield. The allylic reaction involves the interaction of SeO_2 with olefin and followed by [2,3]-sigmatropic rearrangement. The *tert*-butyl hydroperoxide, TBHP acts as a co-oxidant that prevents interference during the reaction by reducing the selenium species.

Oxidative cleavage using ruthenium (III) chloride trihydrate in the presence of sodium metaperiodate in biphasic solution of CCl_4, MeCN and water gave the corresponding 63% yield of *N,O*-heterobicyclic octane intermediate **5**. The proposed mechanism of lactonization and lactamization is depicted in Scheme 2. In the synthesis of pyrrolizidine alkaloids, compound **5** presents an important synthetic inter-mediate [4]. Finally, the lactam carbonyl group in **5** was chemoselectively reduced to 71% of compound **6** using borane-dimethylsulfide as a reducing agent.



Scheme 1. Reagents and conditions: (a) Salen catalyst complex, $TMSN_3$, Et_2O, rt, 46 h, 85%. (b) Boc_2O, $Pd(OH)_2$/C, Et_3SiH, EtOH, rt, 24 h, 78%. (c) SeO_2, TBHP, EtOH, refluxed, 24 h, 46%. (d) biphasic solution of CCl_4:CH_3CN:H_2O, $RuCl_3.3H_2O$, $NaIO_4$, 0℃, 24 h, 63%. (e) Borane-DMS, THF, 0°C-rt., 28h, under N_2.



Scheme 2. The proposed mechanism of lactonization and lactamization cascade of lactone lactam **5**

CONCLUSION

In summary, we reported a facial synthesis of hydroxy *N*,*O*-heterobicyclic octanes, a key building block for retronecine bases alkaloids. This synthesis could be achieved through meso-cyclohexadiene epoxide ring opening employing Cr(Salen)-enabled desymmetrization, then $Pd(OH)_2/C$ – catalysed azide reduction, followed by NBoc protection and SeO_2 catalysed allylic hydroxylation, lactonization and carbonyl reduction.

ACKNOWLEDGEMENT

The authors would like to acknowledge the financial support from Universiti Teknologi MARA Malaysia (grant no. 600-RMC/LESTARI SDG-T 5/3 (164 /2019)).

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