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Synthesis of *trans tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl) carbamate: a potential precursor for (-)-muricatacin derivatives

Zurhana Mat Hussin[1], Sufi An-Nur Haris[2] and Mohd Tajudin Mohd Ali [2,3]*

[1] Faculty of Applied Sciences, Universiti Teknologi MARA, Pahang, Malaysia
[2] Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia
[3] Institute of Science, Universiti Teknologi MARA, Shah Alam, Malaysia

***Corresponding author**: Mohd Tajudin Mohd Ali
tajudinali@uitm.edu.my*

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ABSTRACT

This study examined the concise synthesis of dihydroxy *trans*-*N*-Boc cyclohexene, which could serve as a key starting material for the production of various biologically-active γ-butyrolactones, particularly (-)-muricatacin. The synthesis began with *meso*-monoepoxide cyclohexene and encompassing the catalytic opening of the epoxide ring via the Salen complex that yielded *trans*-azido cyclohexene, azide reduction, *N*-Boc protection, and allylic hydroxylation.

Keywords: azide reduction; γ-butyrolactone; epoxidation; (-)-muricatacin; ring opening

1. INTRODUCTION

Muricatacin is an important acetogenin (ACG) isolated from the soursop *Annona muricata* seeds, which attracted global interest for in-depth studies (Myint et al., 1990; Cortes et al., 1991; Myint et al., 1991), due largely to its cytotoxic and anti-proliferative activity against various human tumor cell lines (Makabe, 2007; Murcia et al., 2010). Also, two hydroxyl groups in the syn position of the muricatacin structure played a key function in the production of numerous ACGs, such as reticulatacin, *cis*-solamins A & B (Konno et al., 2010), giganin, and aza-*cis*-solamin B (Konno et al., 2010; Fletcher et al., 2013; Ohnishi et al., 2015).

In the past, the simple structure of compound **1** (-)-muricatacin had been rigorously synthesized using various approaches to maximize the yield while minimizing the number of chemical steps used. These strategies included the chiral pool approaches, enantioselective catalytic methods (Ali and Aliasak, 2017a; Ali et al., 2017b; Ali et al., 2018; Ali et al., 2021), and chiral resolution techniques (Srinivas et al., 2011; Doran, 2015; Cooze et al., 2017), among which, chiral pool approaches were widely used because of its high chemoselectivity towards the functional group by protecting group interventions. Although the chirality of muricatacin could be controlled using the chiral-pool approach, it involves many synthetic pathways.

In general, several chemicals, such as L-threitol (Somfai, 1995), D-xylose (Sreco et al., 2011), L-(+)-tartaric acid (Prasad and Gandi, 2008), D-(-)-lyxose (Tsai et al., 2012), D-mannitol (Kumaraswamy et al., 2010), and D-ribose (Ghosal et al., 2010) could serve as the starting material for the synthesis of muricatacin.

This study examined the synthesis of dihydroxy *trans-N*-boc cyclohexene from *meso*-monoepoxide cyclohexene via the Salen complex that catalyzed the opening of epoxide ring and azide reduction, followed by the amine protection and allylic hydroxylation. The present study was a subsection of our long-term endeavour in synthesizing biologically-active lactones and anticancer compounds. A two-step procedure was developed for functional group protection before the allylic hydroxylation in the production of the key starting material. This study would help shorten the steps required for the synthesis of muricatacin.

2. MATERIALS AND METHODS

2.1 Reagents and instrumentation

All chemicals and solvents used in this study were reagent grades; no further purification was conducted unless stated. All reactions were performed under an N_2 atmosphere in oven-dried round bottom flasks with continuously magnetic stirring. All synthesized products were determined by the thin layer chromatography (TLC) packed with silica gel 60 F_{254} (Merck KGaA) and visualised under UV light. 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}. Nuclear magnetic resonance (NMR) spectra for ^1H- and ^{13}C were recorded on an NMR spectrometer 300 MHz Bruker Avance II (Bruker, Billerica, MA) using tetramethylsilane (TMS) as the internal standard in chloroform solvent ($CDCl_3$) at ambient temperature, the chemical shift (δ) in ppm, and the *J* value in Hz. Mass spectrometry (MS) was assayed using a mass spectrometer GC-7890A, (Agilent, Santa Clara, CA). High-resolution masses were recorded on a separate mass spectrometer Thermoquest, Finnigan TSQ 7000 (Thermo Fisher Scientific, San Diego, CA).

2.2 Synthesis of (1S,6S)-6-azidocyclohex-3-enyloxytrimethylsilane (compound 4)

The catalyst Salen complex compound **3** (0.437 mg, 0.63 mmol, 2 mol%), was added into 4 mL of dry diethyl ether (Et_2O) (extra dry over molecular sieve) containing compound **2** 7-oxabicyclo[4.1.0]hept-3-ene (3.0 g, 31.2 mmol, 1 equiv.) and continuously stirred for 15 min. The mixture was then gradually added with trimethylsilylazide (3.8 mL, 32.8 mmol, 1.05 equiv.). The stirring was continued for 46 h at room temperature, after which the solvent was removed under vacuum to give a yellowish crude product. Purification by the column chromatography on silica gel (hexane: ethyl acetate, 9: 1) generated 47% (3.1 g) yield with 85% enantioselectivity. of compound **4** (yellowish oil). R_f = 0.58 (SiO_2, hexane:ethyl acetate 9:1); ^1H NMR (300 MHz, $CDCl_3$): δ 5.43-5.59 (m, 2H), 3.62-3.72 (m, 1H), 3.42-3.52 (m, 1H), 2.40-2.52 (m, 2H), 2.05-2.10 (m, 1H), 1.93-2.04 (m, 1H), 1.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.7 (2C), 123.2 (2C), 70.1, 63.5, 33.0, 30.2, 0.0 (3C); IR (film): ~ ν 3343, 2958, 2906, 1655, 1252, 1108, 668 cm^{-1}. MS [CI, NH_3]: *m/z* = 212.1 $[M + H]^+$.

2.3 Synthesis of tert-butyl (1S,6S)-6-(hydroxy) cyclohex-3-enylcarbamate (compound 5a) and tert-butyl (1S,6S)-6-(trimethylsiloxy)cyclohex-3-enylcarbamate (5b)

The reagent di-tert-butyldicarbonate (Boc_2O; 0.45 g, 2.04 mmol, 2 equiv.) was added to 4 mL ethanol containing compound **4** (0.21 g, 1.02 mmol, 1 equiv.) and followed by 20% $Pd(OH)_2/C$ (10.2 mg) at room temperature and the sequential addition of triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.). The resultant mixture was continuously stirred for 24 h and filtered through Celite. The filtrate was concentrated under a reduced pressure, purified using the column chromatography packed with silica gel; the yellowish crude product was eluted with petroleum ether: ethyl acetate (15: 0.5) and crystallized from hexane: ethyl acetate (8:2) to yield 0.18 g (78%) compound **5a** as a white solid and 0.032 g (12%) compound **5b** as yellowish oil. R_f = 0.25 (SiO_2, hexane: ethyl acetate 21: 7); melting point 76-78°C, ^1H NMR (300 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): 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.

Meanwhile, compound **5b** was prepared from compound **2** in the same manner as compound **5a**. R_f = 0.75 (SiO_2, hexane: ethyl acetate, 21: 7); ^1H NMR (300 MHz, $CDCl_3$): δ5.55-5.60 (m, 2H), 4.73 (brs,1H), 3.66-3.72 (m, 1H), 3.27-3.33 (m, 1H), 2.52-2.58 (m, 1H), 2.46-2.48 (m, 1H), 2.12-2.18 (m, 1H), 1.95-2.01 (m, 1H), 1.46 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 157.1, 124.2 (2C), 124.0 (2C), 76.9, 68.9, 51.0, 32.9, 29.9, 28.3 (3C), 0.0 (3C); IR (film): ν = 3020, 2929, 1735, 1589, 1217, 1347, 756.8, 669.2 cm^{-1}. HRMS [CI, NH_3] *m/z* = 285.24, calculated for $[C_{14}H_{27}NO_3Si$: 285.1760, found 285.1758].

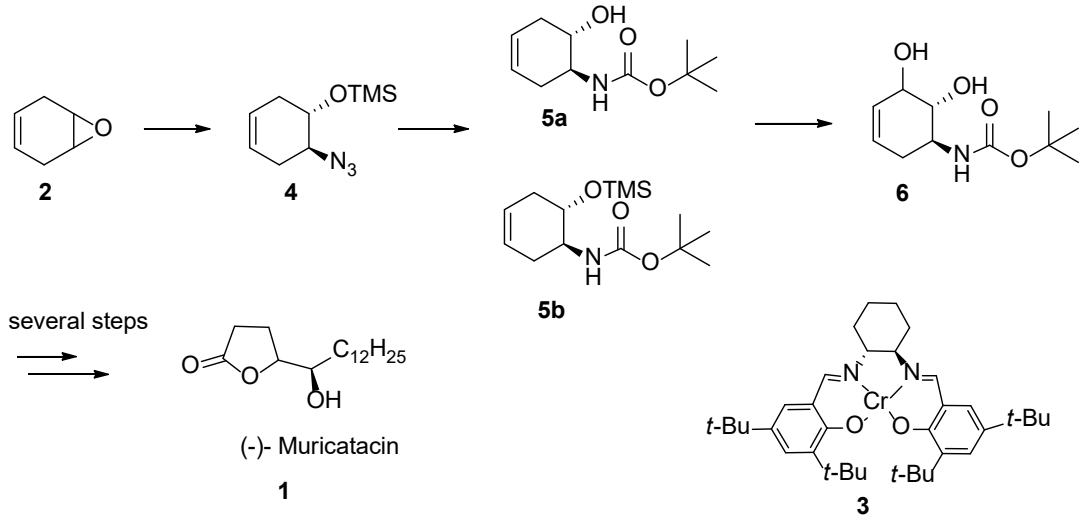
2.4 Synthesis of tert-butyl (5,6-dihydroxycyclohex -3-en-1-yl)carbamate (compound 6)

The reagent of SeO_2 (grounded, 0.091 g, 0.82 mmol, 1 equiv.) was added to 3 mL ethanol containing compound **5a** (0.165 g, 0.77 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 10 min, sequentially added with *tert*-butylhydroperoxide (TBHP, 0.025 mL, 1.4 mmol, 2 equiv.), and further refluxed for 24 h. The resultant products were concentrated under a reduced pressure and purified using the column chromatography on silica gel with petroleum ether: ethyl acetate 27: 3 to yield 0.09 g (56%) compound **6** as a white solid. R_f = 0.4 (SiO_2, hexane: ethyl acetate 21: 7); melting point 73-75°C, ^1H NMR (300 MHz, $CDCl_3$): δ 5.40-5.50 (m, 2H), 5.2 (brs, IH), 3.66-3.75 (m, 2H), 3.25-3.44 (m, 1H), 2.45-2.63 (d, 2H, *J* = 15.6), 2.15-2.25 (d, 1H, *J* = 18), 1.90- 2.05 (d, 1H, *J* = 19), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 124.5 (2C), 124.4 (2C), 79.3, 69.4, 56.4, 52.1, 33.9, 31.3, 28.3 (2C); IR (film): 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) $[M + Na^+]$; HRMS (Cl, NH_3); calculated for $C_{11}H_{19}NO_4$: 229.1314, found 252.1207 $[M + Na]^+$.

3. RESULTS AND DISCUSSION

Scheme 1 shows the synthesis of compound **6** *tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl)carbamate, which was a key intermediate for the production of (-)-muricatacin. The synthesis of compound **6** began with compound **2** *meso*-monoepoxide cyclohexane (36% in yield), which was produced in two steps from benzene via the Birch reduction to give 1,4-cyclohexadiene followed by the epoxidation with *m*-CPBA (Perlman and Albeck, 2001). The introduction of azide functionality in the initial step practically produced *N*-based substituents that could be manipulated in side-chain reactions; it was achieved through asymmetric ring-opening of compound **2** *meso*-monoepoxide using trimethylsilylazide and the compound **3** Salen catalyst complex. In this study, the Martinez method was used with the Salen catalyst serving as a ligand in the epoxide ring-opening reaction due to its tunable steric effect, electronic properties, and its ability to coordinate with various metallic ions (Cooze et al., 2017). The asymmetric ring-opening gave the *R,R* configuration of the compound **4** azido trimethylsiloxy cyclohexene in 47% yield with high ee, i.e., 85%; 72%, 81% ee (Martinez et al., 1995).

The azide reduction and *N*-Boc protection of compound **4** azido trimethylsiloxy cyclohexene using $Pd(OH)_2/C$ and triethylsilane in the presence of Boc_2O gave rise to a mixture of compounds **5a** (78%) and **5b** (12%). Finally, the allylic hydroxylation of compound **5a** using SeO_2 and *tert*-butyl hydroperoxide produced the compound **6** *tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl)carbamate, which was the targeted key starting material for the synthesis of (-)-muricatacin. The chemoselectivity of compound **6** *tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl)carbamate towards functional groups rendered its synthesis feasible (Fernandes et al., 2020). In future studies, we would consider manipulating one protecting group and five steps for the synthesis of muricatacin starting from the compound **6**.



Scheme 1. The synthesis of compound **6** *tert*-butyl (5, 6-dihydroxycyclohex-3-en-1-yl)carbamate via three reactions with various reagents: (i) compound **3** (*R,R*) Salen complex (2 mol%), trimethylsilyl azide ($TMSN_3$), diethyl ether (Et_2O), room temperature (rt), 46 h, 47% yield, and 85% enantiomeric excess (ee), (ii) *ditert*-butyl dicarbonate (Boc_2O), palladium hydroxide/carbon ($Pd(OH)_2/C$), Et_3SiH, rt, 24 h, 78% **5a** and 12% **5b**, (iii) ethanol (EtOH), selenium dioxide (SeO_2), *tert*-butyl hydrogen peroxide (TBHP), refluxed, 24 h, 56%

4. CONCLUSION

The synthesis of the key precursor of compound **6** *tert*-butyl (5,6-dihydroxycyclohex-3-en-1-yl)carbamate from *meso*-monoepoxide cyclohexene could be achieved using three synthetic routes via the catalytic epoxide ring-opening reaction, azide reduction, *N*-Boc protection, and allylic oxidation. The functionality groups on the cyclohexene ring could potentially be manipulated to produce variable synthetic drugs, particularly (-)-muricatacin.

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