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Vibrational Circular Dichorism for Absolute Configuration of (1*S*,2*S*)-Azido Trimethylsilylcyclohexene: Useful for Muricatacin Intermediate Synthesis

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A simple technique for absolute configuration determination of (1*S*,2*S*)-azido trimethylsilylcyclohexene **3** enantiomer is described. Samples were synthesized from racemic monoepoxide **1**, via asymmetric epoxide ring opening catalyzed by (*R*,*R*)-salen complex, *L*-**2** in the presence of trimethyl silylazide, $TMSN_3$. (1*S*,2*S*)-azido trimethylsilylcyclohexene **3** and its corresponding racemic adduct were analyzed using VCD spectrometer. The VCD spectrums of boths compounds were recorded as linear regressions (dABS.) vs wavenumbers (cm^{-1}). The major selected bands were analyzed to determine the absolute configuration of (1*S*,2*S*)-azido trimethylsilylcyclohexene **3**. Compound **3** then underwent reduction and protection sequence to give **4**. Allylic hydroxylation of **4** gave rise to compound **5** which was subjected to oxidative cleavage and lactonization steps that successfully afforded Muricatacin intermediate **6**.

Keywords: Azido trimethylsilylcyclohexene; absolute configuration; vibrational circular dichorism (VCD); salen complex; Muricatacin

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Natural remedies derived from plants have been used for centuries around the world in traditional medicine for a wide range of diseases. Based on this natural products play a pivotal role in the search and development of new drugs entities to combat a variety of malignant and infectious diseases.

For some time, natural product chemists have been discovering new potentially active compounds with chiral carbons present in the molecule from natural products [1]. Identification of carbon stereoinduction is a vital part in molecular structure determination. Several approaches to determine the stereochemical integrity such as applying NMR and X-ray diffraction methods have been in practice for decades but the drawback for NMR spectrometer is its inability to discriminate the enantiomers without additional support techniques. While X-ray diffraction analysis relies heavily on sample preparation where this technique requires crystal compounds for analysis. Thus, vibrational circular dichroism (VCD) techniques has become popular as it can provide stereo information of enantiomers in solutions.

VCD is the extension of ECD into infrared regions of the spectrum where vibrational transitions occur in the ground electronic state of the molecule. Electronic Circular dichroism (ECD) is based on the differential absorption of left and right-handed circularly polarized light. Therefore, the spectra of chromophores can have positive and negative bands in the observed wavelength range (far UV) [2]. The use of VCD to determine the absolute configuration of natural products have been extensively studied by organic and medicinal chemistry scientist.

The use of VCD for absolute configuration determination of chiral metabolites has been investigated on terpenoids (epoxythymol areolal) type molecules [3], monoterpenoids (podocephalyl acetate) [4], lactones [5], diterpenoids 3-oxirane [6], horminone and taxoquinone [7], icetexone and conacytone [8], picraviane A [9], guaiaretic acid aromatic compounds [10], aryltetralin lactone [11] and cascarosides [12].

In this work, we report a method in identifying the absolute configuration of (1*S*,2*S*)-azido trimethylsilylcyclohexene **3** enantiomers using VCD technique as well as the synthetic strategy for the synthesis of Muricatacin intermediate from compound **3**.

EXPERIMENTAL

Reagents and Materials

All commercial reagents were used as supplied without further purification. All non-aqueous reactions were carried out under an inert atmosphere of dry nitrogen using glassware dried via heating under reduced pressure. All used solvents were purified according to standard procedure where necessary. Column chromatography was performed using Merck

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9385 Kieselgel 60-45 (230-400 mesh) with Merck Millipore silica gel 60. Thin layer chromatography was carried out using aluminum backed plates coated with Merck Kieselgel 60 GF254. Plates were visualized under UV light at 254 nm.

Melting point were determined with a Buchi SMP 20 without corrections. ^{1}H NMR-spectra and ^{13}C NMR-spectra were recorded on Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shifts were reported in δ (ppm) relative to ($CDCl_3$, 7.26 ppm) and tetramethylsilane (TMS, 0.00 ppm) as internal standards. The coupling constant (*J*) was reported in Hertz (Hz). IR-Spectra were recorded on a Bio-Rad Excalibur FTS 3000 spectrometer, equipped with a Golden Gate Diamond Single Reflection ATR-System. Gas Chromatography was done with Agilent Technologies 7693 equipped with chiral column (cyclodex-B). Mass spectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles. Optical rotation was measured at rt on a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm or 0.1 dm cell. VCD measurements experiments were carried out using JASCO model FVS-6000 spectrometer equipped with BaF_2 window. The scan range was 2000- 850 cm^{-1} and resolution of 4 cm^{-1} with a path length 25-100 μm. All samples were prepared in 0.1 M $CHCl_3$.

Synthesis of (1*S*,2*S*)- Azido Trimethylsilylcyclohexene 3

To a mixture of epoxide **1** (0.61 g, 6.32 mmol, 1 eq) in 2.1 ml of diethyl ether, complex *L*-**2** catalyst was introduced (0.088 mg, 0.126 mmol, 2 mol%). The mixture was stirred for 15 minutes and subsequently trimethylsilylazide (0.88 ml, 6.63 mmol, 1.05 eq) was added slowly. The reaction mixture was stirred for 46 hours at room temperature then the solvent was evaporated under reduced pressure to give a yellowish crude product, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 9:1) to yield 0.84 g or 68% pale-yellow oil of **3**. R_f = 0.83 (SiO_2, hexanes/ethylacetate 9:1); $[\alpha]_D^{20}$ = -14.8 (c = 0.4, CH_2Cl_2), 84% ee; (Lit[11]: 72%, 83% ee).

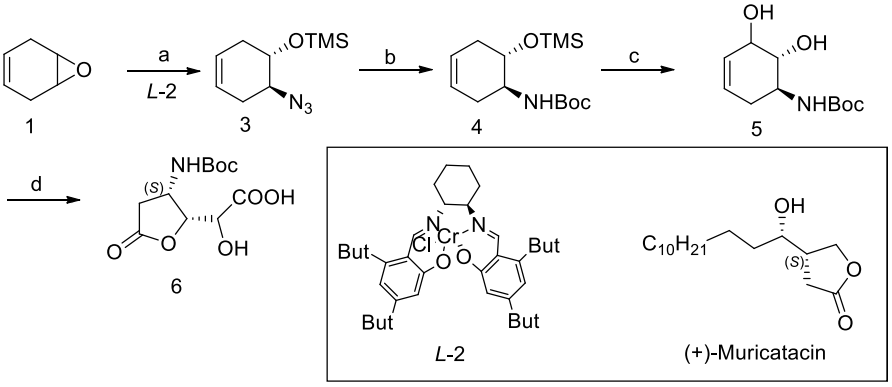
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.48-5.61 (m, 2H, H-1,H-2), 3.73-3.84 (m, 1H, H-5: $(CH_3)SiOCH$), 3.49-3.59 (m, 1H, H-4:N_3CH), 2.32-2.48 (m, 2H, H-3: N_3CHCH_2), 2.08-2.20 (m, 1H, H-6: $(CH_3)SiOCHCH_2$), 1.90-2.03 (m, 1H, H-6: $(CH_3)SiOCHCH_2$), 1.98 (s, 9-H, TMSO); **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ = 124.6 (C=C), 123.9 (C=C), 71.9 (C_{quart}, C-5), 62.9 (C_{quart}, C-4), 34.7 (C-6), 30.9 (C-2), 0.0 (TMSO-C); **IR** (Film): $\tilde{\nu}$ = 2957, 2905, 2107, 1438, 1250, 1140, 881, 840, 748, 667 cm^{-1}. **MS** [CI, NH_3] : m/z (%) = 212.1 (11) [M + H^+], 184.1 (29.9) [(M + H^+) – N_2].

Synthesis of Azido Trimethylsilylcyclohexene *rac*-3

To a mixture of epoxide **1** (0.50 g, 6.02 mmol, 1 eq) in 2.1 ml of diethyl ether, trimethylsilylazide (0.88 ml, 6.63 mmol, 1.05 eq) was added. The reaction mixture was stirred for 24 hours at room temperature then the solvent was evaporated under reduced pressure to give yellowish crude product, which was then purified by column chromatography on silica gel (petroleum ether: ethyl acetate, 9:1) to yield 0.54g of *rac*-**3**.

Synthesis of *tert*-butyl (6-(trimethylsilyl)oxy) cyclohex-3-en-1-yl)carbamate 4

The reagent di-*tert*-butyldicarbonate (0.45 g, 2.04 mmol, 2 equiv.) was added to 4 mL ethanol containing compound **3** (0.21 g, 1.02 mmol, 1 equiv.) followed by 20% palladium hydroxide in carbon (10.2 mg) at room temperature and the sequential addition of triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.) was performed. The resultant mixture was continuously stirred for 24 h and filtered through Celite.



Scheme 1. The synthesis of (1*S*,2*S*)- Azido Trimethylsilylcyclohexene from 1,4-Cyclohexadiene.
Reagent and conditions: (a) (*R*,*R*)-Salen complex *L*-**2** (2 mol%), $TMSN_3$ (1.05 equiv), rt, 46 h, 68%, 84% ee (b) Boc_2O, $Pd(OH)_2/C$, Et_3SiH, rt, 24 h, 78% . (c) EtOH, SeO_2, TBHP, rt, 24 h, 56%. (d) $RuCl_3.3H_2O$ (8.3% equiv., 0.03 mmol), $NaIO_4$ (4.1 equiv.), CCl_4-MeCN-H_2O (1:1:2), 0°C, 29%.

The filtrate was concentrated under reduced pressure, purified using the column chromatography packed with silica gel; the yellowish crude product was eluted with pet ether: ethyl acetate (15: 0.5) and crystallized from hexane: ethyl acetate (8:2) to yield 0.18 g (78%) compound **4** as a white solid. R_f = 0.25 (SiO_2, hexanes: ethyl acetate 21: 7); M.p. 76-78ºC, ^{1}H 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.

Synthesis of *tert*-butyl (5-hydroxy-6-(trimethylsilyl) oxy) cyclohex-3-en-1-yl)carbamate 5

Selenium dioxide reagent (grounded, 0.091 g, 0.82 mmol, 1 equiv.) was added to 3 mL ethanol containing compound **4** (0.165 g, 0.77 mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 10 min, then added with *tert*-butylhydroperoxide (0.025 mL, 1.4 mmol, 2 equiv.) was sequentially added, and further refluxed for 24 h. The resultant products were concentrated under reduced pressure and purified using the column chromatography on silica gel with pet ether: ethyl acetate 27: 3 to yield 0.09 g (56%) compound **5** as a white solid. R_f = 0.4 (SiO_2, hexanes: ethyl acetate 21: 7);); M.p. 73-75ºC, ^{1}H 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 [$M + Na]^+$.

Synthesis of 2-(3-((*tert*-butoxycarbonyl) amino)-5-oxotetrahydrofuran-2-yl)-2-hydroxyacetic acid, 6

To a stirred solution of compound **5** (0.018 g) in 4 ml of biphasic solution of carbon tetrachloro methane: acetonitrile:water (ratio 1:1:2) 0.09 g (8.3% equiv., 0.03 mmol) ruthenium trichloride hydrated ($RuCl_3$. $3H_2O$) at was added at 0 ºC. Then, 0.34 g (4.1 equiv., 1.61 mmol) of sodium periodate was added to the mixture and the reaction was stirred continuously for 8 hrs. Subsequently, the mixture was diluted with 10 ml H_2O, extracted with 15 ml DCM and dried over MgSO4. This extract was then filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate: methanol, 9:1 to obtain 0.05 g (29%) of oily compound **6**. R_f = 0.83 (Hexane: Ethyl acetate, 9:1), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 1H), 5.06-5.14 (m, 1H), 4.56-4.65 (m, 1H), 4.14-4.35 (m, 1H), 2.80-2.99 (m, 2H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 163.8, 149.5, 79.9, 71.1, 64.7, 49.1, 36.5, 27.9. IR (Film): ν = 2927, 2253, 1728, 1466, 1383, 1262, 1095. MS [CI, NH_3] *m/z* (%) = 276.1 ($M + H^+$]; calculated for $C_{11}H_{17}NO_7$: 275.1.

RESULTS AND DISCUSSION

The synthesis of (1*S*,2*S*)- azido trimethylsilylcyclohexene **3** began with the enantioselective asymmetric ring opening reaction. The Cr(III)-Salen complex catalyst is highly effective for enantioselective ring opening of epoxides. This step employed Salen catalyst complex *L*-**2** with trimethylsilylazide to furnish the azido trimethylsiloxy cyclohexene **3** in 68% and 84% *ee* as depicted in Scheme 1. Determination of enantiomeric excess (*ee*) was conducted by using GC (Chiral column). The results showed almost similar enantiomeric excess compared with the authentic value [13]. The chemical structure configurations were identified and enantiomer excess were previously determined by chiral GC to be 75%, 83% *ee* [13].

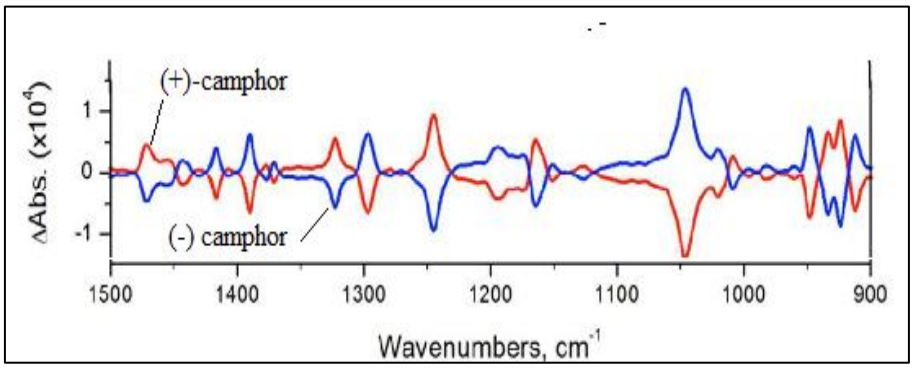


Figure 1. VCD spectra of the different enantiomeric of (+) camphor (red) and (-) camphor (blue) in CCl_4.

This evidence was rationalized by the formation of a chromium-azide coordinated species as an active catalyst, which could be driving the enantioselection of this process, affording the preferred *trans*- azido silyl ether **3**.[13] In addition, the corresponding racemic azido silyl ether *rac*-**3** was also synthesized using similar procedure but in the absence of forementioned catalyst. A 75% yield of *rac*-**3** was produced Scheme 1.

The use of VCD for absolute configuration (AC) determination of chiral metabolites was successfully investigated by [14] on campor.

Figure 1, shows the VCD spectra for (+) camphor and (-) camphor enantiomers in CCl_4 solution. The VCD spectra of both enantiomers are 'mirror-images'. There are several bands appearing at 1296, 1244, 1046, 947, 933 and 924 cm^{-1} with the most sensitive (largest slope) corresponding to the 1046 cm^{-1} band. The (+) camphor exhibits positive slopes, whereas the (-) camphor exhibits negative slopes [14].

Compound **3** and its corresponding *rac*-**3** were subjected to a methodology for the determination of absolute configuration using VCD spectroscopy analysis (JASCO Fvs-6000). Both compounds **3** and *rac*-**3** in 0.1 M $CHCl_3$ were analyzed at 25 °C. The wavenumbers range was setup between 1500 and 850 cm^{-1} (Figure 2).

Figure 2 shows the linear regressions of VCD intensities (dAbs) *vs* wavenumber (cm^{-1}) for both compounds. The spectrum for compound *rac*-**3** is depicted at the top and their corresponding enantiomer, **3** spectrum is at the bottom. For *rac*-**3**, there are several slopes at 1221 (larger slope at the positive band), 1214 (larger slope at the negative band), 1184, 1167, 1153, 1089 and 1054 cm^{-1}.

In compound **3**, there are larger slope at the negative band appeared at 1217, followed by 1184, 1170, 1086 and 1053 cm^{-1}. From this spectrum, we could conclude that compound **3** has (*S*,*S*) configuration since the band at 1217 cm^{-1} appeared at the negative band. Another positive band appeared at 1221 cm^{-1} in *rac*-**3** spectrum (at the top), would be suggested for (*R*,*R*)-**3**.

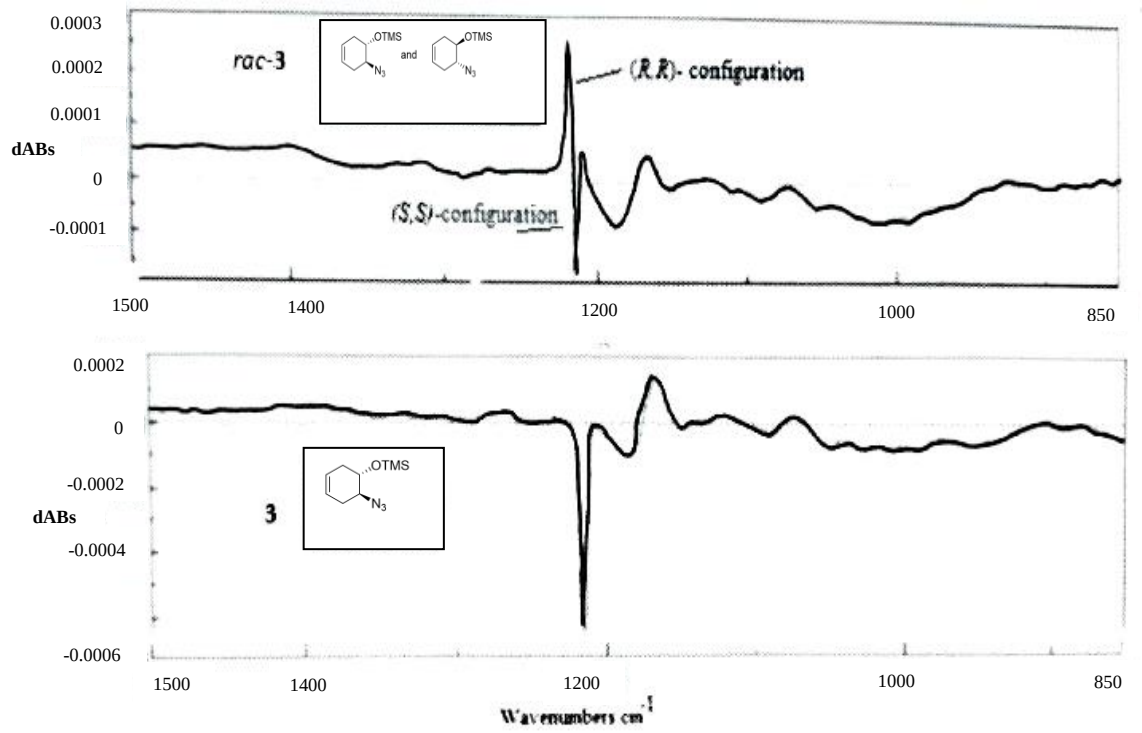


Figure 2. VCD spectra of 0.1 M *rac*-3 (at the top) and 0.1 M 3 (at the bottom) in $CHCl_3$ *VCD Conditions*: 25 °C, wavenumbers between 2000-850 cm^{-1}, number of scan: 2000, length of the cuvette sampler: 10 mm, resolution: 4 cm-1, speed: 5 C/min.

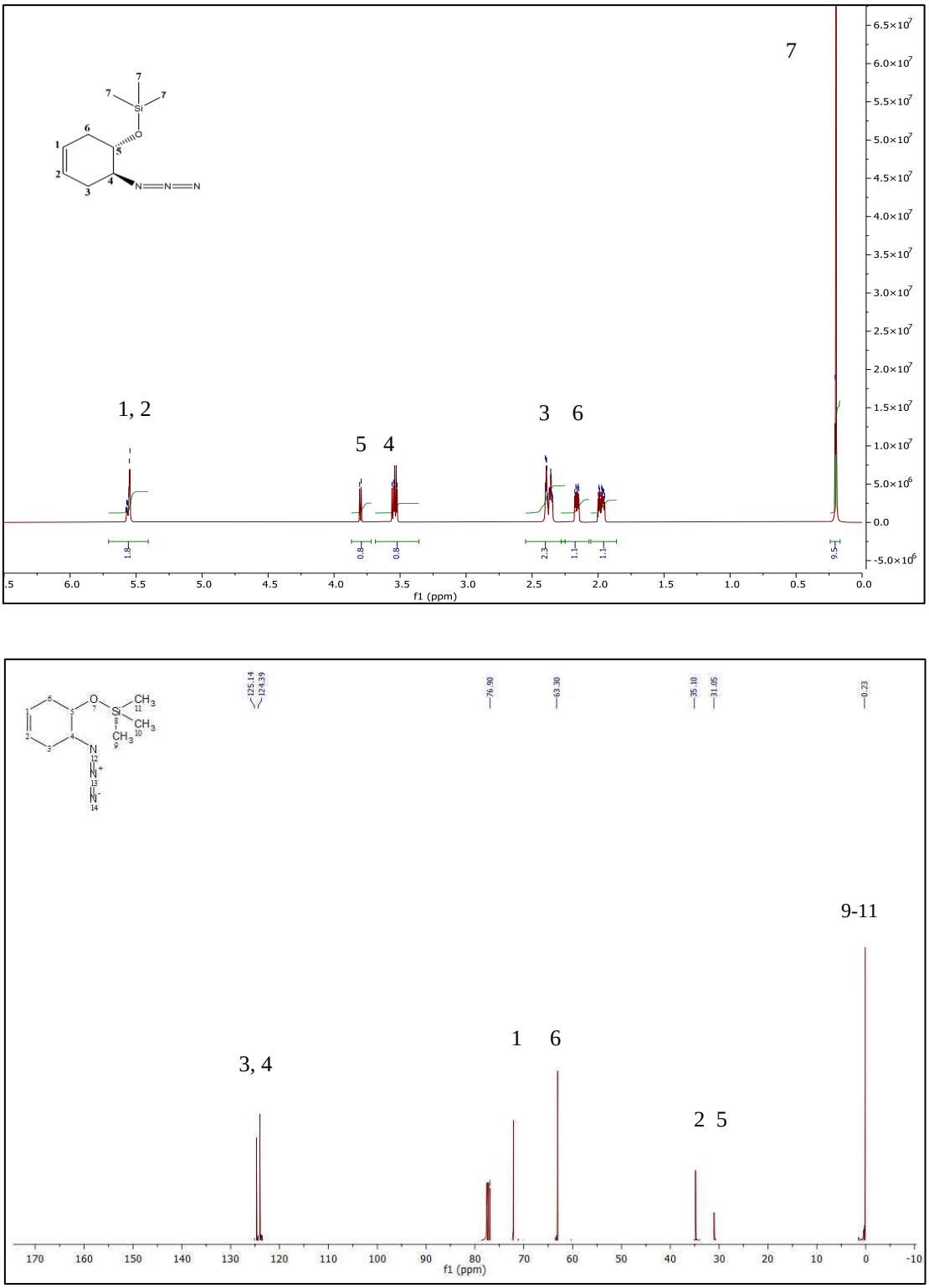


Figure 3. ^{1}H and ^{13}C NMR Spectrum of Compound **3**.

With these results, we have successfully utilised VCD technique as a new method for the absolute configuration determination of both enantiomers of compound **3**. The VCD spectrums obtained were analyzed together with the chemical structure of (1*S*,2*S*)-azido trimethylsilylcyclohexene. The (*S*,*S*) configuration of compound **3** determined by VCD satisfied with the (*S*,*S*) configuration reported by Martinez and co-workers [13].

After confirming the stereo integrity of compound **3** as (1*S*, 2*S*), it was next carried forward in a series of reactions to synthesis lactone **6**, an intermediate that can be used to synthesis muricatacin.

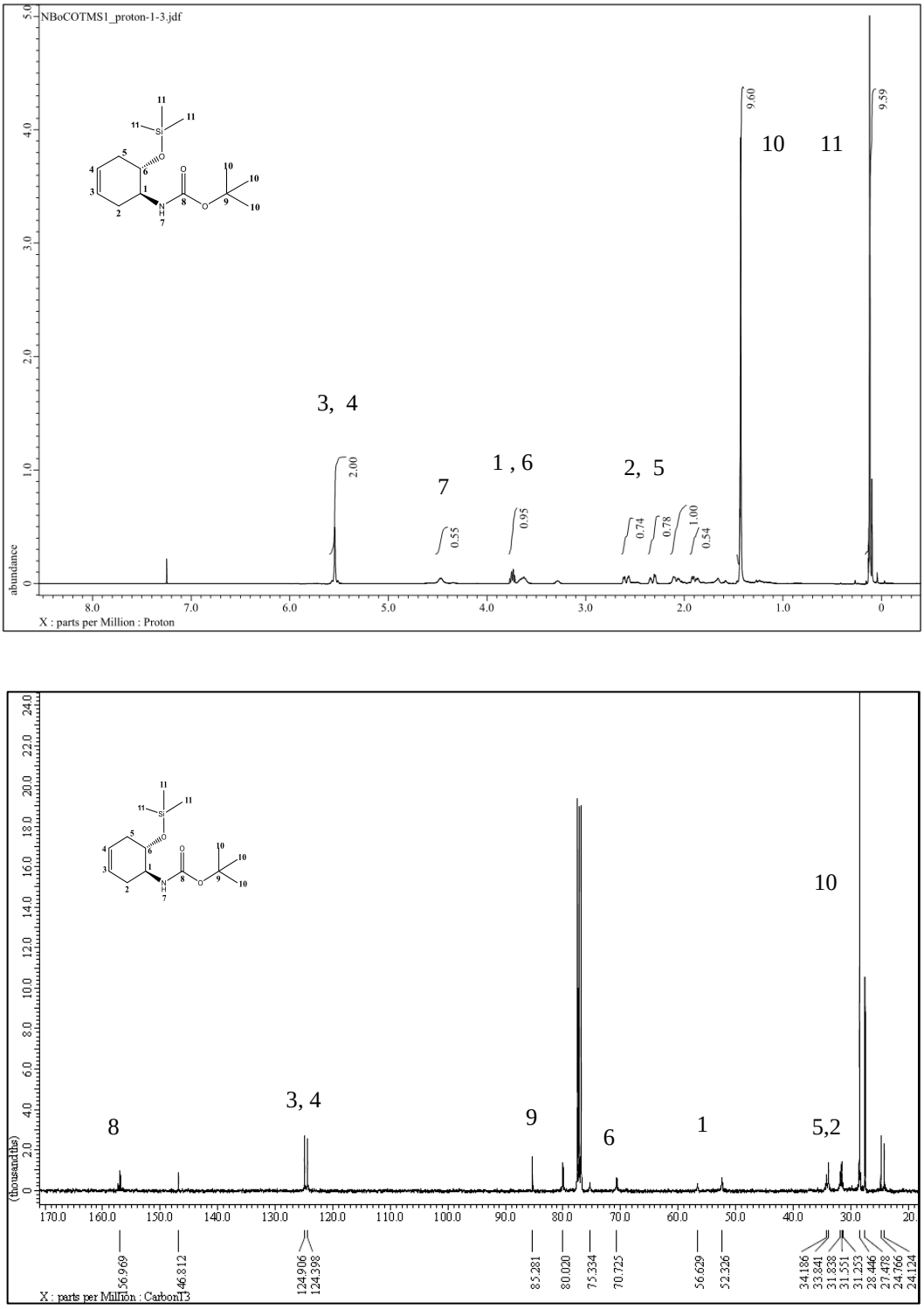


Figure 4. ^{1}H and ^{13}C NMR Spectrum of Compound **4**.

The azide *insitu* reduction of cyclohexene **3** (the NMR spectrums shown in Figure 3) using Boc anhydrate and $Pd(OH)_2/C$ in the presence of triethylsilane Et_3SiH gave compound **4** in good yield of 78% (Figure 4 NMR spectrums). Subsequently, allylic hydroxylation was performed to **4** by utilising SeO_2 and catalysed by TBHP to afford compound **5** (Figure 5 NMR spectrums) in a moderate 56% yield. The following treatment of **5**, with $RuCl_3.3H_2O$ in the presence of $NaIO_4$ in a biphasic solution of CCl_4-MeCN-H_2O successfully furnished muricatacin intermediate **6** in low yield (29%). In this step, compound **5** went through two reactions sequence that involve cyclohexene ring cleavage and lactonization. Ring closure is facilitated by the formation of hydrogen bonding from migrating hydrogen atom to the hydroxyl functionality and creating H_2O as the leaving group. Nucleophilic attack of the nitrogen lone pair towards carbonyl group afforded lactone **6**. [15-17] The reaction mechanism is depicted in

Figure 6. Compound **6** is expected to inherit the stereo integrity of compound **3** which is required for (+)-muricaticin synthesis. Compound **6** is a useful intermediate that can be manipulated further towards the natural product muricatacin or its analogues (Scheme 1).

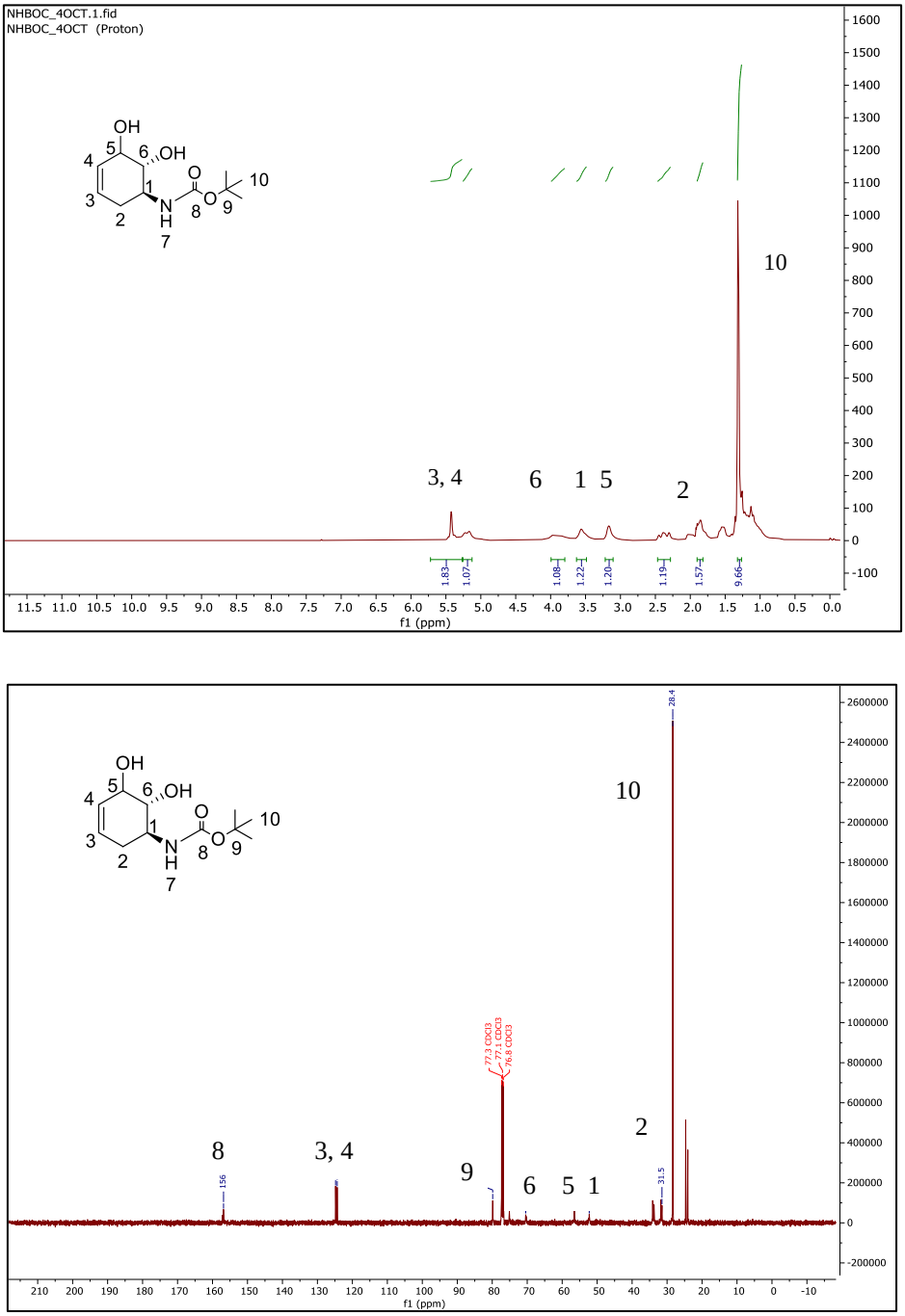


Figure 5. ^{1}H and ^{13}C NMR Spectrum of Compound **5**.

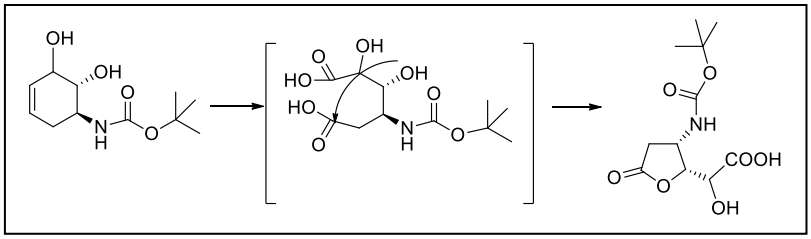


Figure 6. The proposed mechanism for lactonization of **5**.

CONCLUSION

In this study, we have successfully determined the absolute configuration of (1*S*,2*S*)-azido trimethylsilyl-cyclohexene **3**, using VCD analysis and have also synthesized muricatacin intermediate **6** from compound **3** via reduction-protection, allylic hydroxylation and alkene cleavage-lactonization steps.

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