Supporting Information

Improved Synthesis and Isolation of Bedaquiline

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1. Experimental Details

General: All reagents and solvents were purchased from Sigma Aldrich and Merck unless stated otherwise. All air and moisture-sensitive reactions were carried out in anhydrous solvents under argon using oven or flame-dried glassware. All solvents were distilled prior use: THF, toluene, and diethyl ether were distilled from sodium (Na) and benzophenone ketyl and hexane from calcium hydride. Reactions at -78°C were conducted on an ice bath made from dry carbon-dioxide and acetone. Flash column chromatography was carried out using silica gel 60 (70- 230 mesh), and thin-layer chromatography were carried out using Merck Kieselgel F254 aluminum-backed silica plates. All reagents were of analytical grade.

1.1 Instruments

Bruker Avance III 400 MHz Nuclear Magnetic Resonance (NMR) spectrometer was used to record all ^{1}H NMR spectra deuterated chloroform as the solvent. ^{1}H chemical coupling constants are reported in parts per million (ppm) downfield from tetra-methylsilane (TMS), and coupling constants (*J*) are reported in Hertz [Hz]. The following abbreviations are used to designate signal multiplicity: (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet.

Shimadzu Liquid Chromatography-Mass Spectrometer (LC/MS-2020) was used to monitor all reactions YMC-Triart C18 Column (150 x 4.6 mm, 5 μm) and a mass spectrometer detector.

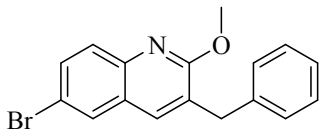
The solvents, acetonitrile, and methanol (Aldrich, co.ltd) were purchased and used after degassing for 30 minutes. All the spectra were viewed at 220nm.

Sepiatec Preparative Super-critical Fluid Chromatography was used to separate the (RS, SR)-BDQ diastereomer using the Chiralpak IA (0.4 x 1cm) column (Diacel Chemical Industries, Ltd). The mobile phase was composed of carbon dioxide, 6% of (50/50 methanol: isopropanol) as a modifier with 0.3% isopropyl amine (IPA) as an additive. The injection volume used was 100µl at a flow rate of 5 ml/min, and back pressure was 150 bar at a column compartment temperature of 40 °C using the stacked injection programme. All spectra were viewed at 220nm.

Chiral High-Performance Liquid Chromatography (Agilent technologies) was used for the determination of enantiomeric excess using a Chiralpak IA (0.4 x 1cm) column (Diacel Chemical Industries, Ltd). The solvent system that was used was 0.5% isopropanol in hexane with a 0.5 ml/min flowrate and 5µl injection volume, and the column temperature used was 25°C. All the spectra were viewed at 220nm.

2. Preparation of reagents

3-benzyl-6-bromo-2-methoxyquinoline



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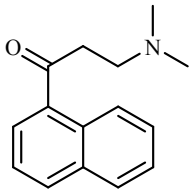
Compound **1** was purchased from DLD Scientific, South Africa and was tested to be >95% of purity through ^{1}H NMR analysis. White solid; m.p 84°C; Rf: 0.5 (50/50: EtOAc/ Hexane) ^{1}H NMR (400MHz,) δ= 7.21- 7.75 (m, 9H), 4.07 (s, 3H), 4.02 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$) 144.1, 138.8, 135.7, 131.8, 129.2, 129.0, 128.5, 126.0, 117.3, 53.7, 36.0 ppm. MS (ESI): m/z 327, found 328 $[M+H]^+$

Isolation of 3-(dimethylamino)-1-propionaphthone



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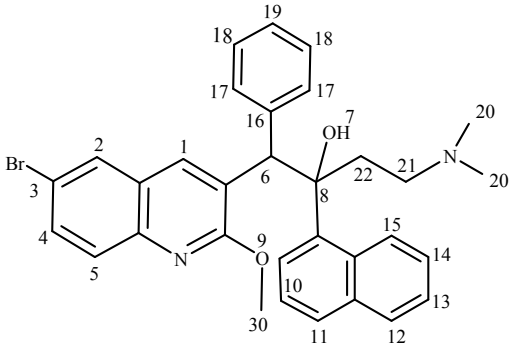
3-(dimethylamino)-1-propionaphthone-HCl (200 mg) was added to 5% $NaHCO_3$ in water (50 ml), thereafter dichloromethane (3x25 ml) was used for the extraction. The organic layers free from HCl (confirmed by using pH paper) was dried over anhydrous magnesium sulphate ($MgSO_4$) and concentrated in *vacuo*. The yellow oil of the neutral 3-(dimethylamino)-1-propionaphthone was further washed with toluene to remove any aqueous traces followed by submission to the high vacuum pump for 3 hours to remove residual solvent. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.56 (d, 1H, J= 8.49 Hz), 7.98 (d, 1H, J= 8.29), 7.87 (d, 2H, J= 6.68), 7.60 -7.48 (m, 3H), 3.24 (t, 2H), 2.81 (t, 2H); 2.28 (s, 6H). ^{13}C NMR (100MHz, $CDCl_3$) 203.7, 136.4, 134.3, 132.8, 130.4, 128.7- 124.7, 55.0, 45.7, 40.8 ppm. MS (ESI): m/z 226, found 228 $[M+H]^+$

3. Experimental Procedures and Characterization Data

1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol



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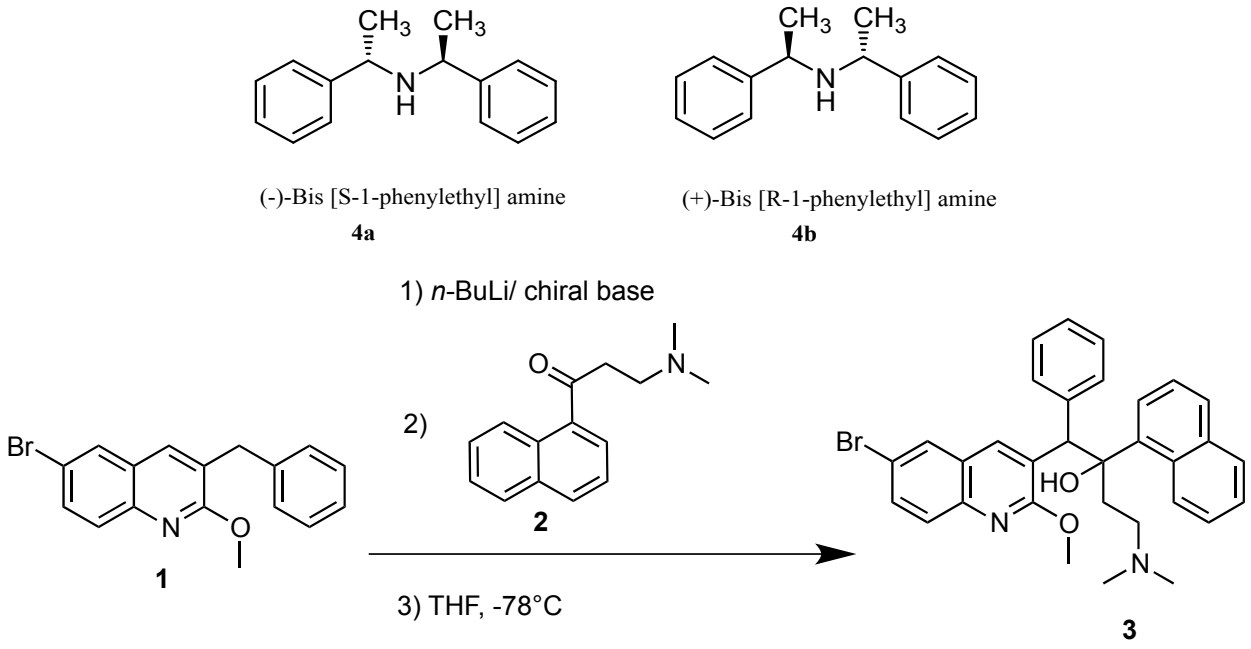
The *dr* was measured by integration of the chiral proton (H6) where 5.89ppm (desired) and 5.73 ppm (undesired) from the crude ^{1}H NMR spectrum.

General Procedure for the synthesis of bedaquiline:

All glassware was pre-dried in the oven, and further flame dried before use. To a solution of *N, N*-diisopropylamine (0.10 ml, 5 equiv.) in freshly distilled THF (2.0 ml), a volume of 0.47 ml of

1.6M *n*-butyllithium (*n*-BuLi) (as a solution in hexane was obtained from Merck. and was titrated by using *N*-benzylbenzamide as the indicator to confirm its concentration)[1] (0.76 mmol, 5 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 15 minutes and then warmed up to 0°C and stirred further for 15 minutes. The light brownish solution was recooled at -78°C. A solution of 3-benzyl-6-bromo-methoxyquinoline (50 mg, 1 equiv.) in THF (1.0 ml) was slowly added. After 30 minutes of stirring, a solution of 3-(dimethylamino)-1-propionaphthone (42 mg, 1.2 equiv.) in THF (1.0 ml) was added dropwise at -78°C. After 3 hours, the reaction was warmed up to room temperature and quenched with 1.0 ml saturated brine (NaCl) then extracted with ethyl acetate (3x5.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a clear yellow oil. The crude product was analyzed on the LC-MS and further characterized by ^{1}H NMR.

Procedure for the chiral synthesis using bis(1-phenylethyl)amine enantiomers:



Scheme S1: Chiral synthesis using bis(1-phenylethyl)amine enantiomers

Formation of a chiral base: To a solution of **4a or b** (68.6 mg, 2 equiv.) in THF (2.0 ml), 0.29 ml of 1.6M *n*-BuLi in hexane (0.46mmol, 3 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 5 minutes and warmed up to room temperature and further

stirred for 1 hour. The clear yellow solution was recooled to -78°C and again stirred for 1 hour to form a pinkish solution of the chiral base complex.

Lithiation step: A solution of **1** (50 mg, 1 equiv.) in THF (0.50 ml) was slowly added to the *in* situ formed chiral base solution from above and stirred at -20°C. After exactly 1 hour, a solution of **2** (41.5 mg, 1.2 equiv.) in THF (0.5 ml) was added dropwise over 10 min via a cannula, and the resulting solution was stirred at –78 °C. After 3 hours, the reaction was warmed up to room temperature and quenched with aqueous NaCl (1.0 ml) then extracted with EtOAc (3x5.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a clear yellow oil. The crude product was analyzed on the LC-MS and characterized by the ^{1}H NMR.

Chiral synthesis using bis(1-phenylethyl)amine hydrochloride salt:

The salt was made according to the reported procedure.[1] To a solution of **4a or b·HCl** salt (79.6 mg, 2 equiv.) in THF (2.0 ml), 0.28 ml of 1.6M *n*-BuLi in hexane (0.46 mmol, 3 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 5 minutes and warmed up to room temperature and stirred further for 1 hour. The clear yellow solution was recooled to -78°C and again stirred for 1 hour to form a pinkish solution of a chiral base complex.

Lithiation step: A solution of **1** (50 mg, 1 equiv.) in THF (0.50 ml) was slowly added to an *in situ* formed chiral base from above and stirred at -20°C. After exactly 1 hour, a solution of **2** (41.5 mg, 1.2 equiv.) in THF (0.50 ml) was added dropwise over 10 min via a cannula, and the resulting solution was stirred at –78 °C for 3 hours. The reaction was warmed up to room temperature and quenched with aqueous NaCl (1.0 ml) then extracted with EtOAc (3x5.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a clear yellow oil. The crude product was analyzed on the LC-MS and characterized by the ^{1}H NMR.

Table S1. Optimization of equivalents using *n*-BuLi:**4a** in THF

Entry	Equivalents of base	Deprotonation temperature /°C	% Conversion
1	5:5	-78	0
2	3.5:2.5	-78	trace amount
3	3:2	-78	5

% conversion was determined by LC-MS using the YMC-Triart-C18 column unless stated otherwise. The deprotonation was allowed to take place for 30 minutes using *n*-BuLi:**4a**. All reactions were carried out at -78°C on a 0.15 mmol scale. The deprotonation step took place over 30 minutes and the reaction with the electrophile for 3 hours.

Table S2. Optimization of deprotonation time using *n*-BuLi:**4a**

Entry	Deprotonation time/minutes	%Conversion
1	15	10
2	60	33
3	90	5 + side products
4	120	side products

% conversion was determined by LC-MS using the YMC-Triart-C18 column unless stated otherwise. The deprotonation was allowed to take place for 30 minutes using *n*-BuLi:**4a**. All reactions were carried out at -78°C on a 0.15 mmol scale.

Table S3. Optimization of deprotonation temperature using *n*-BuLi:**4a**

Entry	Deprotonation temperature/°C	% Conversion
1	-60	trace amount
2	-40	5
3	-20	15
4	0	side products

% conversion was determined by LC-MS using the YMC-Triart-C18 column unless stated otherwise and the *dr* was determined by crude ^{1}H NMR. The deprotonation was conducted at -20°C using *n*-BuLi:**4a** and all reactions were carried out at -78°C on a 0.15 mmol scale.

Table S4. Optimization of the chiral base **4a** with additive

Entry	Base	*dr*	%Conversion
1	*n*-BuLi/ 4a.LiCl[a]	45:55	33
2	*n*-BuLi/ 4a.LiCl[b]	30:70	32

% conversion was determined by LC-MS using the YMC-Triart-C18 column unless stated otherwise and the *dr* was determined by crude ^{1}H NMR. [a] was made by the addition of LiCl and [b] was made from adding *n*-BuLi to 4a.HCl. The deprotonation was conducted at -20°C and all reactions were carried out at -78°C on a 0.15 mmol scale.

Scaled up procedure using 4b·HCl

The salt was made according to the reported procedure.[1] To a solution of **4b·HCl** salt (1.6 g, 2 equiv.) in THF (20.0 ml), 5.61 ml of 1.6M *n*-BuLi in hexane (9.2 mmol, 3 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 10 minutes and warmed up to room temperature and stirred further for 1 hour. The clear yellow solution was recooled to -78°C and again stirred for 1 hour to form a pinkish solution of a chiral base complex.

Lithiation step: A solution of **1** (1.0 g, 1 equiv.) in THF (10.0 ml) was slowly added to an *in situ* formed chiral base from above and stirred at -20°C. After exactly 1 hour, a solution of **2** (0.83 g, 1.2 equiv.) in THF (10.0 ml) was added dropwise over 20 min via a cannula, and the resulting solution was stirred at –78 °C for 3 hours. The reaction was warmed up to room temperature and quenched with aqueous NaCl (20.0 ml) then extracted with EtOAc (5x10.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a clear yellow oil. The crude product was further purified by flash column chromatography 1:1 (EtOAc/Hexane). Rf: 0.30 undesired (35mg) and 0.44 desired (285mg) diastereomers as white solids. The *RS*, *SR* was then subject to semi-prep SFC for separation, which provided the desired enantiomer 1*R*,2*S* (130 mg). m.p 104 °C.$[\alpha]_D^{25}$ = –175 (c = 1, DMF)[2] and 1*S*,2*R* (142 mg) with the NMR data as reported below.

The characterization data compared well with literature. Optical purity was established by chiral HPLC analysis (Chiralpak IA, 2-propanol: hexane = 0.5: 99.5, 0.5 mL/min, λ = 220 nm): Rt = 10.1 (*RS*), 11.4 (*SR*) min.

For the desired diastereomer (*RS, SR*)-BDQ, ^{1}H NMR (400MHz ,$CDCl_3$) δ = 8.89 (s, 1 H, H7), 8.61 (d, J = 8.6 Hz, 1 H, H15), 7.96 (d, J = 2.0 Hz, 1 H, H2), 7.92 (d, J = 7.4 Hz, 1 H, H9), 7.87 (d, J = 8.1 Hz, 1 H, H12), 7.72 (d, J = 8.8 Hz, 1 H, H6), 7.68–7.56 (m, 3 H, H4, H11, H14), 7.48 (t, J = 7.6 Hz, 1 H, H13), 7.30 (t, J = 7.7 Hz, 1 H, H10), 7.17–7.10 (m, 2 H, H17), 6.93–6.83 (m, 3 H, H18, H19), 5.89 (s, 1 H, H6), 4.21 (s, 3 H, H22), 2.60–2.51 (m, 1 H, H20), 2.18–2.02 (m, 2 H, H20′, H21), 1.99 (s, 6 H, H22), 1.95–1.85 (m, 1 H, H21′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 143.7, 141.6, 140.5, 138.7, 134.6, 131.9, 129.9, 129.8, 129.7, 128.4, 128.1, 127.8, 127.3, 127.1, 126.8, 125.7, 125.2, 125.1, 125.0, 124.4, 116.9, 82.4, 56.2, 54.1, 49.5, 44.6, 33.4, 29.6 ppm. MS (ESI): m/z 555.5, found 556 $[M+H]^+$

For the undesired diastereomer (*RR, SS*)-BDQ, ^{1}H NMR (400MHz ,$CDCl_3$) δ = 8.58 (s,1 H, H1), 8.48 (d, J = 8.7 Hz, 1 H, H15), 7.99 (dd, J = 7.4, 0.9 Hz,1 H, H9), 7.88 (d, J = 7.3 Hz, 2 H, H17), 7.82–7.75 (m, 2 H, H12,H2), 7.60–7.50 (m, 2 H, H14, H11), 7.47–7.32 (m, 4 H, H5, H18,H4, H13), 7.30–7.21 (m, 2 H, H19, H10), 5.73 (s, 1 H, H6), 3.25 (s, 3 H, H22), 2.49 (td, J = 14.3, 3.0 Hz, 1 H, H20), 2.26 (td, J =12.2, 3.2 Hz, 1 H, H20′), 2.14–1.90 (m, 9 H, H21, H21′, H22) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 143.2, 141.6, 141.1, 137.8,134.6, 131.2, 130.0, 129.6, 129.5, 128.1, 128.0, 127.9, 127.6, 127.4,127.1, 126.5, 126.4, 125.4, 124.9, 124.8, 124.3, 116.2, 81.5, 56.1,52.7, 50.9, 44.5, 34.1, 29.6 ppm. MS (ESI): m/z 555.5, found 556 $[M+H]^+$

Chiral synthesis using sparteine enantiomers:

Formation of a chiral base: To a solution of **5a or 5b** (71 mg, 2 equiv.) in THF (2.0 ml), 0.28 ml of 1.6M *n*-BuLi in hexane (0.46 mmol, 3 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 5 minutes and warmed up to room temperature and further stirred for 1 hour. The clear yellow solution was recooled to -78°C and again stirred for 1 hour to form chiral base complex.

Lithiation step: A solution of **1** (50 mg, 1 equiv.) in THF (0.50 ml) was slowly added to the *in situ* formed chiral base solution from above and stirred at -20°C. After exactly 1 hour, a solution of **2** (42 mg, 1.2 equiv.) in THF (0.50 ml) was added dropwise over 10 min via a cannula, and the resulting solution was stirred at –78 °C. After 3 hours, the reaction was warmed up to room temperature and quenched with aqueous NaCl (1.0 ml) then extracted with EtOAc (3x5.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was tested on the TLC and further analyzed on the LC-MS however no product formation was observed.

Chiral synthesis using bisoxazoline enantiomers:

Formation of a chiral base: To a solution of **6a or 6b** (101 mg, 2 equiv.) in THF (2.0 ml), 0.2855 ml of 1.6M *n*-BuLi in hexane (0.46 mmol, 3 equiv.) was added dropwise at -78°C under the flow of argon. The solution was stirred for 5 minutes and warmed up to room temperature and further stirred for 1 hour. The clear yellow solution was recooled to -78°C and again stirred for 1 hour to form a chiral base complex.

Lithiation step: A solution of **1** (50 mg, 1.0 equiv.) in THF (0.50 ml) was slowly added to the *in situ* formed chiral base solution from above and stirred at -20°C. After exactly 1 hour, a solution of **2** (42 mg, 1.2 equiv.) in THF (0.50 ml) was added dropwise over 10 min via a cannula, and the resulting solution was stirred at –78 °C. After 3 hours, the reaction was warmed up to room temperature and quenched with aqueous NaCl (1.0 ml) then extracted with EtOAc (3x5.0 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The crude product was tested on the TLC and further analyzed on the LC-MS however no product formation was observed.

4. ^{1}H NMR, ^{13}C NMR, and SFC Spectra

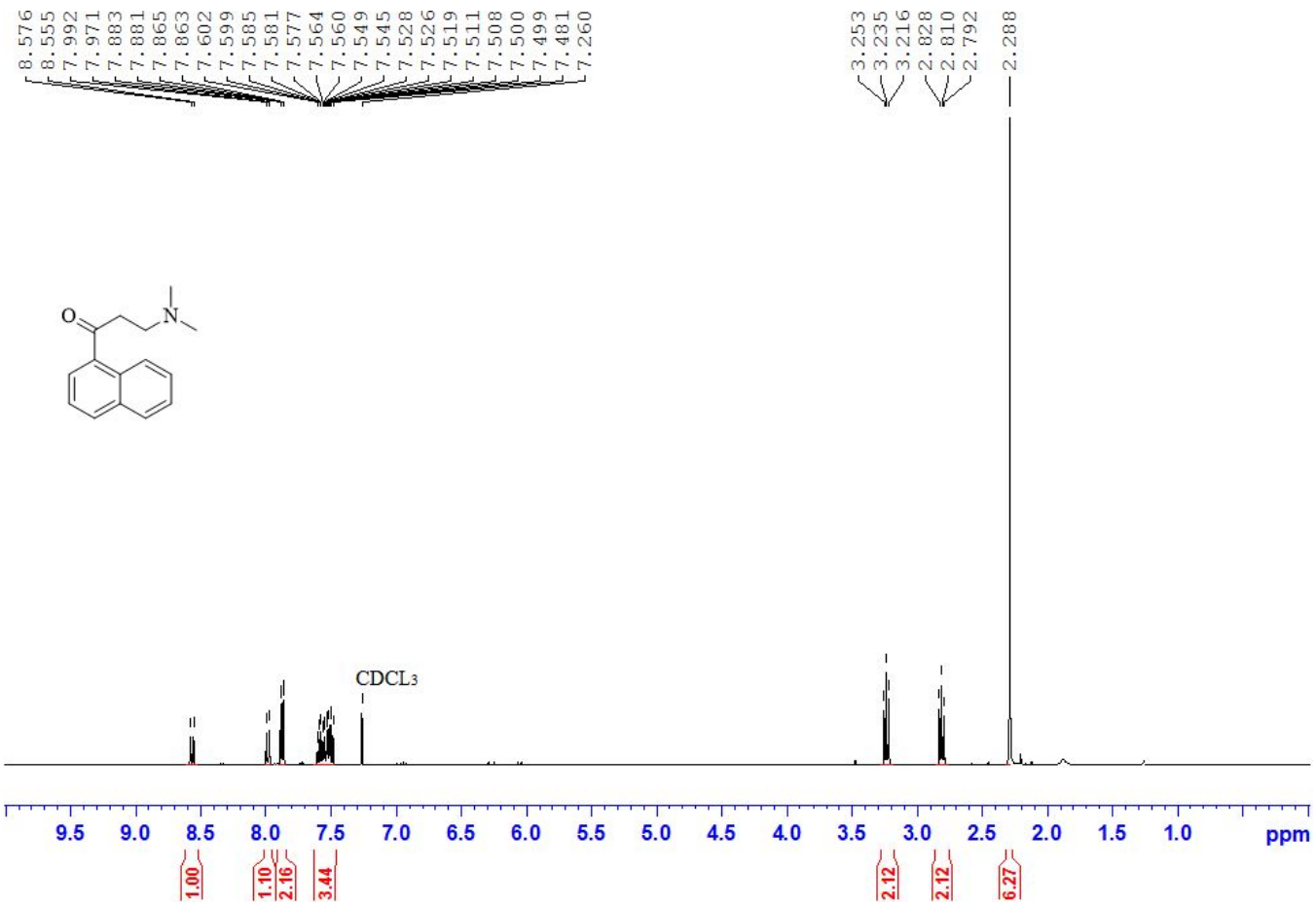


Figure S1-^{1}H NMR Spectrum of Compound 2 in $CDCl_3$

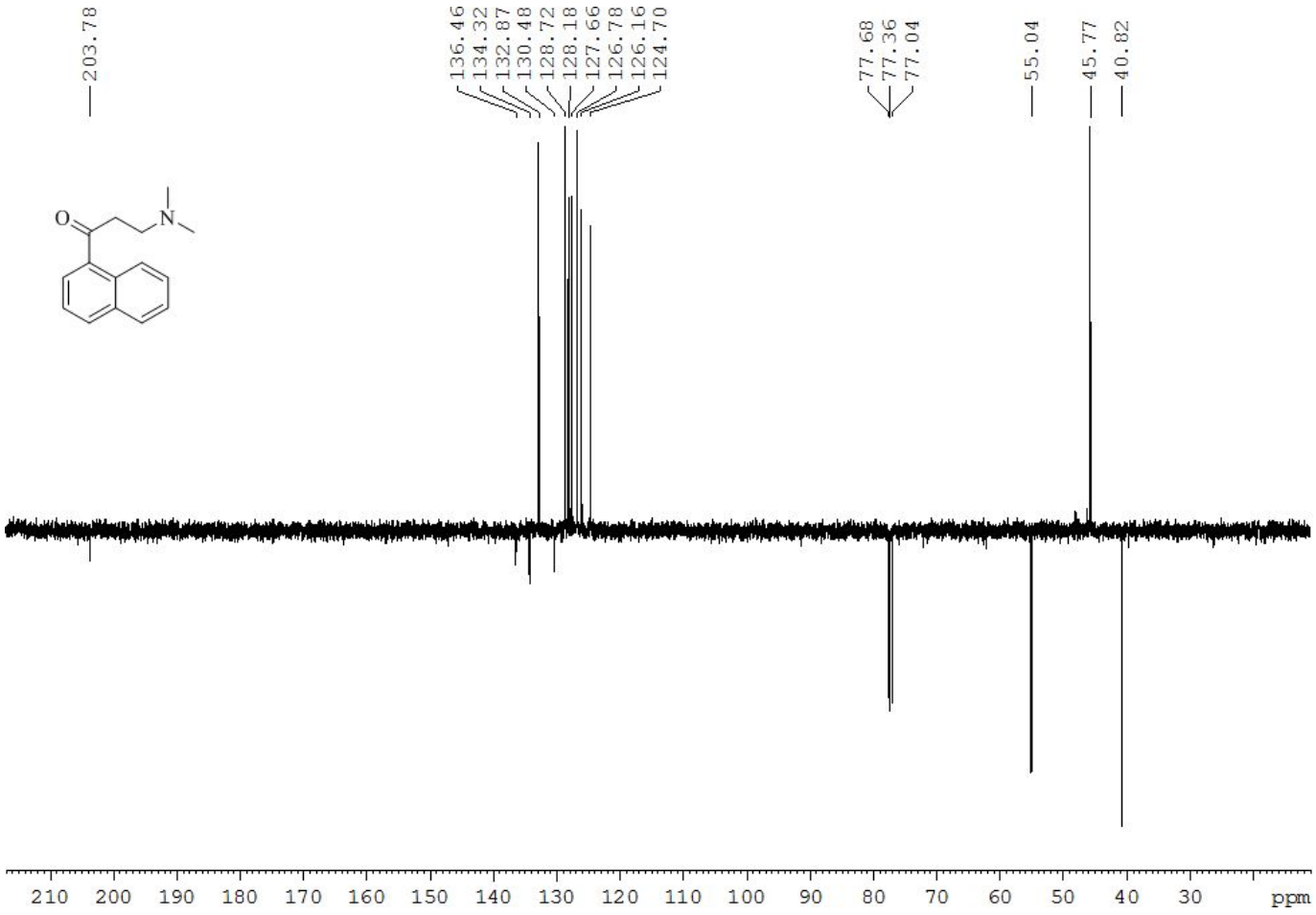


Figure S2-^{13}C NMR Spectrum of Compound 2 in $CDCl_3$

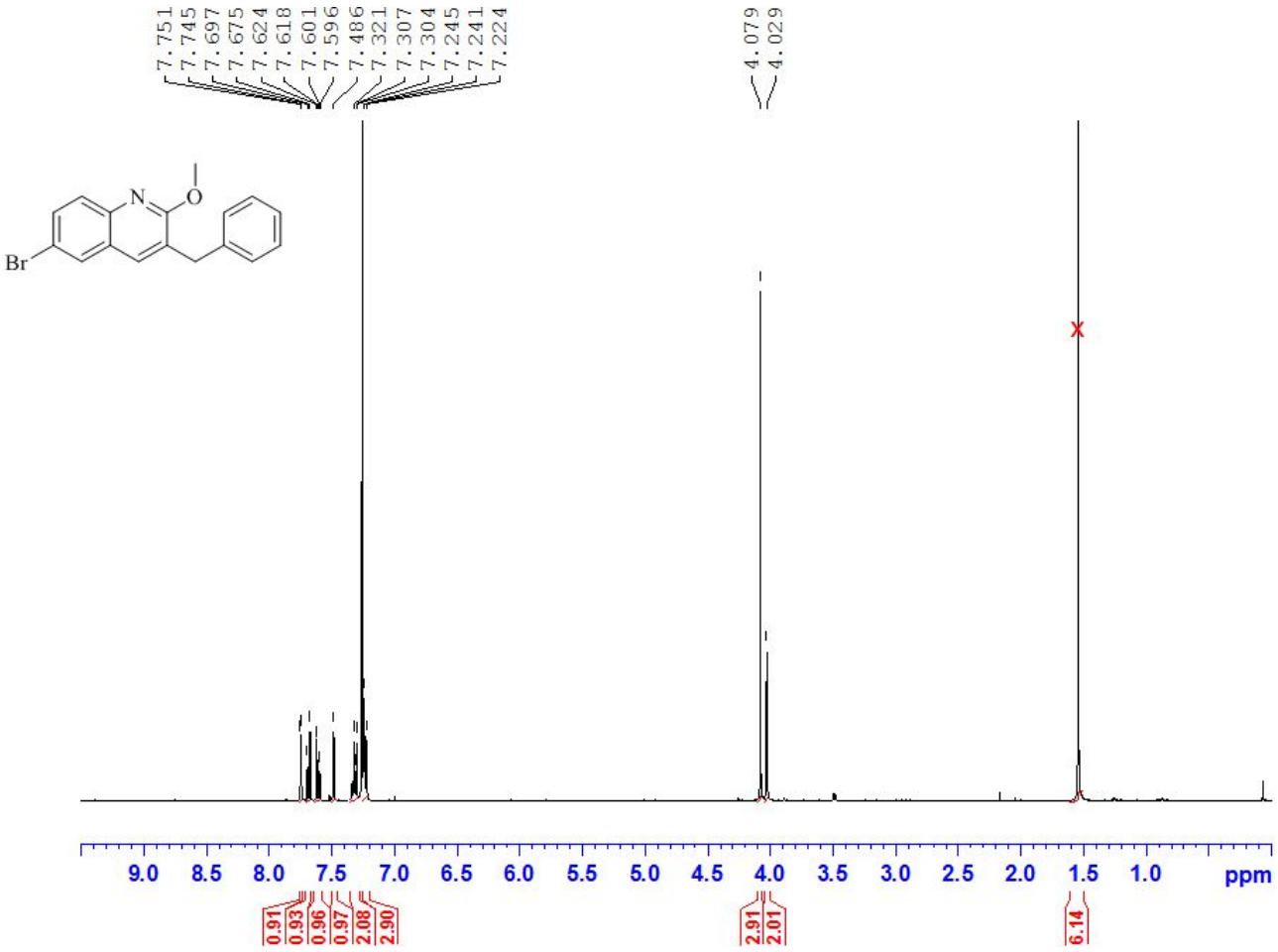


Figure S3-^{1}H NMR Spectrum of Compound 1 in $CDCl_3$

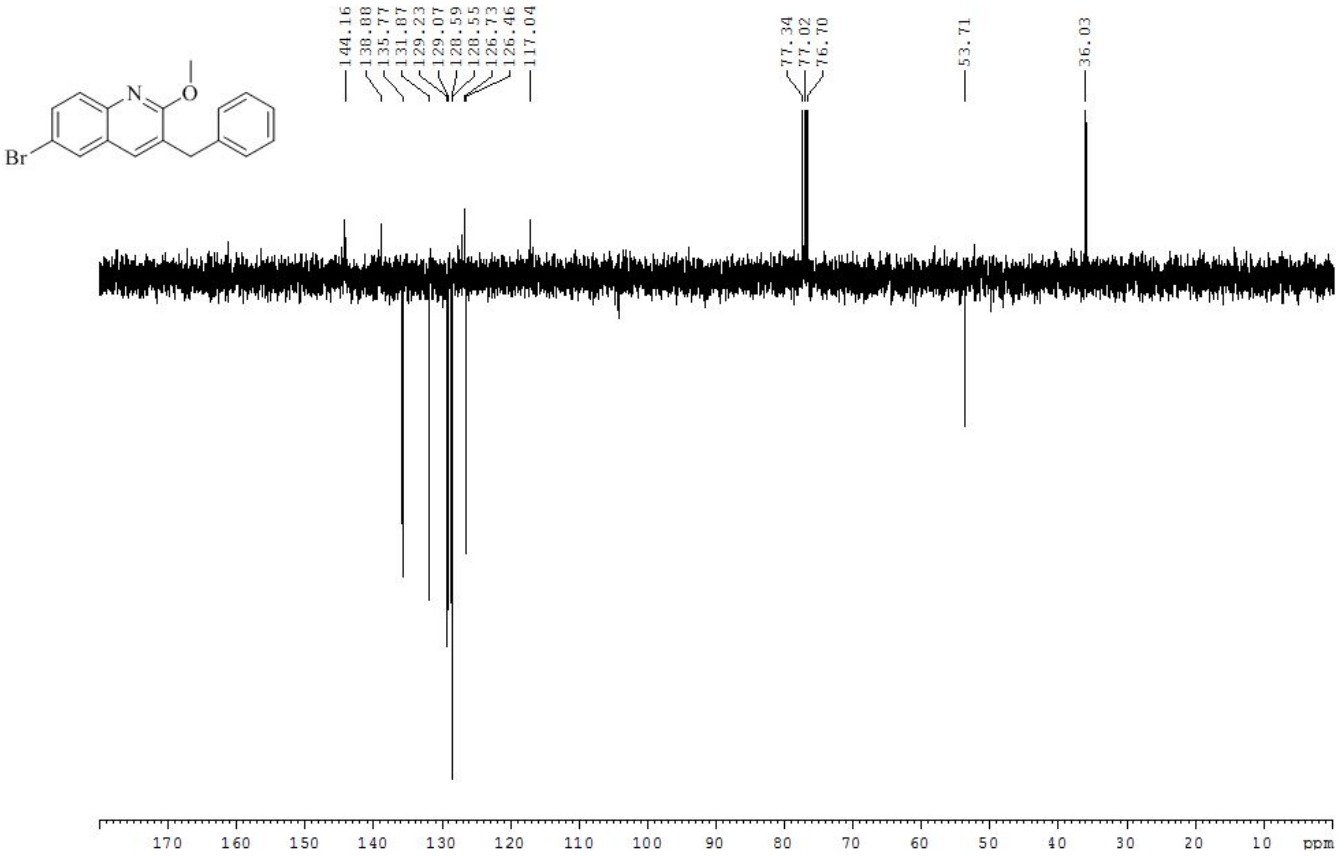


Figure S4-^{13}C NMR Spectrum of Compound 1 in $CDCl_3$

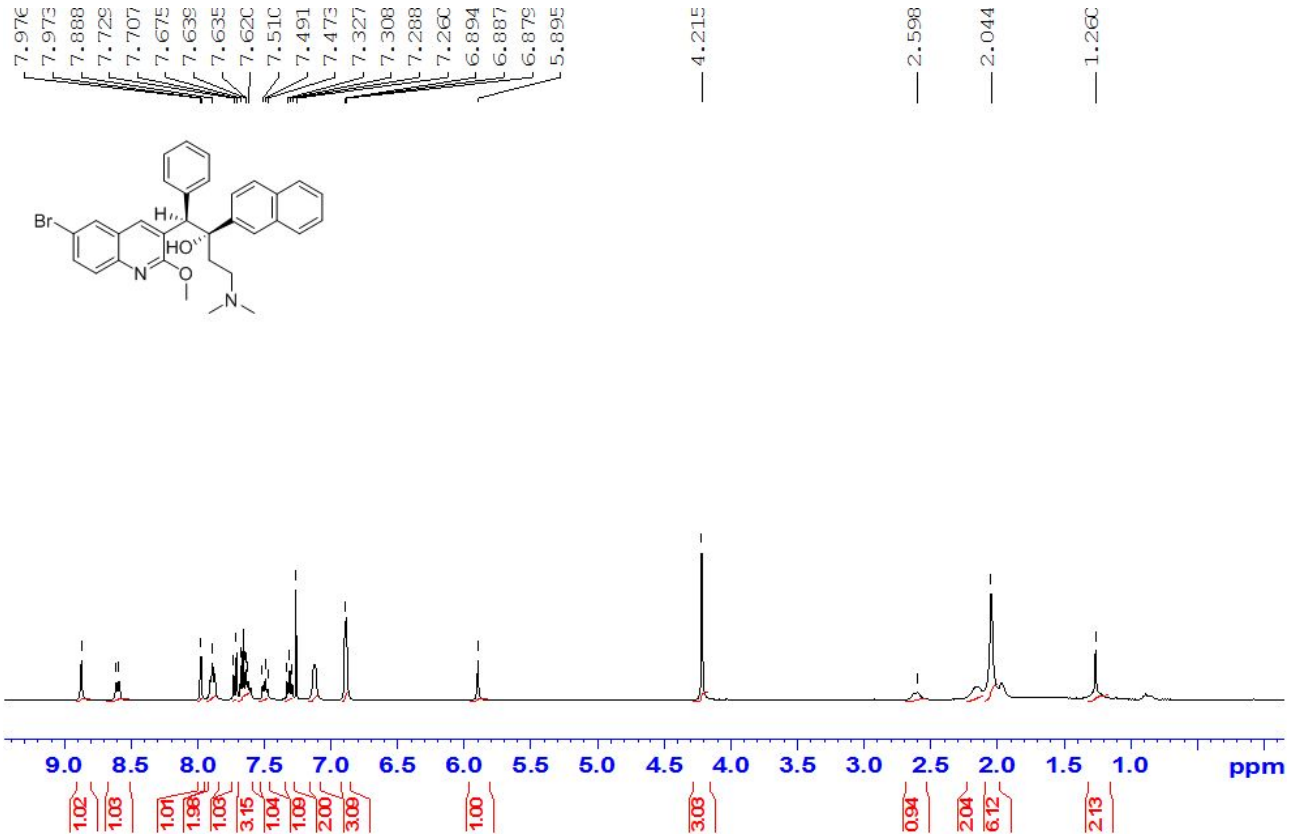


Figure S5-^{1}H NMR Spectrum of (*RS, SR*) diastereomer (desired) in $CDCl_3$

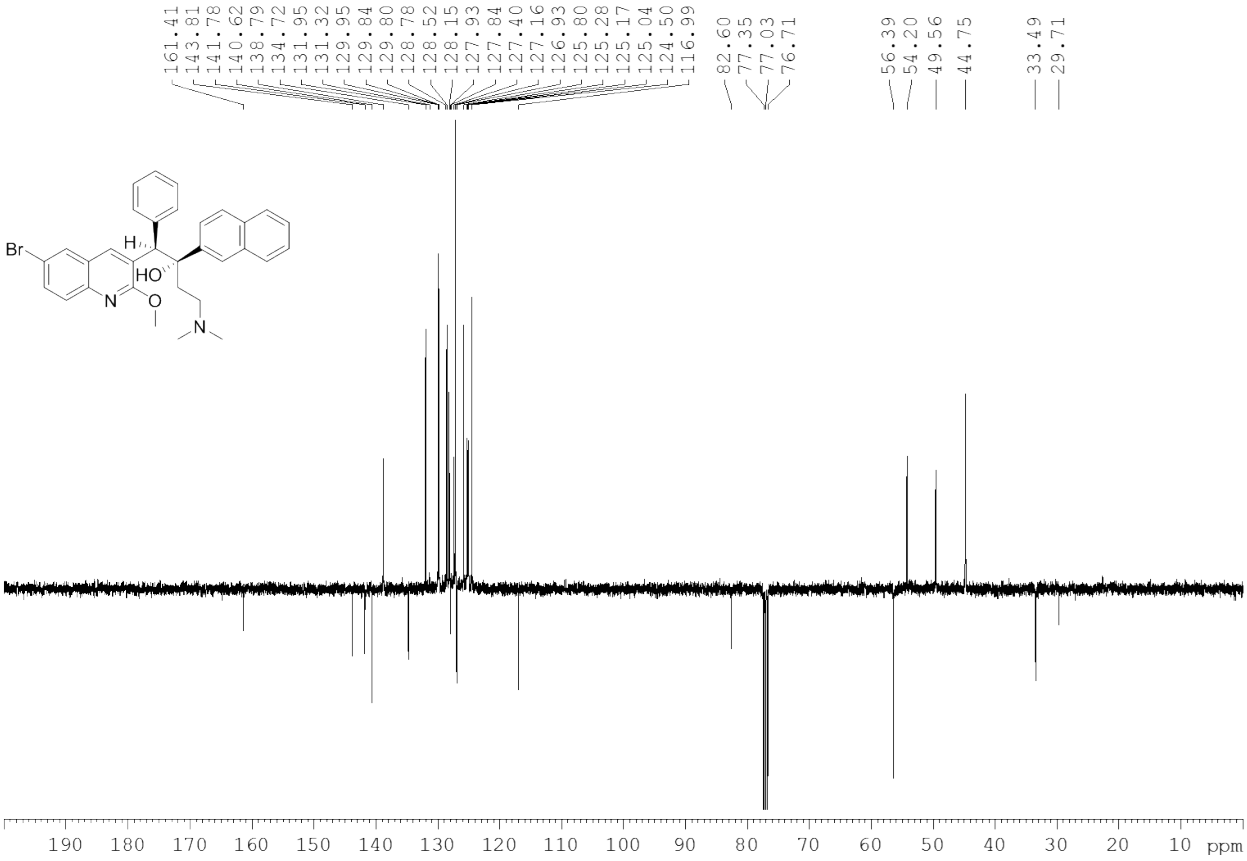


Figure S6-^{13}C NMR spectrum of (1R, 2S)-BDQ diastereomer in $CDCl_3$

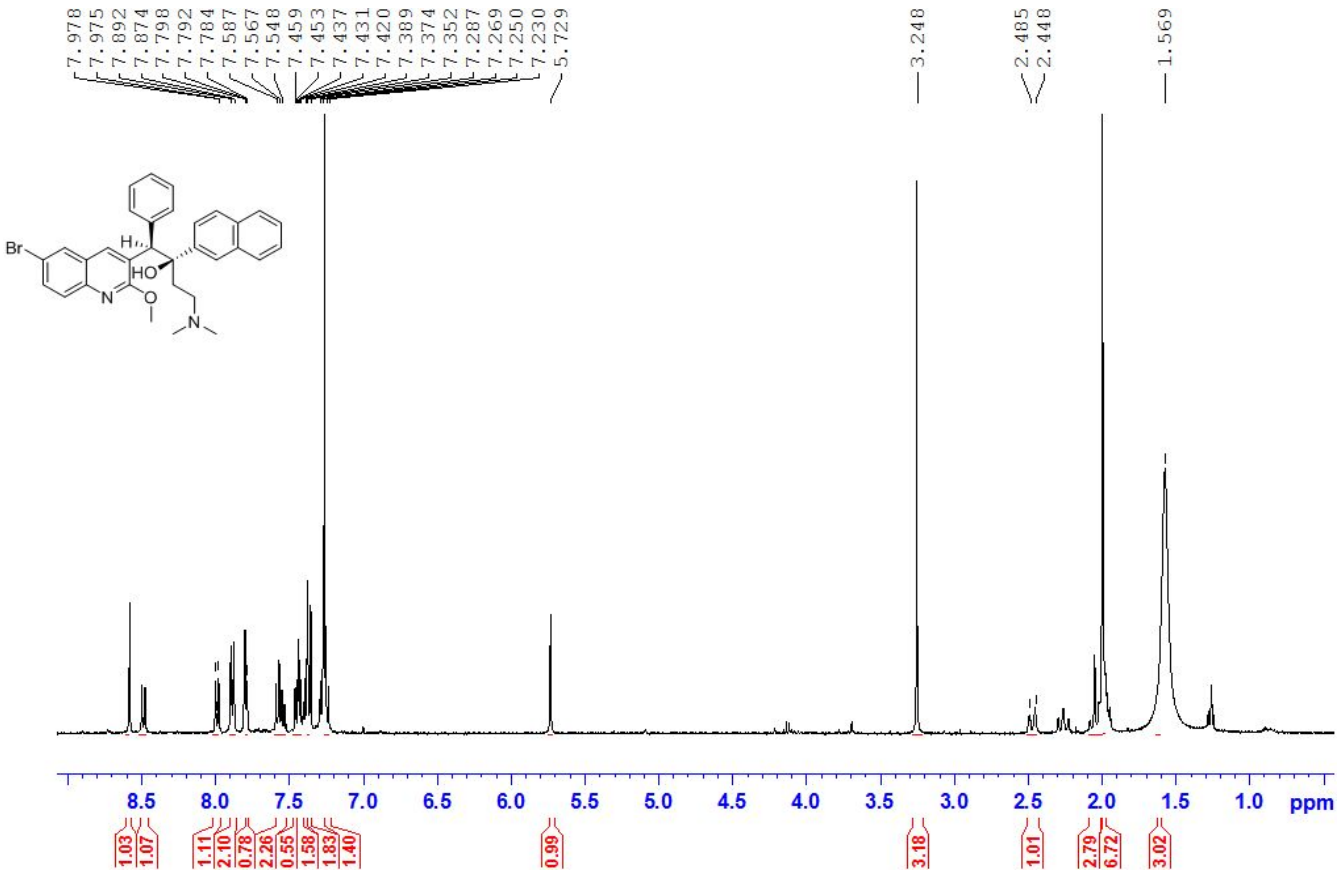


Figure S7-^{1}H NMR Spectrum of (*RR, SS*) diastereomer (undesired) in $CDCl_3$

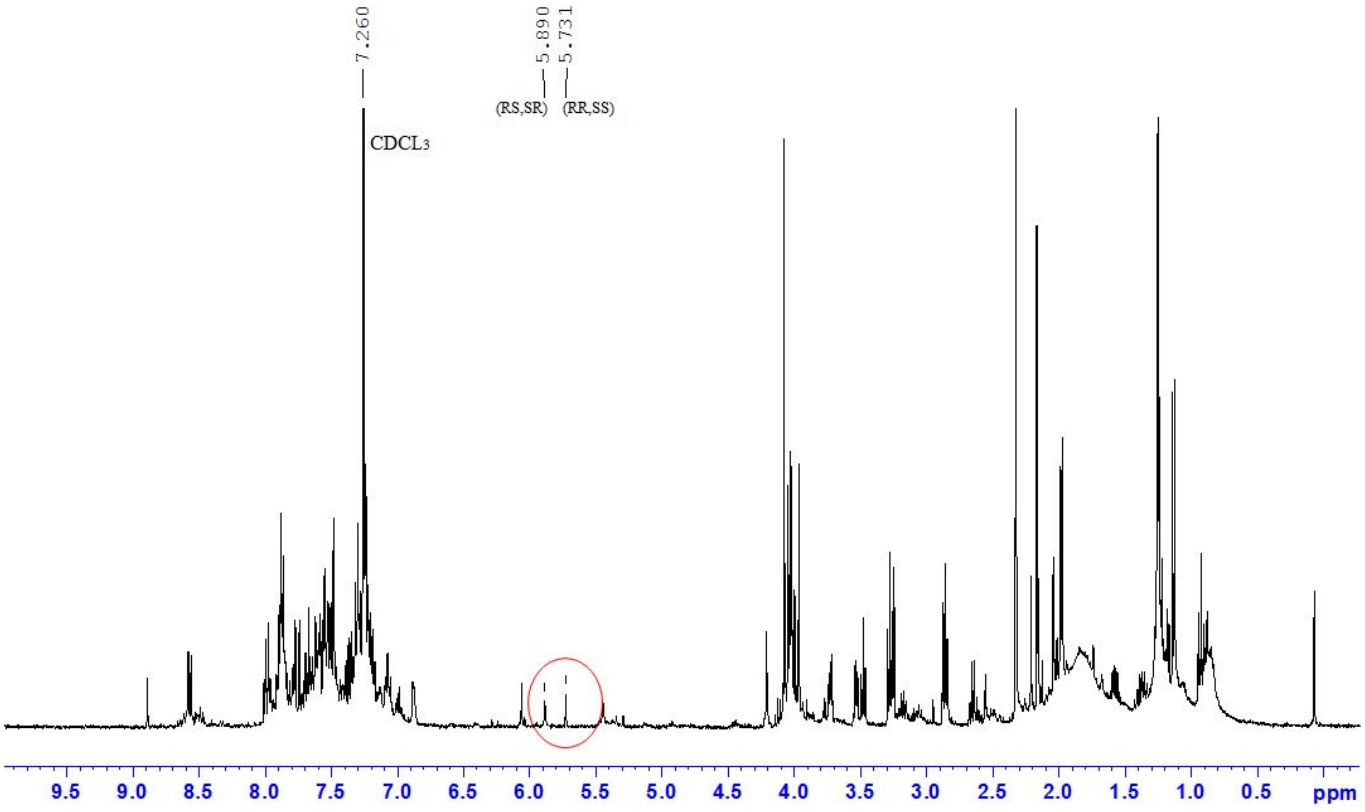


Figure S8-^{1}H NMR Spectrum of a crude mixture obtained using LDA as a base(50:50 *dr*).

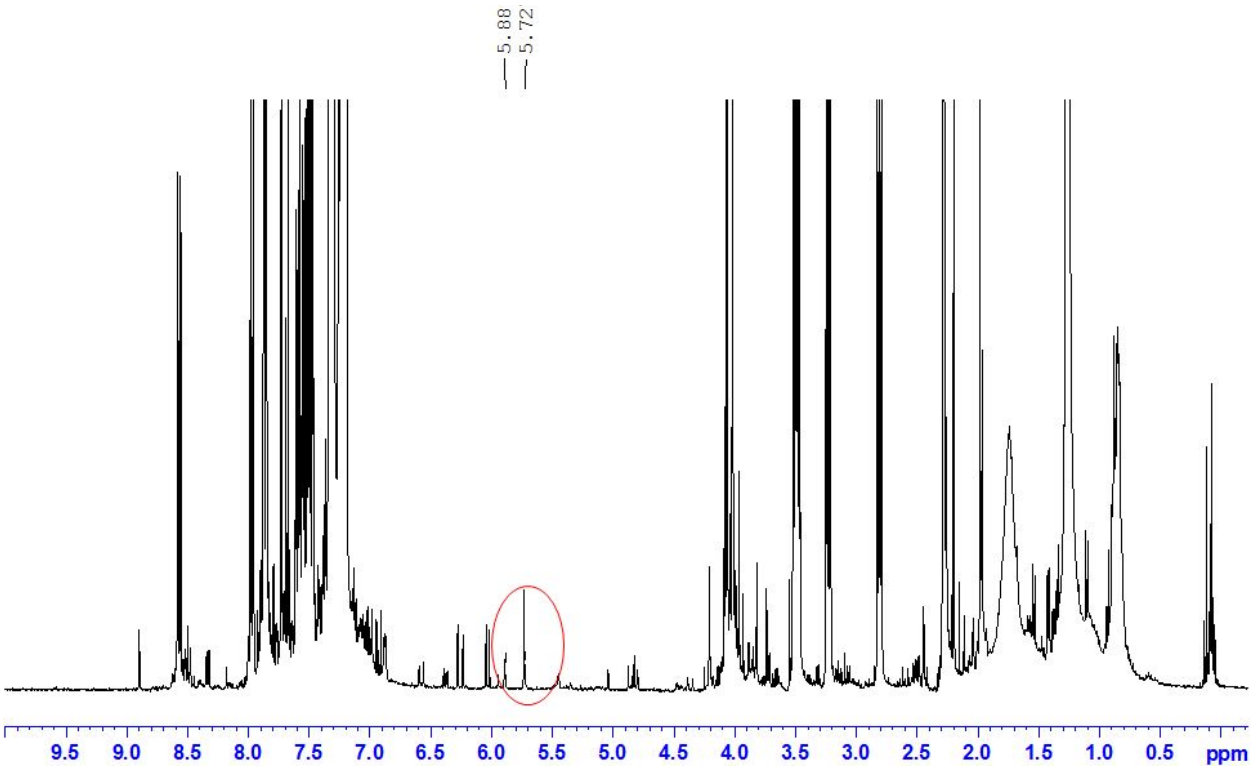


Figure S9-^{1}H NMR Spectrum of a crude mixture in $CDCl_3$ made from *n*-BuLi/4a hydrochloride salt chiral complex (30:70 *dr*).

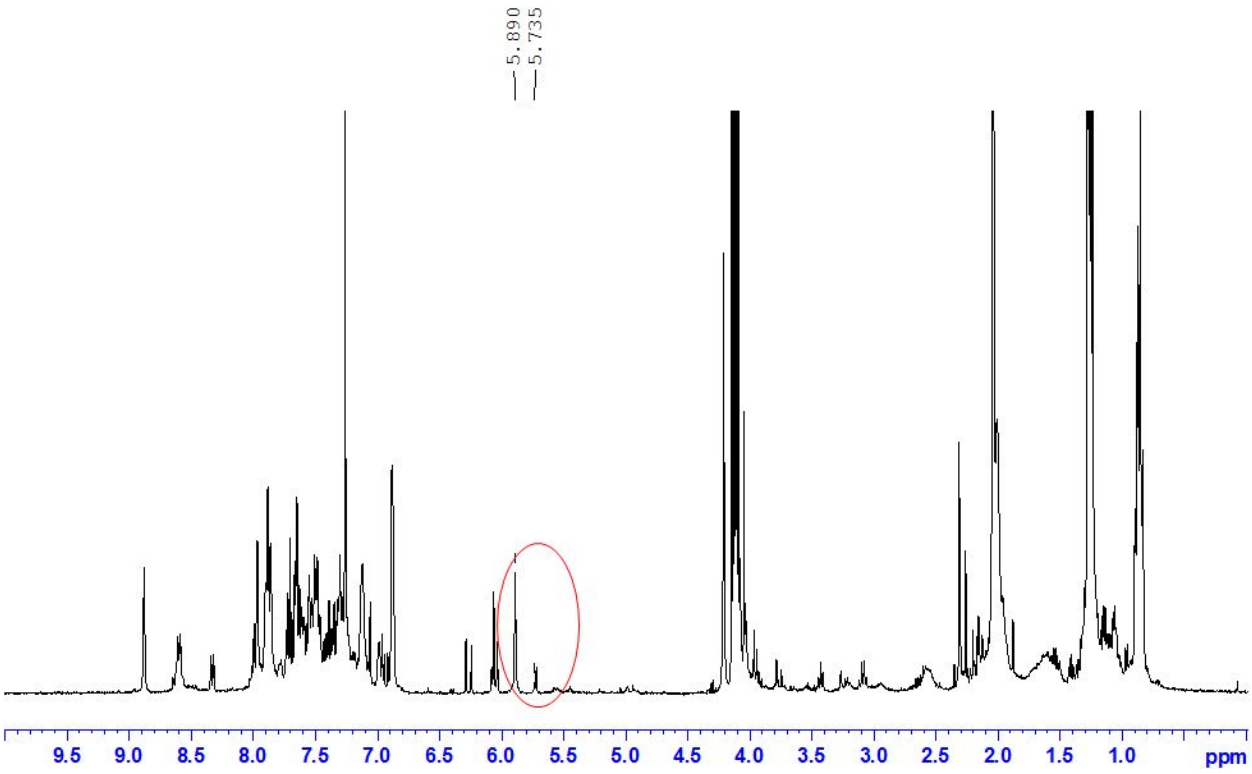


Figure S10-^{1}H NMR Spectrum of a crude mixture in $CDCl_3$ made from *n*-BuLi/4b hydrochloride salt chiral complex (90:10 *dr*).

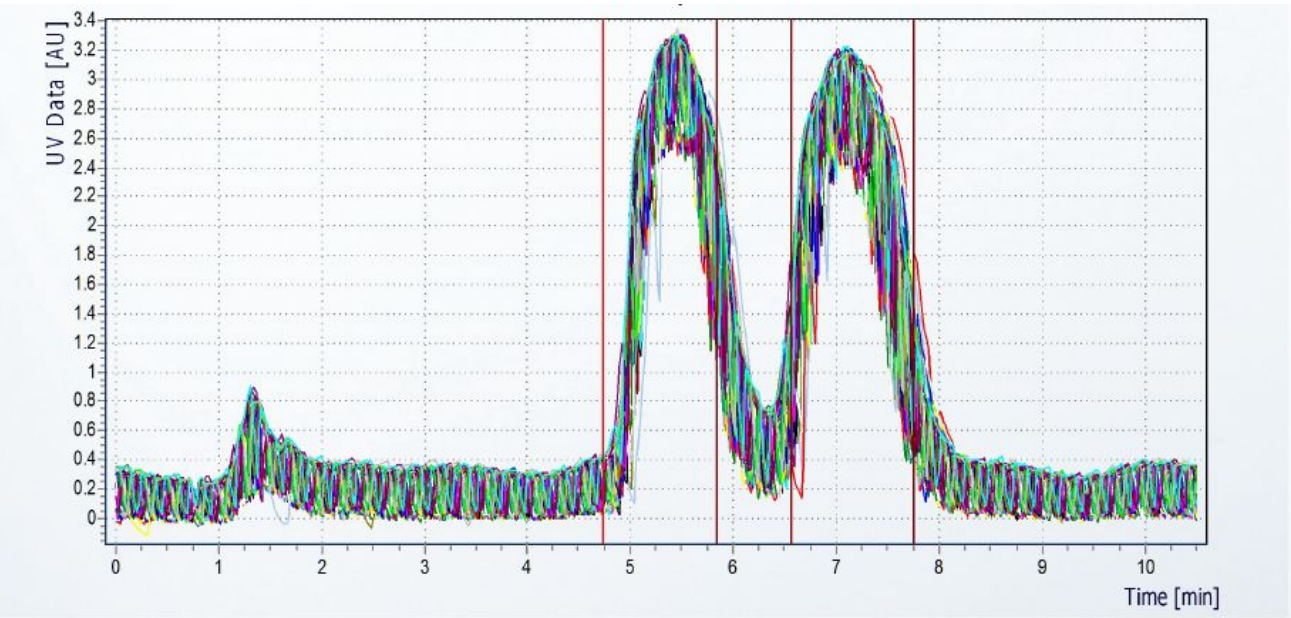


Figure S11-SFC stacked injection spectrum of a racemic mixture of (*1R, 2S*)-BDQ and its enantiomer respectively.

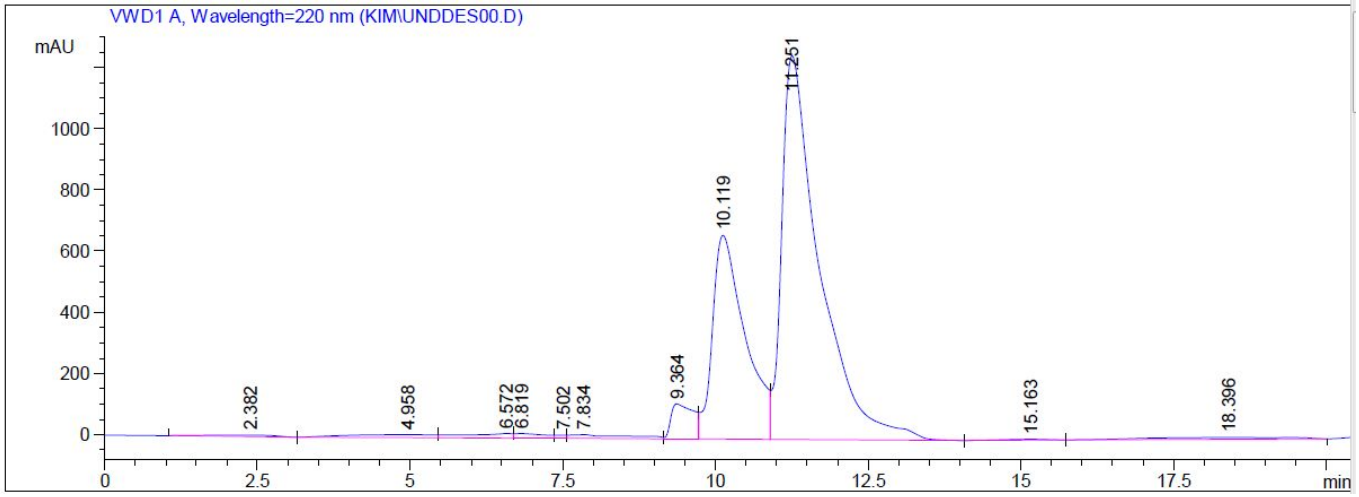


Figure S12-Chiral HPLC spectrum of the racemic mixture of BDQ enantiomers

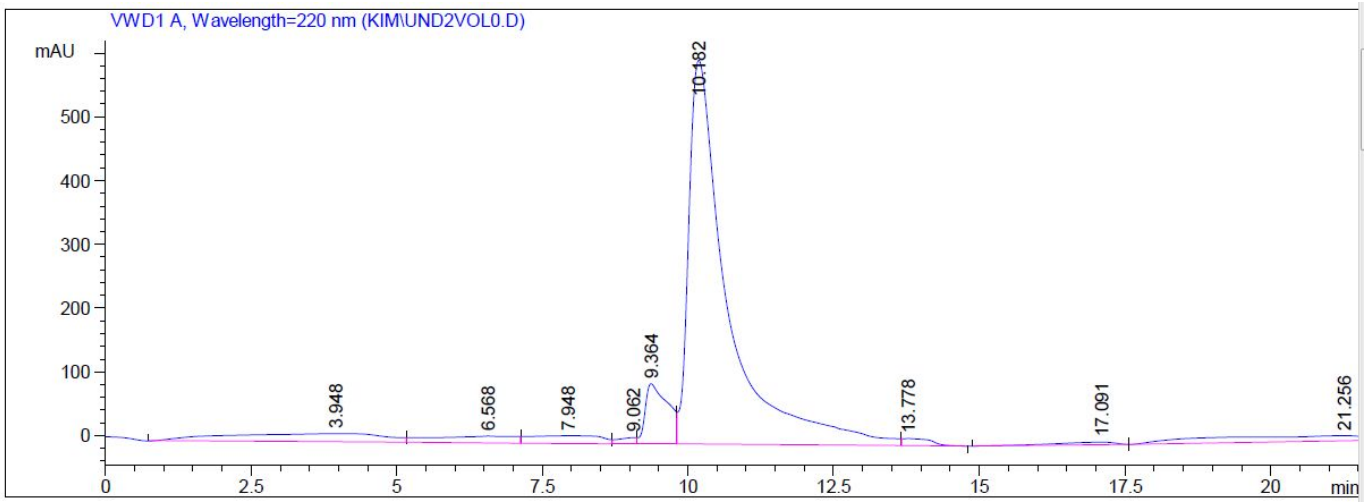


Figure S13-Chiral HPLC spectrum of (1R, 2S)-BDQ (desired isomer)

5. References

(1) Vaulont, I.; Gais, H. J.; Reuter, N.; Schmitz, E.; Ossenkamp, R. K. Asymmetric Synthesis of 3-Oxacarbacyclin and 3-Oxaisocarbacyclin by a Common Enantioselective Deprotonation Based Route. *Eur. J. Org. Chem.* **1998,** *1998*, 805-826.

(2) Chandrasekhar, S.; Babu, G. K.; Mohapatra, D. K. Practical Syntheses of (2S)-R207910 and (2R)-R207910. *Eur. J. Org. Chem.* **2011,** *2011*, 2057-2061.