

Mild and Efficient Enantioselective Synthesis of All Stereoisomers of Cordiarimide B and Their Antioxidant Study

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Four isomers of cordiarimide B were synthesized by coupling (*S*)-2-amino-1-phenylethanol and (*R*)-2-amino-1-phenylethanol with L and D glutamic acid. Biological studies revealed that two isomers showed potent antioxidant activity. Among these two, the most promising isomer is compound (3*S*,11*S*) 18, possesses four folds more active than the (3*S*,11*R*) 20 isomer. The other two isomers (3*R*,11*S*) 22 and (3*R*,11*R*) 24 are biologically not active. Structure-activity relationship studies indicated that the stereochemistry of the hydroxyl (-OH) group at C-3 position of 2-amino-1-phenylethanol played a crucial role in modulating the antioxidant activity. This finding could help in rational designing of cordiarimide B as novel antioxidant drug molecules.

Keywords: Cordiarimide B, Glutarimide alkaloids, Aminopheylethnaol, Antioxidant activity.

INTRODUCTION

There are many glutarimide containing compounds which possess interesting biological and medicinal properties [1,2]. The majority of glutarimide based alkaloids have been isolated from plant sources such as genus *Cordia*, which belongs to Boraginaceae family. Traditionally, these alkaloids are used for treatment of antiandrogenic [3], anti-inflammatory [4], antifungal [5,6] and larvicidal [6] in tropical America, Africa and Asia regions. Many glutarimide derivatives have properties of partial agonists in the central nervous system (CNS) [7] having broad range of actions, ranging from convulsive and analeptic (agonist) to anticonvulsive and hypnotic (antagonist). However, the mode of action of these alkaloids is not yet elucidated.

Recently two glutarimide alkaloids cordiarimides A (3) and B (4) are reported in literature [8]. Both alkaloids cytotoxicity against the MOLT-3 cell line and inhibit superoxide anion radical formation. Structurally cordiarimide B (4) has two stereo centres at positions 3 and 11, displayed 20 times more active for suppression of superoxide anion generation (Fig. 1) [8]. Cordiarimide B has two stereo centers, hence it exist in 4 isomeric forms. The biological activity of naturally occurring isomer 4 (3*S*,11*S*) is known. The biological activity of other isomers of cordiarimide B is not studied due to lack of availability.

In order to cast more light on structural activity relationship (SAR) and their mechanism of action, development of efficient synthetic methods to access all the stereo isomers of cordiarimide B in enantiomerically pure form is important. Herein we report a simple, straightforward and racemization free method for large scale synthesis of all the stereoisomers of cordiarimide B.

EXPERIMENTAL

The starting materials were purchased from Aldrich Chemical Co. India, Bangalore. Reagents and solvents were purchased from Avra Synthesis. Pvt. Ltd. India Hyderabad and were used without further purification. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher-Johns melting point apparatus and they are uncorrected. ¹H and ¹³C NMR spectra were recorded using a Bruker AVANCE 300; the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus and on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 C via direct inlet probe. Only the molecular and parent ions (*m/z*) are reported. IR spectra were recorded on a Bruker TENSOR 27 FT instrument. Optical rotations were measured on WZZ-1 automatic polarimeter with a 2 cm cell at the sodium D-line.

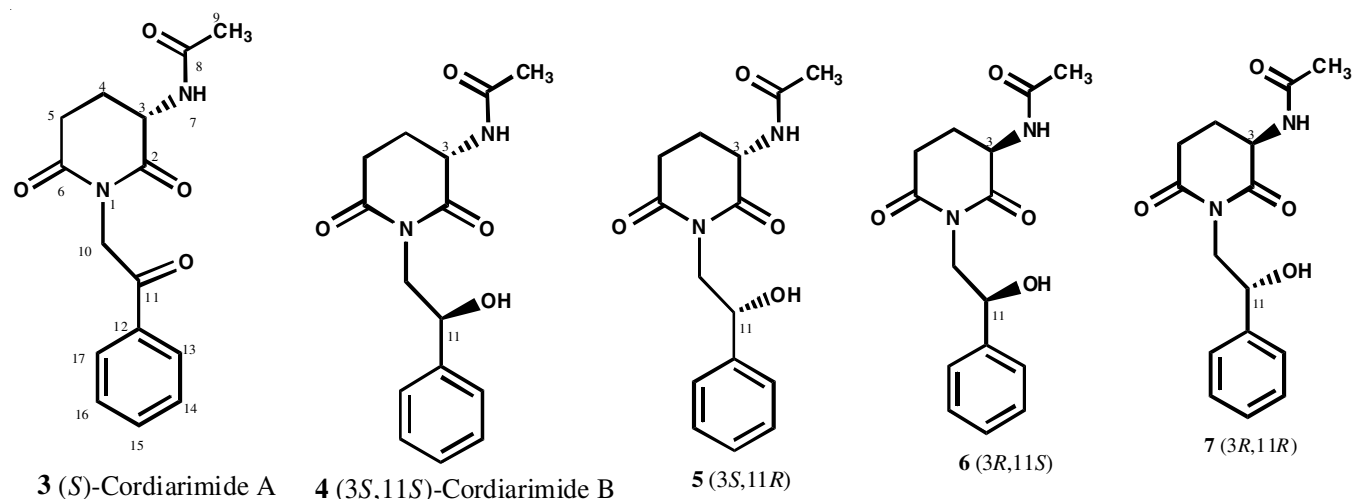


Fig. 1. Stereoisomers of cordiarimide-B alkaloid

(*S*)-2-Hydroxy-2-phenylacetamide (14): To the cooled solution of (*S*)-mandelic acid (10 g, 66 mmol) in 100 mL dichloromethane under nitrogen atmosphere was added trimethylamine (18.4 mL, 132 mmol) in one shot. After 20 min, ethylchloroformate (7.6 mL, 79 mmol) was added through dropping funnel over 30 min. The resulting solution was stirred at 0 °C for further 20 min and continued to stir at room temperature for 3 h. After the reaction is completed, the reaction mixture is transferred to separating funnel and washed with 5 % HCl followed by distilled water. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure yield thick liquid which was dissolved in 100 mL of 20 % ammonia solution in methanol and stirred at room temperature for overnight. The methanol was removed under rota evaporator yield compound **14** as white solid (9.7 g, 97.6 %). The compound was found to be 98 % pure. $[\alpha]_D^{25} = 55$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm^{-1}): 1726, 3443. ^1H NMR (300 MHz CDCl_3): δ 3.75 (s, 1H, OH), 5.069 (s, 1H, CH), 5.73 (s, 1H, NH), 6.07 (s, 1H, NH), 7.2–7.4 (m, 5H Ar-H); ^{13}C NMR (100 MHz CDCl_3) δ 76.77, 126.74, 126.91, 128.90, 176.01. HRMS m/z calcd. for $\text{C}_8\text{H}_9\text{NO}_2$ $[\text{M}+1]^+$: 152.06, Found: 152.0505.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylacetamide (15): (*S*)-2-Hydroxy-2-phenylacetamide (8 g, 53 mmol) and imidazole (4.3 g, 63 mmol) were dissolved in 50 mL dry dichloromethane under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and stirred for 20 min. (*S*)-2-(*tert*-Butyldimethylsilyloxy)chloride (TBDMS-Cl) (8.7 g, 58 mmol) was added portion wise over the period of 30 min. After the addition is completed, the reaction mixture was stirred at room temperature for 6 h. The completion of the reaction was confirmed by TLC. The reaction mixture was diluted with 50 mL of dichloromethane solvent and washed with 1 M HCl (3 $\times$ 10 mL) followed by three times with water (10 mL). The organic layer was dried over MgSO_4 and concentrated in vacuum followed by column chromatography purification yield compound **15** as white solid (13.5 g, 96.5 %), $[\alpha]_D^{25} = +34$ (c 0.1, DCM). IR (KBr, $\nu_{\max}$, cm^{-1}): 1726, 3443. ^1H NMR (300 MHz CDCl_3): δ 0.18 (s, 6H, TBDMS), 0.98 (s, 9H, TBDMS), 5.02 (s, 1H, CH) 7.3 (s, 2H NH_2) 7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz): δ 0.015, 25.3, 29.9, 87.4, 126.3, 139.5, 174.2. HRMS m/z calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_2\text{Si}$ $[\text{M}+1]^+$: 265.12, Found: 266.1249.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylethanamine (16): To an oven dried round-bottomed flask and magnetic stir bar was transferred 28 mL 2 N $\text{BH}_3\cdot\text{S}(\text{CH}_3)_2$ in toluene argon atmosphere. The solution was stirred at 0 °C for 2 h. To this solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetamide (**15**) (12 g, 45 mmol) in 25 mL toluene was added using dropping funnel over the period of 1 h. During the addition, temperature of the reaction was maintained at 0 °C. After the addition was completed the reaction mixture was slowly allowed to room temperature, then refluxed until the completion of reaction (about 5 h), as determined by TLC. The reaction was quenched by the addition of 25 mL of 2 N NaOH and concentrated under reduced pressure. The mixture was extracted with EtOAc (3 $\times$ 30 mL) followed brine (1 $\times$ 15 mL), dried over anhydrous MgSO_4 and concentrated *in vacuo*. The crude product obtained was subjected to purification by column chromatography (Hexane: EtOAc; 1:9) gave the chiral aminoalcohol **16** (10 g, 88 %). $[\alpha]_D^{25} = +45$ (c 0.1, DCM); (KBr, $\nu_{\max}$, cm^{-1}): 3439, 1607; ^1H NMR (300 MHz CDCl_3): δ 0.20 (s, 6H, TBDMS), 0.97 (s, 9H, TBDMS), 3.02 (d, 1H, CH_2) d.22 (s, 1H, CH_2), 4.76 (t, 1H, CH) 5.3 (s, 2H NH_2) 7.38 (m, 5H, Ar-H). ^{13}C NMR (100 MHz): δ -0.20, 25.1, 31.3, 48, 3, 89.9, 126.3, 138.2, 140.5, HRMS m/z calcd. for $\text{C}_{14}\text{H}_{25}\text{NOSi}$ $[\text{M}+1]^+$: 252.17, Found: 250.098.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-phenylethanamine (18): This compound was synthesized using (*R*)-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetamide (**24**) according to the procedure used for the synthesis of compound (**16**). $[\alpha]_D^{25} = -43$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm^{-1}): 3445, 1617; ^1H NMR (300 MHz CDCl_3): δ 0.18 (s, 6H, TBDMS), 0.99 (s, 9H, TBDMS), 3.42 (d, 1H, CH_2) 3.66 (d, 1H, CH_2), 4.76 (t, 1H, CH) 5.6 (s, 2H NH_2) 7.58 (m, 5H, Ar-H); ^{13}C NMR (100 MHz): δ -0.15, 25.9, 31.3, 48.4, 73.77, 125.4, 139.1, 141.2. HRMS m/z calcd. for $\text{C}_{14}\text{H}_{25}\text{NOSi}$ $[\text{M}+1]^+$: 252.17, Found: 250.0962.

General procedure for cyclic imide coupling: To a stirred solution of DCC (9.2 g, 44 mmol), DIPEA (10.5 mL, 80 mmol) and NHS (5.1 g, 44 mmol) in dry DCM (30 mL) at 0 °C under nitrogen atmosphere, was added N-Boc protected L-glutamic acid (5 g, 20 mmol). After stirring for 30 min the solution of chiral aminoalcohol **16** (5 g, 20 mmol) in 15 mL DCM was added drop-wise *via* syringe. The resulting mixture was stirred overnight. After the reaction is completed (TLC), the reaction

mixture was filtered through suction filtration. The filtrate is, diluted with DCM (20 mL) and washed with 1 M HCl (3 × 10 mL) followed by 5 % NaHCO₃ (3 × 10 mL) and brine (1 × 15 mL), dried over anhydrous MgSO₄ and concentrated *in vacuo*. The crude residues were purified by column chromatography to afford compound **17** (6.5 g, 85 %) as a white solid.

tert-Butyl (S)-1-[(S)-2-(tert-butyldimethylsilyloxy)-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (17): A white solid (6.2 g, 81 %), $[\alpha]_D^{25} = 9.54$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm⁻¹): 3445, 1617; ¹H NMR (300 MHz CDCl₃): δ 0.13 (s, 6H, TBDMS), 0.98 (s, 9H, TBDMS), 1.31 (s, 9H, Boc) 2.12 (q, 2H, CH₂) 2.25 (t, 2H, CH₂), 4.01 (t, 1H CH), 4.16 (d, 2H, CH₂) 5.6 (t, 1H CH₂) 7.58 (m, 5H, Ar-H); 8.04 (s, 1H, NH); ¹³C NMR (100 MHz): δ -0.21, 24.3, 25.8, 27.2, 28.4, 31.3, 58.4, 76.7, 79.4, 127.4, 139.8, 155.2, 169.7, 171.8. HRMS *m/z* calcd. for C₂₄H₃₈N₂O₅Si [M + 1]⁺: 463.25, Found: 462.2032.

tert-Butyl (R)-1-[(S)-2-(tert-butyldimethylsilyloxy)-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (19): A white solid (6.0 g, 78 %), $[\alpha]_D^{25} = -15.28$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm⁻¹): 3445, 1617; ¹H NMR (300 MHz CDCl₃): δ 0.12 (s, 6H, TBDMS), 0.96 (s, 9H, TBDMS), 1.33 (s, 9H, Boc) 2.21 (q, 2H, CH₂) 2.34 (t, 2H, CH₂), 4.21 (t, 1H CH), 4.21 (d, 2H, CH₂) 5.63 (t, 1H CH₂) 7.52 (m, 5H, Ar-H); 8.06 (s, 1H, NH); ¹³C NMR (100 MHz): δ -0.23, 24.6, 26.1, 27.8, 28.2, 32.3, 58.9, 77.1, 79.5, 127.9, 140.1, 155.6, 170.7, 172.3. HRMS *m/z* calcd. for C₂₄H₃₈N₂O₅Si [M + 1]⁺: 463.25, Found: 462.2035.

tert-Butyl (S)-1-[(R)-2-(tert-butyldimethylsilyloxy)-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (21): A white solid (6.1 g, 79 %), $[\alpha]_D^{25} = 7.54$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm⁻¹): 3445, 1617; ¹H NMR (300 MHz CDCl₃): δ 0.11 (s, 6H, TBDMS), 0.93 (s, 9H, TBDMS), 1.36 (s, 9H, Boc) 2.19 (q, 2H, CH₂) 2.41 (t, 2H, CH₂), 4.19 (t, 1H CH), 4.25 (d, 2H, CH₂) 5.67 (t, 1H CH₂) 7.58 (m, 5H, Ar-H); 8.07 (s, 1H, NH); ¹³C NMR (100 MHz): δ -0.21, 23.6, 25.7, 28.1, 28.8, 32.6, 59.2, 77.6, 78.3, 128.4, 141.2, 156.1, 171.2, 173.1. HRMS *m/z* calcd. for C₂₄H₃₈N₂O₅Si [M + 1]⁺: 463.25, Found: 462.2034.

tert-Butyl (R)-1-[(R)-2-(tert-butyldimethylsilyloxy)-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (23): A white solid (5.8 g, 75 %), $[\alpha]_D^{25} = 11.30$ (c 0.1, DCM); IR (KBr, $\nu_{\max}$, cm⁻¹): 3445, 1617; ¹H NMR (300 MHz CDCl₃): δ 0.19 (s, 6H, TBDMS), 0.12 (s, 9H, TBDMS), 3.32 (d, 1H, CH₂) 3.57 (d, 1H, CH₂), 4.81 (t, 1H, CH) 5.4 (s, 2H NH₂) 7.35 (m, 5H, Ar-H); 8.17 (s, 1H, NH); ¹³C NMR (100 MHz): δ -0.20, 24.9, 32.3, 47.9, 72.98, 123.4, 138.1, 140.2, 157.1, 170.9, 172.6. HRMS *m/z* calcd. for C₂₄H₃₈N₂O₅Si [M + 1]⁺: 463.25, Found: 462.2035.

General procedure for TBDMS deprotection: To a solution of **17** (1g, 2.1 mmol) in THF (6 mL) was added TBAF (7 mL, 1.0 M in THF, 0.69 mmol). The solution was stirred at 0 °C for 2 h and poured into saturated NH₄Cl. The mixture was extracted with EtOAc followed by drying with Na₂SO₄ and concentration of combined organic layers under reduced pressure. Residue was purified by silica gel column chromatography (hexanes/EtOAc, 7:3) to obtain **18**.

tert-Butyl (3S)-1-[(S)-2-hydroxy-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (18): White solid (0.7 g, 93 %), $[\alpha]_D^{25} = 11.30$ (c 0.1, DCM); ¹H NMR (300 MHz CDCl₃):

δ 2.27 (t 2H CH₂) 4.31 (t 2H CH₂) 5.37 (t 1H CH) 7.25 (m 5H Ar-H) 8.0 (s 1H NH); ¹³C NMR (100 MHz): δ 23.91, 25.41, 30.48, 58.80, 77.05, 127.45, 155.4, 175.422. HRMS *m/z* calcd. for C₁₈H₂₄N₂O₅ [M + 1]⁺: 349.17 found: 349.314.

tert-Butyl (3R)-1-[(S)-2-hydroxy-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (20): White solid (0.72g, 97 %), $[\alpha]_D^{25} = -7.542$ (c 0.1, DCM); ¹H NMR (300 MHz CDCl₃): δ 2.47 (t 2H CH₂) 3.31 (t 2H CH₂) 5.12 (t 1H CH) 7.25 (m 5H Ar-H) 8.12 (s 1H NH), ¹³C NMR (100 MHz): δ 24.5, 25.42, 29.59, 30.75, 36.2, 67.84, 77.36, 128.5, 155.52, HRMS *m/z* calcd. for C₁₈H₂₄N₂O₅ [M + 1]⁺: 349.17 found: 349.312.

tert-Butyl (3S)-1-[(R)-2-hydroxy-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (22): White solid (0.68 g, 90 %), $[\alpha]_D^{25} = 8.23$ (c 0.1, DCM); ¹H NMR (300 MHz CDCl₃): δ 2.15 (t 2H CH₂) 4.05 (t 2H CH₂) 5.07 (t 1H CH) 7.3 (m 5H Ar-H) 8. (s 1H NH); ¹³C NMR (100 MHz): δ 24.4, 28.75, 30.3, 34.6, 42.0, 50.1, 51.6, 53.7, 77.4, 173.2, HRMS *m/z* calcd. for C₁₈H₂₄N₂O₅ [M + 1]⁺: 349.17 found: 349.313.

tert-Butyl (3R)-1-[(R)-2-hydroxy-2-phenylethanamine]-2,6-dioxopiperidine-3-yl-carbamate (24): White solid (0.71 g, 94 %), $[\alpha]_D^{25} = 9.45$ (c 0.1, DCM); ¹H NMR (300 MHz CDCl₃): δ 2.20 (t 2H CH₂) 4.05 (t 2H CH₂) 5.71 (t 1H CH) 7.3 (m 5H Ar-H) 8. (s 1H NH); ¹³C NMR (100 MHz): δ 24.69, 27.84, 34.77, 65.53, 76.84, 125.7, 151.5, 170.9, 174.5, HRMS *m/z* calcd. for C₁₈H₂₄N₂O₅ [M + 1]⁺: 349.17 found: 349.315.

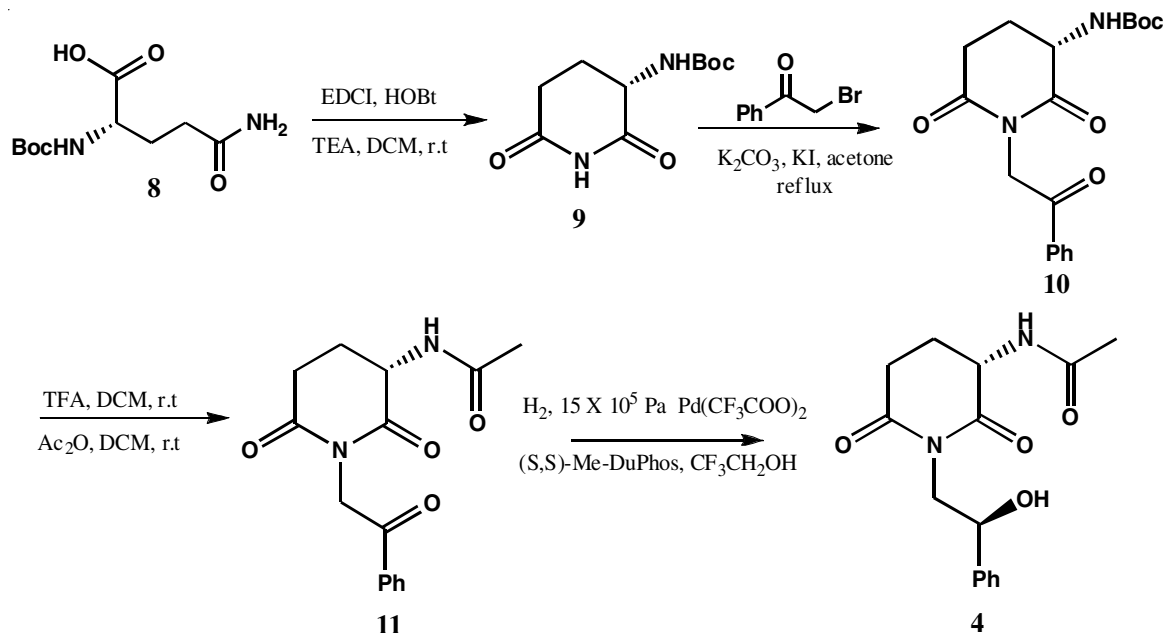
RESULTS AND DISCUSSION

Teng *et al.* [9] reported the synthesis of cordiarimide B (**Scheme-I**). This is the only methodology available in literature so far and which is not suitable for large-scale synthesis. Epimerization at C-3 carbon during alkylation of diamide nitrogen is a major drawback of the reported method to access pure isomers. Also, in reported method moderate diastereo selectivity was achieved during reduction of the keto group by using expensive Zhou's catalyst [10].

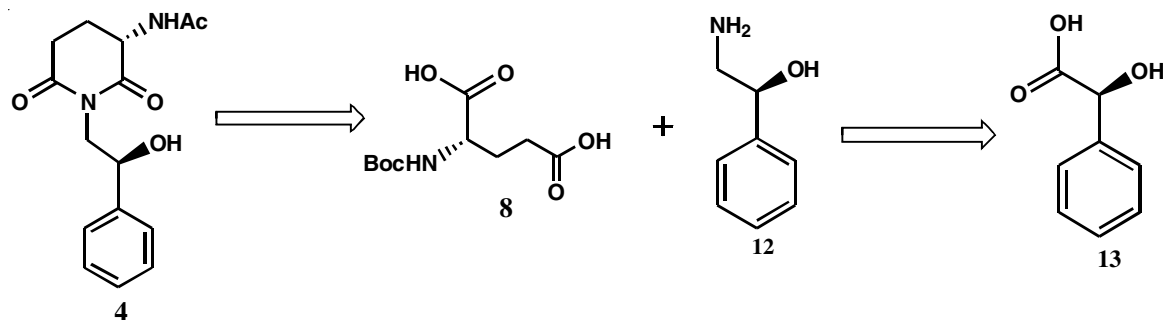
Retro synthetic analyses: The present retro synthetic analysis of cordiarimide B is outlined in **Scheme-II**. The two stereogenic centers of cordiarimide B can be easily introduced by N-Boc (L)-glutamic acid and (S)-mandelic acid as starting materials. These two compounds are commercially available in enantiomerically pure form. In this synthetic plan no center of inversion/stereo selective reduction and no harsh reaction conditions were required. Therefore, the enantiopurity of both chiral molecules is retained.

Synthesis of chiral 2-amino-1-phenylethanol: Our first focus is on the preparation of chiral 2-amino-1-phenylethanol **16** and **21**. Commercially available (S)-mandelic acid **13** was activated with ethylchloroformate in dichloromethane solvent at 0 °C, then the activated ester was stirred with excess of ammonia solution in methanol to form amide compound **14**.

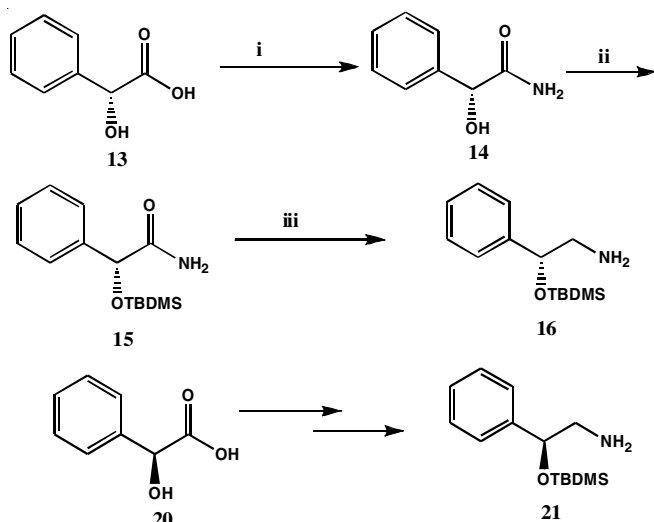
The alcohol group of amide **14** was protected in order to reduce side reaction by treating with TBDMS-chloride, in presence of imidazole in dichloromethane solvent at 0 °C. The amide group of compound **15** was reduced using 2 M solution of borandimethyl sulphide (BMS) in THF under reflux condition to form (S)-aminoalcohol **16** in 83 % yield (**Scheme-III**).



Scheme-I: Literature method of synthesis of cordiarimide B (4) [Ref. 9]



Scheme-II: Present retro synthetic analysis of cordiarimide B



Reagents and conditions: i) a) Ethylchloroformate, Et₃N, DCM, 0 °C; b) NH₃, MeOH; ii) TBDMS-Cl, imidazole, DMF, 0 °C; iii) 2 M BH₃:THF, THF

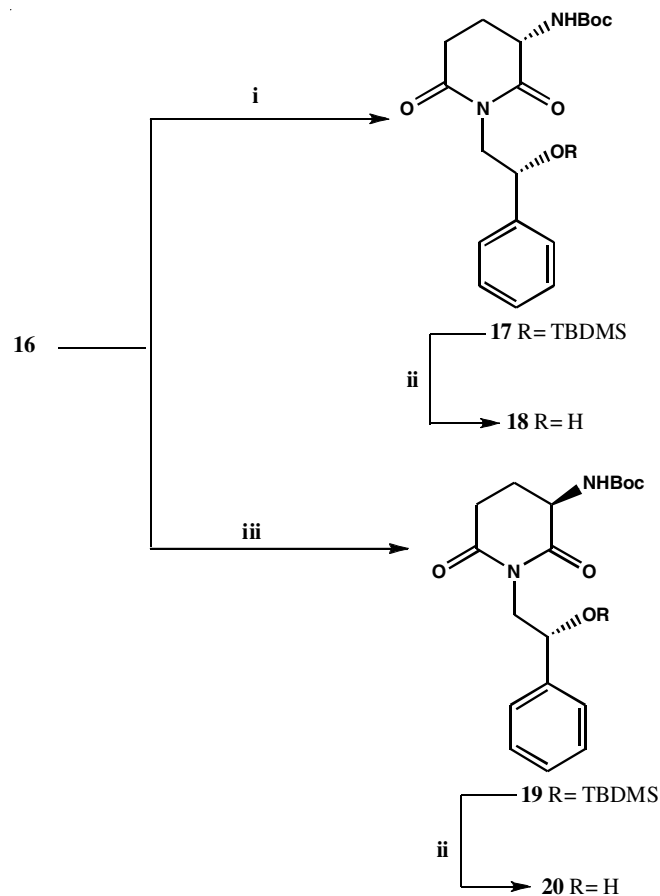
Scheme-III: synthesis of (3S,11S)-cordiarimide B (4)

By following similar reaction sequence and conditions with (*R*)-mandelic acid **20** we were also able to synthesize the (*R*)-aminoalcohol **21** in 80 % yield.

Synthesis of (3S,11S) and (3S,11R)-isomers: Our next plan was to couple these chiral 2-amino-1-phenylethanols with L-glutamic acid to construct cordiarimide B. Compound **16** was coupled with N-Boc(L) glutamic acid **8** using DCC as coupling reagent [11-14] in presence of NHS and DIPEA in dichloromethane solvent at room temperature yield cyclic imide compound **17** in 70 % yield (Scheme-IV).

To achieve effective and high yield formation cyclic diamide, we tried several coupling agents and conditions as tabulated in Table-1. The present result found that 2.5 equivalent of DCC, with NHS activation in DCM:DMF 1:1 solvent system is best to get maximum yield. The TBDMS group of compound **17** was removed by treating with TBAF in THF at room temperature yield the (3S,11S) compound **18** in 93 % isolated yield. We obtained the compound **18** up to 5 g scale using this synthetic procedure. Similarly, by coupling aminoalcohol **16** with N-Boc protected D-glutamic acid under similar reaction conditions we obtained the (3S,11R)-compound **20** in 73 % overall yield from two steps.

Synthesis of (3R,11S) and (3R,11R) isomers: Using (*R*)-2-amino-1-phenylethanol (**21**), we followed similar coupling condition with (L) and (D), N-Boc-glutamic acids to prepare compound **22** and **24**. Finally, we obtained (3S,11R) isomer compound **23** in 93 % yield and (3R,11R) isomer compound

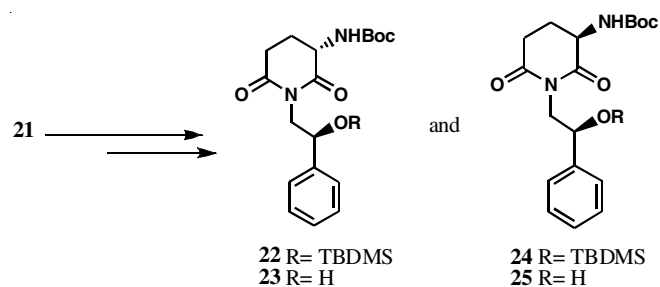


Reagents and conditions: i) N-Boc(L) glutamic acid, DCC, NHS, TEA, DCM:DMF (1:1); ii) TBDF, DCM; iii) N-Boc(D) glutamic acid, DCC, NHS, TEA, DCM:DMF(1:1)

Scheme-IV: Synthetic route of (3*S*,11*S*) and (3*S*,11*R*)-isomers

Entry	Coupling agent	Activation	Solvent	Base	Yield (%)
1	HBTU	HoBt	DMF	DIPEA	25
2	TBTU	HoBt	DMF	DIPEA	20
3	HBTU	NHS	DMF	DIPEA	30
4	TBTU	NHS	DMF	DIPEA	28
5	EDC,HCl	NHS	DCM	TEA	35
6	DCC	NHS	DCM	TEA	40
7	DCC	NHS	DCM:DMF (1:1)	TEA	70

25 in 90 % yield by removing TBDMS group by treating with TBAF in THF at room temperature (**Scheme-V**).



Scheme-V: Synthetic route of (3*R*,11*S*) and (3*R*,11*R*) isomers

We retain Boc protection group as such on C-3 position, because it can be easily removed for preparation of libraries of derivatives of cordiarimide B by sulfonation, alkylation and acylation reactions to carryout SAR study.

Inhibition study of radical formation by DPPH assay: DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical method is an antioxidant assay based on electron-transfer that produces a violet solution in ethanol. This free radical is stable at room temperature and easily reduced in the presence of an antioxidant molecule. This results colourless ethanol solution and easily measured by absorbance. The DPPH assay was performed using the method described by Kedare and Singh [15] in which vitamin C was used as a control. The relative antioxidant activity of the compounds synthesized in this study is shown in Fig. 2. The natural stereoisomer compound (3*S*,11*S*) **18** shows 90 % antioxidant activity, while its diastereoisomer compound (3*S*,11*R*) **20** exhibit 65 % antioxidant activity compared to control compound vitamin-C. Interestingly inversion of hydroxyl group stereochemistry results in diminishing the antioxidant properties completely. This is evident by complete loss of antioxidant property of the two isomers compound (3*R*,11*S*) **23** and compound (3*R*,11*R*) **25**.

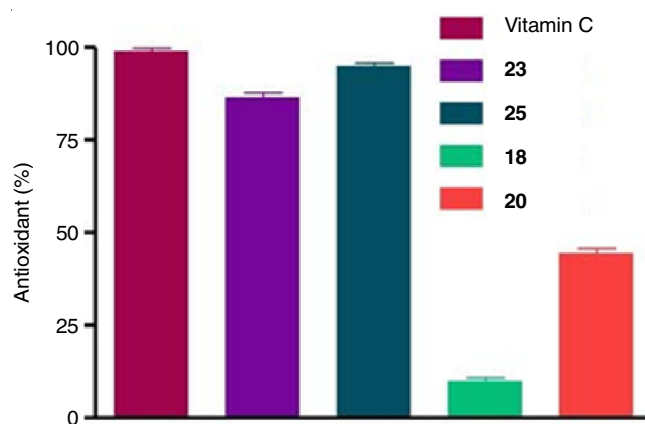


Fig. 2. Antioxidant assay of stereo isomers of cordiarimide B

Conclusion

A simple method for the synthesis of optically pure four isomers of N-Boc protected cordiarimide B is successfully developed. This method is a good complement to the already reported protocols for the versatile synthesis of cordiarimide B compounds. Given the importance of SAR study of multi-stereo centered natural compounds with respect to stereochemistry /stereoisomers in drug development and agrochemical industry, this work will be of greater interest in the biosciences.

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