Organic Chemistry: An Indian Journal

Review| Vol 16 Iss 8

Formal Synthesis Of Tetramethyl 1-*O*-Methyl Curculigine Aglycon

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Received: 18-Sept-2020, Manuscript No. OCAIJ -22-002-PreQc-22; **Editor assigned:** 05-Aug-2022, PreQC No. OCAIJ -22- 001-PREQC-22(PQ); **Reviewed:** 19-Aug-2022, QC No. OCAIJ -22-001-PreQc-22; **Revised:** 24-Aug-2022, Manuscript No. OCAIJ -22-001-PREQC-22(R); **Published:** 31-Aug-2022

Abstract

Curculigine isolated from the rhizomes of Curculigo capitulate and Curculigo recurvata plants of Hypoxidaceae family found potent against arrhythmia. Due to their biological importance we achieved the formal synthesis of Tetramethyl derivative of 1-O-Methyl curculigine Aglycon by applying Jacobsen's hydrolytic and kinetic resolution strategy. Key intermediate was synthesized in four steps with 27% overall yield and 86% enantioselectivity.

Keywords: ***Enantioselective, Formal Synthesis, Antiarrhythmic, hydrolytic and kinetic resolution, curculigine Aglycon.***

Introduction

Antiarrhythmic drugs are the group of pharmaceutical agents which are used to suppress abnormal rhythms of heart. Acetylenic norlignane glucosides isolated from the rhizomes of *Curculigo capitulate* and *Curculigo recurvata* of Hypoxidaceae family [1] show potent activityagainst ouabain-induced arrhythmia [2]. Structurally related norlignans like curcapicycloside and 1-*O*-methyl nyasicoside (FIG. 1) are also isolated in small concentration which are then characterised as its peracetylated glucoside penta-*O*-methylated ether. Considering the biological importance of this potent norlignane we attempt here enantioselective formalsynthesis of Tetramethyl 1-*O*-Methyl curculigine Aglycon derivative of curculigine by using Jacobsen's hydrolytic and kinetic resolution strategy [3, 4].

Citation: Bhangare DN, Mahale VB, Lokhande MN, et al. Formal Synthesis of Tetramethyl 1-O-Methyl Curculigine aglycon. Org Chem Ind J. 2022;16(3):67.

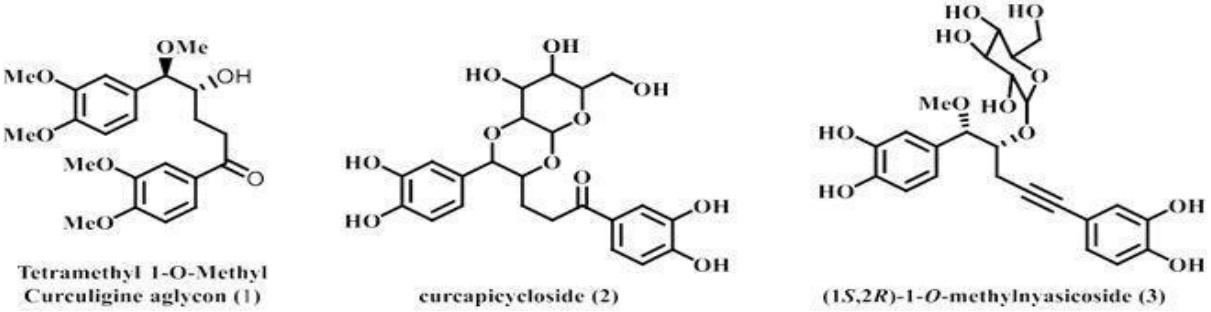

Fig 1: Curculigenin Analogue

Most of the medicinally important curculigine were obtained from their natural sources. Few literature reports are available for their synthesis in which G. H. Posner [5] achieved synthesis of Tetramethyl 1-*O*-Methyl curculigine Aglycon by Sharpless asymmetric dihydroxylations strategy using AD-Mix-β and methyl sulphonamide. While in other method Shoei-Sheng Lee [2] prepared Curculigenin *O*-glucosides by hydration of (1*R*)-1-*O*-Methylnyasicoside with HgO and Conc. H_2SO_4.

Experimental

All Reactions were carried in oven-dried glassware with distilled and dried solvents. TLC wasperformed on Merck Kiesel gel 60, F254 plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetateand hexane as the mobile phase. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR machine. ^{1}H and ^{13}C NMR spectroscopic data were collected at 300 MHz and 75 MHz respectively. ^{1}H NMR chemical shifts are given in ppm followed by multiplicity, number of protons and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with JASCO digital polarimeter. GCMS spectroscopic data were collected using Mass Spectrometer at Shimadzu Analytical Centre, Department of Chemistry, Savitribai Phule Pune University, Ganeshkhind, Pune, India. University of Pune.

2-((3,4-dimethoxyphenyl) (methoxy) methyl) oxirane (7)

A mixture of allyl alcohol (5.15 mmol, 1.0 g), MeOH (0.260 mL g, 6.44 mmol) was taken in CH3CN (20 mL) and NBS (0.916 g, 5.15 mmol) was added slowly via solid addition funnel, with stirring at 25 0C and progress of reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with EtOAc (15 ml) and washed with water and brine. The organic layer was dried over anhydrous Na2SO4 and concentrated under reduced pressure to give crude product, which was taken in THF (20 mL) and NaOH powder (206 mg, 5.15 mmol) was added slowly with stirring at 0 0C for 2 h. The reaction mixture was diluted with EtOAc (15 mL) and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na2SO4 and concentrated under reduced pressure to give crude products which was purified by column chromatography to give 880 mg of crude product. Yield: 72%, IR (CHCl3) 2963.2, 2920.1, 2846.5, 1593.1, 1513.0, 1502.8, 1462.1, 1454.1,
1411.6, 1255.9, 1231.1,1135.5, 1085.8, 1023.2, 805.0. 1H NMR δ 2.61 (dd, J 4.8, 2.8 Hz, 1H);
2.74 (t, J 4.6, 1H); 3.18 (m, 1H); 3.36 (s, 3H); 3.89 (s, 3H); 3.84(d, J 6.4 Hz, 1H); 3.91 (s, 3H);
6.90-6.86 (m, 3H). 13C NMR δ 44.15, 55.13, 55.76, 56 77, 84.65, 109.50, 110.88, 119.44,
130.36, 148.91, 149.14.

(+)-(2*S*,3*S*)-3-(3,4-dimethoxyphenyl)-3-methoxypropane-1,2-diol (8) and (-)-(*R*)-2-((*R*)-(3,4-dimethoxyphenyl)(methoxy)methyl)oxirane (9)

To a solution of (S,S)-A (0.012 g, 0.02 mmol) in toluene (1.0 mL) acetic acid (120 mg, 2.0 mmol) was added. Then, reaction mixture was stirred at room temperature in open air for 30 min. the colour of reaction mixture changed from orange red to a dark brown. Then, it was concentrated to get the Co-salen complex as brown coloured solid. To solution of Co-salen complex A-OAc (0.004 g, 0.5 mol%) and methoxy epoxide (0.80 g 3.56 mmol) in THF (0.5 mL) at 0 0C was added H2O (0.032 g, 1.78 mmol) drop wise over 5 min. The reaction was stirred at 25 0C for 24 h. After completion of reaction, solvent was removed in vaccuo and crude product was purified by column chromatography to give 380 mg chiral methoxy epoxide 9 in 47 % yield and chiral alkoxy diol 397 mg 8 in 50% yield. The optical rotation of chiral

methoxy epoxide 9 [α]25D= -19.4 (c, 0.18, MeOH) which was matched with literature [4] {[α]25 = -20.6 (c 0.18, MeOH)}. The analytical data of compound 9 is same as to racemic

epoxy alcohol 7. The optical rotation value of methoxy diol 8 is [α]25

= -29.90 (c 0.8, CHCl3);

1H NMR δ 1.68 (br s, 1H); 2.15 (br s, 1H); 3.25 (s, 3H); 3.30-3.64 (m, 2H); 3.90 (s, 6H); 4.13 (d, 1H, J 7.87 Hz); 6.85; 7.19-7.24 (m, 3H); 13C NMR δ 29.65, 55.86, 55.88, 56.81, 75.50, 84.81, 109.76,110.92(2C), 120.22(2C), 130.07 ppm.

Result and Discussion

The synthesis was initiated with 3,4-dimethoxy benzaldehyde 4 which was subjected to Wittig olefination [6] with triethyl phosphonoacetate in dry THF using NaH as a deprotonating agent at 0 0C. It gave white crystalline (E)-ethyl 3-(3,4-dimethoxyphenyl) acrylate 5 in 95% yield and more than 98% trans selectivity. The presence of olefinic proton at 6.29 δ and 6.85δ in 1H NMR confirmed the formation of product. This unsaturated ester was then converted to cinnamyl alcohol 6 by chemo selective reduction using lithium aluminium hydride in presence of benzyl chloride in dry THF at 0 0C [7], this reaction proceeds smoothly to offered compound 6 with 86% yield. The shifting of olefinic proton to 3.23-3.29δ and 4.25δ in 1H NMR confirmed the formation of product. Then, trans cinnamyl alcohol 6 converted to syn-alkoxy epoxide by Ende's [8, 9] method in which trans cinnamyl alcohol 6 first treated with N-bromosuccinamide, and methanol in acetonitrile to get intermediate methyl ether bromide which was after extraction in ethyl acetate and without further purification treated with base to afford racemic methyl ether epoxide 7. Here trans cinnamyl alcohol gives 100% syn-methyl ether epoxide. The characteristics epoxide peaks in 1H NMR indicate the formation of product [FIG 2]

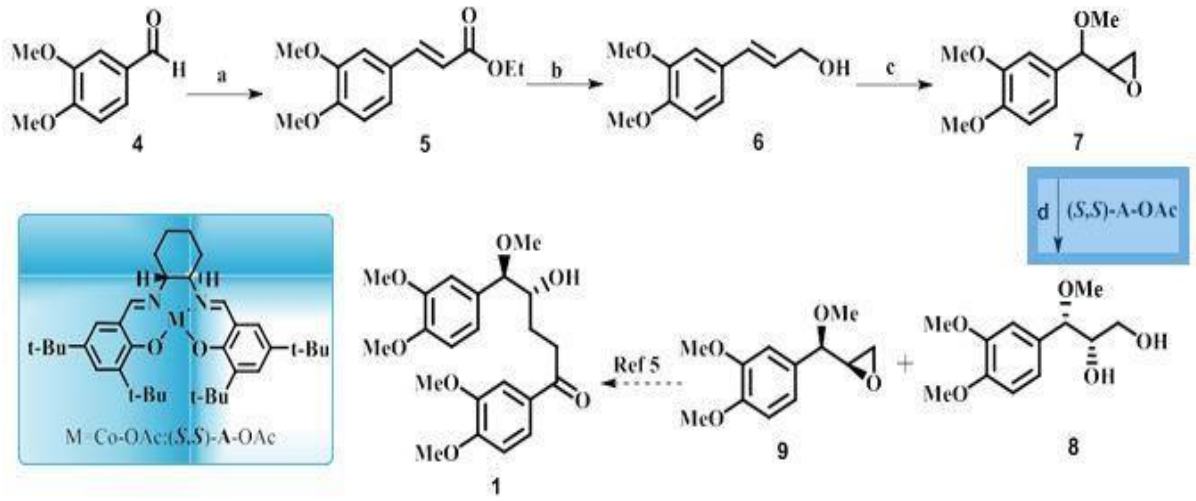

FIG 2: Formal Synthesis of Tetramethyl 1-*O*-Methyl curculigine Aglycon

Reagents and conditions: (a) NaH, triethyl phosphonoacetate, THF, 0 ^{0}C to rt, 12h, 95%; (b) $LiAlH_4$, BnCl, THF, 1h, 86%; (c) (i) NBS, MeOH, CH_3CN:H_2O, 0 ^{0}C to rt, 3 h; (ii) NaOH, THF, 3.5 h, 72% for two steps; (d) (*S*,*S*)-Co-OAc salan **A,** 0.55equi. H_2O, 24h, 47% **9** and 50% **8**.

Racemic methyl ether epoxide **7** have terminal epoxide and hence resolved by Jacobsen's hydrolytic and kinetic resolution method [3] using (*S, S*)-Co-salan catalyst and 0.55equivalentof water. Here, selective hydrolysis of one enantiomer produce optically pure diol **8** and otherunhydrolyzed optically pure epoxide **9**. After chromatographic separation of diol and epoxidetheir optical purity was confirmed by their optical rotation values which were matches with literature report.

The optical purity of methyl ether epoxide **9** was also determined by chiral HPLC using Lux 5u Cellulose-1 column. The optical purity of compound **9** was found to be more than 86%. Thespectral and optical rotation data of **9** were in accordance with data previously reported [5]. This compound has been previously converted to Tetramethyl 1-*O*-Methyl curculigine Aglycon **1** by Posner [5]. and hence the procedure described in here represents a formal synthesis of Tetramethyl 1-*O*-Methyl Curculigine aglycon.

Conclusion

We successfully achieved formal synthesis of Tetramethyl derivative of 1-*O*-Methyl curculigine aglycon.by applying Jacobsen's hydrolytic and kinetic resolution strategy. The keyintermediate was obtained in four steps with 27% overall yield and more than 86% enantioselectivity.

Acknowledgment

Author Bhangare DN, thankful to CSIR New Delhi for financial support during this work and Department of Chemistry, Savitribai Phule Pune University for facility.

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