Research Paper

Total Synthesis of a Natural Product in Poly(ethylene glycol): (±)-Centrolobine

ANNAREDDY SYAMPRASAD REDDY, RAMBABU CHEGONDI and SRIVARI CHANDRASEKHAR*
Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

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A natural product, (±)-centrolobine was synthesized using only one non-conventional solvent [poly(ethylene glycol)-400] as a reaction medium for all the reactions involved such as allylation of aldehyde, olefin metathesis, Wittig olefination followed by intramolecular oxa-Michael reaction and hydrogenation.

Graphical Abstract

Keywords: Natural Product; Poly(ethylene Glycol); Centrolobine; Total Synthesis

Introduction

The use of volatile solvents in a chemical transformation occupies the maximum volume and recovery and/or minimizing this is an ever demanding process. Recently, we (Chandrasekhar *et al.*, 2002; Chandrasekhar *et al.*, 2003; Chandrasekhar *et al.*, 2014) and others (Jiang and Ragauskas, 2006; Huaxing *et al.*, 2005; Li *et al.*, 2005; Zhang *et al.*, 2004) have demonstrated a new solvent medium, poly(ethylene glycol) (PEG) as an eco-friendly system for various functional group transformations. The importance of PEG as a biologically compatible polymer for drug delivery is well demonstrated and well approved by FDA for internal consumption (Harris, 1992; Herold *et al.*, 1989; Veronese *et al.*, 2002). Thus, we believe the synthesis of any bioactive molecule in this solvent medium will certainly attract attention by both academic and pharma research groups. The efforts

culminated in achieving the total synthesis of (±)-centrolobine in five steps including two one-pot reactions using poly(ethylene glycol) as a reaction medium in all the steps. Centrolobine (**1**, Fig. 1) is a tetrahydropyranic compound isolated from the heart wood of *Centrolobium robustum* (porcupine tree) and the stem of *Brosimum potabile* (Craveiro *et al.*, 1970; de Albuquerque *et al.*, 1964; Galeffi *et al.*, 1965). The synthesis of **1** has attracted attention due to its activity against *Leishmania amazonensis promastigotes*; a parasite associated with

Fig. 1: (±)-Centrolobine

*Author for Correspondence: E-mail: srivaric@iict.res.in; Fax: +91-40-27160512

leishmaniasis [Leishmaniasis is a major health problem in Brazil. Leon and co-workers conducted a screen of traditional remedies from the Amazon rainforest to find new *anti-leishmanial* compounds. (-)-Centrolobine is one of the active ingredients in a herbal tea made from the wood of *Cenrolobum robustum* that is used by the native people of the Amazon as a tonic cure] (Araujo *et al.*, 1998; Boulard *et al.*, 2004; Colobert *et al.*, 2002; Carreno *et al.*, 2003; Chan and Loh 2005; Chandrasekhar *et al.*, 2005; Evans *et al.*, 2003; Latif *et al.*, 2015; Marumoto *et al.*, 2002).

Results and Discussions

(±)-Centrolobine should be obtainable from lactol **2** and phosphonate **3** via Wittig olefination followed by intramolecular oxa-Michael reaction as key steps. The lactol **2** was further synthesized from commercially available aldehyde **4** using allylation, olefin metathesis followed by hydrogenation reactions (Scheme 1). The

Scheme 1: Retrosynthesis of (±)-Centrolobine

retrosynthetic strategy is designed in such a way that all reactions could be performed in PEG.

The synthesis began with the preparation of homoallylic alcohol **5** which was achieved by metal mediated allylation of aldehyde in the presence of Lewis acid catalyst (Scheme 2). We have subjected 4-methoxy benzaldehyde **4** with allyl bromide using zinc powder in poly(ethylene glycol)-400 in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as a Lewis acid catalyst. To the best of our knowledge this is the first example for allylation of aldehyde in PEG and could give the required product **5** in 89% yield. Encouraged by this result the recovery and reusability of the reagent system (PEG/Zn- $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) was also tried, but to our disappointment the yield of the product is decreasing for each run [The reaction medium, solvent and reagents, was recycled after first run, used for second run which afforded 54% yield and the third run gave only 32% yield of product **5**]. Next task was the conversion of compound **5** to α, β -unsaturated aldehyde **6** and was achieved by olefin metathesis in PEG again for the first time. The compound **5** was treated with acrolein in the presence of Grubbs 2nd generation (Fürstner, 2000; Grubbs *et al.*, 1995; Schrock and Hoveyda, 2003; Trnak and Grubbs, 2001) catalyst in poly(ethylene glycol)-400 for 24 h to afford the product **6** in 69% yield. The compound **6** was subjected to hydrogenation on PtO_2 in PEG-400. This resulted in the formation of lactol **2** in quantitative yields. Yet another new one-pot Wittig olefination-

Scheme 2 : Total synthesis of (±)-Centrolobine in poly(ethylene glycol)

intramolecular oxa-Michael pyranlation was achieved in PEG-400 using known phosphonate **3** (Solladie *et al.*, 1999) and $\text{Ba}(\text{OH})_2$ as base to realize the tetrahydropyranyl ether **7** with exclusive 2, 6- *syn*-diastereoselectivity. The diastereoselectivity was unequivocally confirmed using detailed analysis of ^1H NMR spectral data [The relative configuration of ($\pm$)-centrolobine was confirmed by NOE enhancements as shown in Fig. 2]. Finally, debenzylolation and deoxygenation of keto functionality in compound **7** was also accomplished in one-pot by hydrogenation in PEG, to afford the target molecule **1** in 70% yield.

Fig. 2: NOE enhancements observed in compound **7**

In all the steps, after completion of the reaction, the reaction mixture was diluted with anhydrous diethyl ether, stirred for **5** min and allowed to settle for 10 min. Cooling in an ice-salt bath caused solidification of the PEG and the ether layer was decanted. This process was repeated twice to get the product into the ether layer and evaporation of the ether furnished the pure product, which can be used in next step without further purification except for second step (product **6** was purified by column chromatography). However, a small portion of the product in each stage was purified to take the analytical data. The spectral data of thus generated ($\pm$)-centrolobine (overall yield 40%) was in full agreement with the ones reported for (-)-centrolobine (Galeffi *et al.*, 1965). The use of PEG as a solvent (reusable solvent) allowed us to recover Pd/C and PtO_2 catalysts in hydrogenation reactions.

In conclusion, we have accomplished the total synthesis of a natural product with complete stereocontrol in poly (ethylene glycol) as a single solvent media for all the reactions involved. The

solvent used for extracting the products in principle could be recycled if performed on large scale. The enantioselective synthesis of the same molecule using non-conventional solvents as reaction media is underway in our laboratory.

Experimental Section

All the commercial reagents were used without further purification unless indicated otherwise. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on Thermo Nicolet Nexus 670 spectrometer. Melting points are uncorrected. NMR spectra were recorded in CDCl_3 on a Varian Gemini 200 and Bruker 300, NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as the internal standard. Coupling constants (*J*) are quoted in Hertz. Column chromatographic separations were carried out on silica gel (60-120 mesh). Mass spectra were obtained on Finnegan MAT 1020B or micro-mass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

1-(4-Methoxyphenyl)but-3-en-1-ol (**5**)

To a stirred suspension of Zn powder (260 mg, 4 mmol) in poly (ethylene glycol) (400 MW, 3 g), was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (37 mg, 0.1 mmol), and aldehyde **4** (136 mg, 1 mmol) and allyl bromide (242 mg, 2 mmol) at room temperature under nitrogen atmosphere. The stirring continued vigorously for 6 hours at the same temperature. The reaction mixture was diluted with diethyl ether (5 mL) and stirred for 5 min., cooled to -10°C (ice-salt bath). The ether layer was decanted and the same ether treatment repeated twice (2 x 5 mL). The combined ether layer was washed with water, brine and dried over anhydrous Na_2SO_4 . The volatiles were evaporated on rotary evaporator to afford **5** (89% yield), which was used in next step without purification. The spectral data was identical with the literature data (Cai *et al.*, 2004).

(*E*)-5-Hydroxy-5-(4-methoxyphenyl)pent-2-enal (**6**)

To a solution of homoallyl alcohol **5** (178 mg, 1 mmol) in poly (ethylene glycol) (400 MW, 2g) was added

acrolein (224 mg, 4 mmol) and Grubbs (2nd generation) catalyst (42 mg, 0.05 mmol) under nitrogen atmosphere and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with diethyl ether (5 mL) and stirred for 5 min., cooled to -10°C (ice-salt bath). The ether layer was decanted and the same ether treatment repeated twice (2 x 5 mL). The combined ether layer was washed with water, brine and dried over anhydrous Na_2SO_4 . The volatiles were evaporated on rotary evaporator to afford crude compound **6**, which was purified by silica gel column chromatography and the obtained pure product **6** (69% yield) was used in next step. ^1H NMR (CDCl_3 , 300 MHz): δ 9.42 (d, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 6.88-6.78 (m, 1H), 6.17-6.08 (m, 1H), 4.82-4.78 (m, 1H), 3.8 (s, 3H), 2.84-2.65 (m, 2H), 2.62 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 194.1, 159.3, 154.5, 135.3, 134.8, 127.0, 114.0, 72.5, 55.3, 42.3; IR (neat): ν 3443, 2923, 2852, 1687, 1512, 1247, 1030, 830 cm^{-1} ; ESIMS (m/z): 229.1 ($\text{M}+\text{Na}$)⁺.

6-(4-Methoxyphenyl)-tetrahydro-2H-pyran-2-ol (2)

To a solution of δ -hydroxy α , β -unsaturated aldehyde **6** (206 mg, 1 mmol) in poly (ethylene glycol) (400 MW, 2 g) was added PtO_2 (12 mg, 0.05 mmol) under hydrogen atmosphere and stirred at ambient temperature (25°C) for 12h. The reaction mixture was diluted with ether and stirred for 5 minutes at 0°C temperature. The ether layer was decanted and the procedure repeated for four times. The ether layer was decanted and the same ether treatment repeated twice (2 x 5 mL). The combined ether layers were washed with water, brine and dried over Na_2SO_4 . The volatiles were removed on a rotary evaporator to afford **2** (98% yield), which was used in next step without purification. The compound **2**, was confirmed by mass [ESIMS (m/z): 231 ($\text{M}+\text{Na}$)⁺] and used for further reaction.

1-(4-(Benzyloxy)phenyl)-2,6-(4-methoxyphenyl)-tetrahydro-2H-pyran-2-yl)ethanone (7)

To a solution of Horner phosphonate **3** (334 mg, 1 mmol) in poly (ethylene glycol) (400 MW, 4 g), was added activated $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (315 mg, 1 mmol) under nitrogen atmosphere and stirred for 10 minutes. To this mixture was added, lactol **2** (208 mg, 1 mmol) at room temperature and stirring continued for 8 h. The reaction mixture was diluted with diethyl ether (10 mL) and stirred for 5 min., cooled to -10°C (ice-salt bath). The ether layer was decanted and the same ether treatment repeated twice (2 x 10 mL). The combined ether layer was washed with water, brine and dried over anhydrous Na_2SO_4 . The volatiles were evaporated on rotary evaporator to afford **7** (95 % yield), which was used in next step without purification. The spectral data was in full agreement with the literature data.

($\pm$)-Centrolobine (1)

To a solution of compound **7** (416 mg, 1 mmol) in poly (ethylene glycol) (400 MW, 3 g) was added 10% Pd/C, one drop of conc. HCl under hydrogen atmosphere and stirred at room temperature for 24 h. The reaction mixture was diluted with diethyl ether (5 mL) and stirred for 5 min., cooled to -10°C (ice-salt bath). The ether layer was decanted and the same ether treatment repeated twice (2 x 5 mL). The combined ether layers were washed with water, brine and dried over anhydrous Na_2SO_4 . The volatiles were evaporated on rotary evaporator to afford crude compound **1**, which was purified by silica gel column chromatography to get the pure ($\pm$)-centrolobine **1** in 70% yield. The spectral data of ($\pm$)-centrolobine was in full agreement with the ones reported for (-)-centrolobine.

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