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Synthesis of bis-tetrahydrofuran core of salzmanolin using intramolecular oxymercuration reaction

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Abstract The bis-THF core of salzmanolin was commenced from D-glucose as starting material. Stereoselective bis-THF ring has been established following intramolecular oxymercuration as the key reaction.

Keywords Acetogenin · Bis-THF · Natural products · Salzmanolin · Stereoselectivity · Oxymercuration

Introduction

In recent years, the *Annonaceous* acetogenins have attracted immense attention due to the remarkably wide range of biological activities like cytotoxic, antitumor, antimalarial, pesticidal, antifeedant, and antitumor activities [1–3]. Structurally, the acetogenins possess a bis-THF ring core flanked by two hydroxyl groups shows the highest anticancer activity [4]. Some reports are there for the synthesis of bis-THF ring core of acetogenins [5–8]. Salzmanolin (**1**) (Fig. 1), a ring hydroxylated unsymmetrical bis-tetrahydrofuran acetogenins, was isolated from the roots of *Annona salzmanii* D.C. by Queiroz et al. [9] in 2003. It shows cytotoxic activity against a cancer cell line (KB, $ED_{50} = 1 \times 10^{-3}$ μg/mL) when compared with normal cells (Vero, $ED_{50} = 1 \times 10^{-2}$ μg/mL). The interesting structural feature and biological activities of **1** attracted us for its total synthesis. Initially, we focused on the synthesis of central core of **1**. Since the relative stereochemistry is reported,

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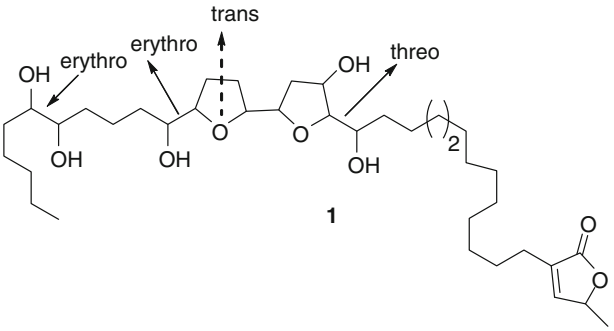
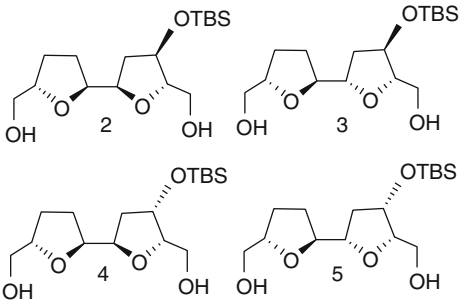


Fig. 1 Structure of salzmanolin

Fig. 2 Possible core structure of salzmanolin



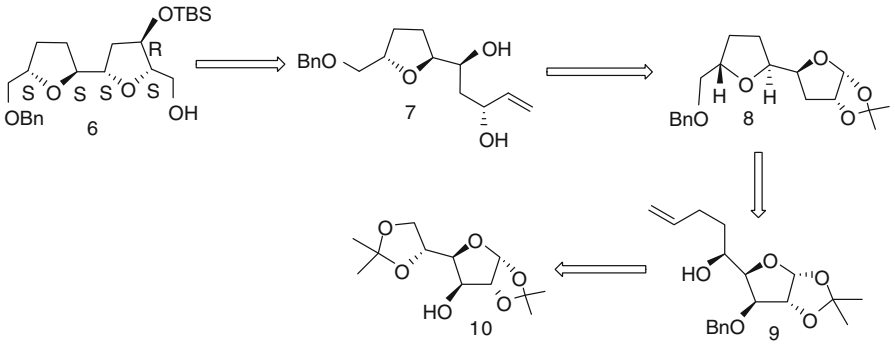
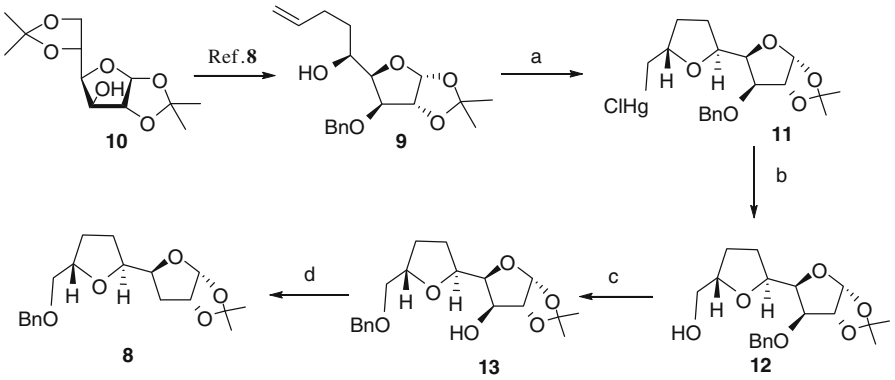


Fig. 3 Retrosynthetic analysis for mono-hydroxylated bis-tetrahydrofuran ring system of salzmanolin

on this basis we assumed few possible structures like compound **2**, **3**, **4,** and **5** (Fig. 2). We have previously reported compound **2** [10]. Now here we have reported benzyl protected compound **3** starting from D-glucose.

The retrosynthetic analysis for the bis-tetrahydrofuran ring system (**6**) is illustrated in Fig. 3. Stereo-controlled synthesis of **8** was planned to utilize an intramolecular oxymercuration reaction on 4-alkenol derivative **9** followed by a second oxymercuration reaction on **7** to form the target compound **6** (Fig. 3).

The intermediate **9** was commenced from D-glucose following the known literature procedure [11]. Having compound **9**, it was planned to install the



Scheme 1 Reagents and conditions: *a* $Hg(OAc)_2$, THF, rt, 2 h, 87 %; *b* O_2, $NaBH_4$, DMF, rt, 4 h, 81 %; *c* (i) Na, naphthalene, THF, 0 °C, 73 % (ii) NaH, BnBr, rt, 3 h, 94 %; *d* (i) NaH, CS_2, MeI, THF, 0 °C, 2 h, 93 %; (ii) Bu_3SnH, AIBN, toluene, 90 °C, 3 h, 94 %

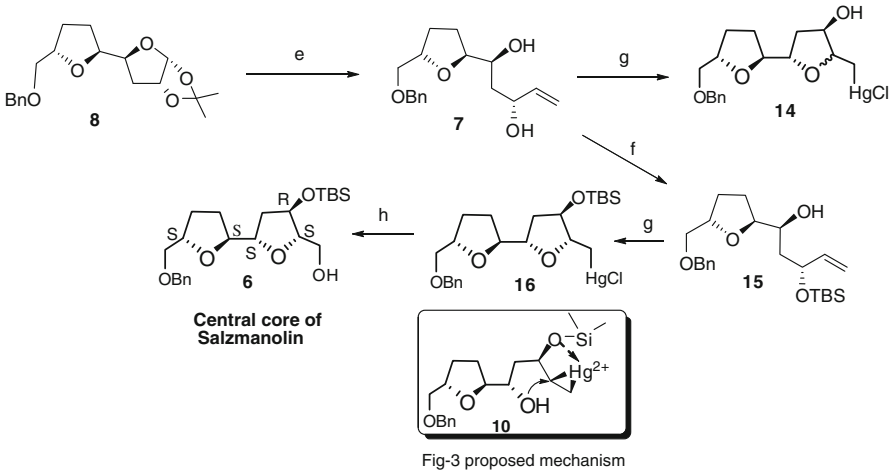


Fig-3 proposed mechanism

Scheme 2 Reagents and conditions: *e* (i) *p*-TSA(cat.), THF-H_2O, 60 °C, 2 h, 68 %; (ii) $Ph_3P{=}CH_2$, THF,0 °C-rt, 10 h 62 %; *f* imidazole, TBSCl, DMAP (cat.), DCM, rt, 2 h, 82 %; *g* $Hg(OAc)_2$, THF, rt, 2 h, 76 %; *h* O_2, $NaBH_4$, DMF, rt, 4 h, 74 %

tetrahydrofuran ring of **11** diastereoselectively. Hence, the intramolecular oxymercuration reaction performed on **9** using mercury (II) acetate in THF led to the formation of **11** exclusively [12, 13]. The relative stereochemistry around the THF ring of **11** was assigned by NOESY studies and was found to be *trans*. The demercuration reaction was carried out under a stream of oxygen in the presence of sodium borohydride in DMF to afford the primary alcohol **12**, which on debenzylation using Na/naphthalene and subsequent regioselective benzyl protection of primary alcohol provided compound **13** in good yield. After having compound **13** in hand, we intended to deoxygenate the secondary-OH group to achieve compound **8**. For this, two-step synthesis was followed. Compound **13**

undergoes Barton–McCombie protocol provided compound **8** in good yield (Scheme 1).

Our next concern was to set up the second tetrahydrofuran ring, and thus, compound **4** was treated with catalytic amount of *p*-TSA in THF-H_2O under reflux condition afforded the hemiacetal, which after purification by silica gel column chromatography, was subjected to one carbon homologation with $Ph_3P{=}CH_2$ to produce the olefin 7 [14]. Intramolecular oxymercuration reaction of 7 using $Hg(OAc)_2$ in THF afforded an inseparable mixture of products **14**. To achieve diastereoselectivity, it was planned to protect the allylic alcohol selectively and then to bring about the intramolecular oxymercuration reaction. To this end, allylic alcohol **7** was selectively protected by the TBS group using TBSCl, imidazole in DCM provided **15**. Intramolecular oxymercuration reaction of **15** using $Hg(OAc)_2$, THF provided compound **16** exclusively. Demercuration of compound **16** using a flow of O_2 in $NaBH_4$ in DMF provided the central core of salzmanolin **6** in good yield (Scheme 2).

Conclusions

Starting from D-glucose, we have synthesized benzyl protected bis-tetrahydrofuran core of salzmanolin using stereoselective intramolecular oxymercuration reaction as the key step. Following the present protocol, the total synthesis of salzmanolin is underway and will be reported in due course.

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