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Synthesis of (+)-xestodecalactone A

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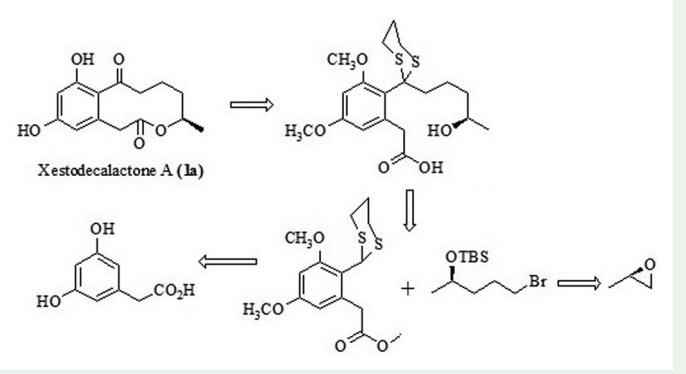
ABSTRACT

The total synthesis of Benzannulated macrolide, (+)-Xestodecalactone A was accomplished starting from commercially available enantiomerically pure propylene oxide and 3,5-dihydroxyphenylacetic acid using Grignard reaction, alkylation of 1,3-dithiane and Yamaguchi macrolactonisation as key steps.



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Benzannulated macrolactones; Xestodecalactones; Grignard reaction; Yamaguchi macrolactonisation

1. Introduction

Macrolide molecules containing a large lactone ring in its structure and considered to be derived from the corresponding hydroxyl acid by internal esterification (Collins 1999). Macrodiolides and macrocyclic monolactones are two types of macrolides. Researchers across the world concentrate on the synthesis of both homo and hetero dimers (macrodilactones) (Alluraiah et al. 2014; Edukondalu et al. 2015; Ramakrishna et al. 2016; Prataparedddy et al. 2017; Ramanujan et al. 2017; Ashok et al. 2018; Alluraiah et al. 2019; Edukondalu et al. 2020; Ramakrishna et al. 2021) and macrocyclic monolactones (Murthy et al. 2014; Prataparedddy et al. 2015; Alluraiah et al. 2016; Prataparedddy et al. 2020).

Benzannulated macrolactones are one of the most important classes of compounds due to their potent biological activities such as antibacterial, antifungal and anticancer

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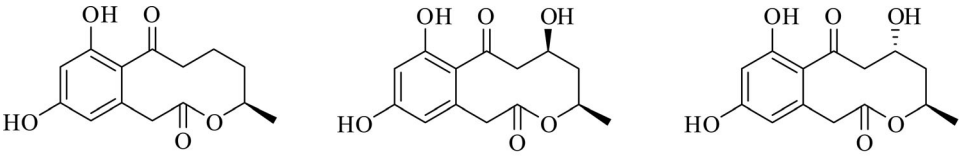


Xestodecalactone A **(1a)** Xestodecalactone B **(1b)** Xestodecalactone C **(1c)**

Figure 1. Structure of Xestodecalactones A–C.

behaviour (Musgrave 1956; Robeson et al. 1985; Lai et al. 1989, 1991; Ghisalberti and Rowland 1993; Sponga et al. 1999; Edrada et al. 2002; He et al. 2004; Zhan et al. 2004; Huang et al. 2008). Selected examples of these macrolides are radicicol (Nozawa and Nakajima 1979), Zearalenone (Stob et al. 1962; Urry et al. 1966), Lasiodiplodins (Aldridge et al. 1971; Li et al. 2005), sonnerlactones (Li et al. 2010), xestodecalactones (Petrier and Luche 1985; Luche and Einhorn 1987; Sharma and Kumar 2004) and curvularin (Musgrave 1956; Gerlach 1977) which received significant attention due to their interesting biological properties.

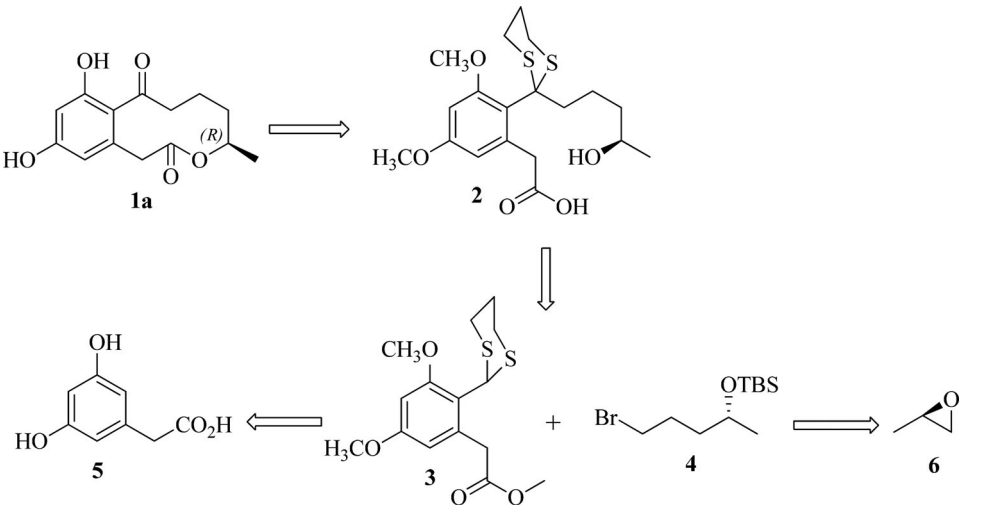
Among of these macrolactones, Xestodecalactones A-C (**1a-c**) are the novel Benzannulated decalactones, isolated from the fungus Penicillium cf. montanense obtained from the marine sponge *Xestospongia exigua* (Edrada et al. 2002). As shown in Figure 1, Xestodecalactones constitute 10-membered macrolides with a fused 1,3-dihydroxybenzene ring. Xestodecalactones A–C have been shown to exhibit antibacterial and antifungal activities (Bringmann et al. 2003). They are also found to be specific inhibitors of the epidermal growth factor (EGF) receptor, tyrosine kinase in vitro. The potential biological importance as well as the unique structural feature of these molecules prompted us to undertake the syntheses of these molecules. To date, several approaches for syntheses of Xestodecalactones A–C have been reported (Bringmann et al. 2004; Yoshino et al. 2006; Liang et al. 2007; Yadav et al. 2008; Rajesh et al. 2009; Yadav et al. 2009; Pal et al. 2012; De Joarder and Jennings 2013, 2015; Rao et al. 2019).

In this communication, we herein, report an alternative synthetic strategy to achieve the total synthesis of Xestodecalactones A (**1a**) utilising the alkylation of 1,3-dithiane and Yamaguchi macrolactonisation as the key steps.

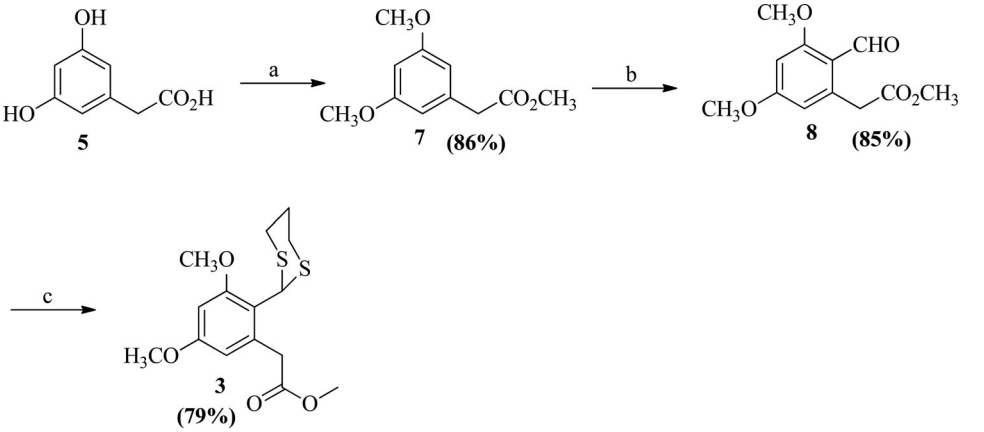
2. Results and discussion

Our retro synthetic approach for the synthesis of xestodecalactone-A was outlined in Scheme 1. The target molecule **1a** could be made from hydroxy acid **2** by intra molecular Yamaguchi macrolactonisation, whereas **2** could be synthesised from the coupling reaction of two key fragments dithiane **3** and bromide **4**. Dithiane intermediate **3** could be obtained from commercially available 3,5-dihydroxyphenylacetic acid **5** and bromide **4** was achieved from known chiral epoxide **6**.

As discussed in the retrosynthetic analysis, the synthesis of the xestodecalactone-A started with the preparation key intermediates **3** from commercially available 3,5-dihydroxyphenylacetic acid **5,** which is outlined in Scheme 2. Accordingly, the 3,5-dihydroxyphenylacetic acid **5** was subjected to O-methylation and esterification with



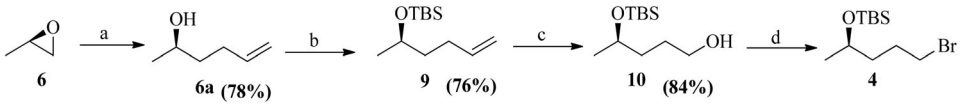
Scheme 1. Retrosynthetic analysis of xestodecalactone-A.



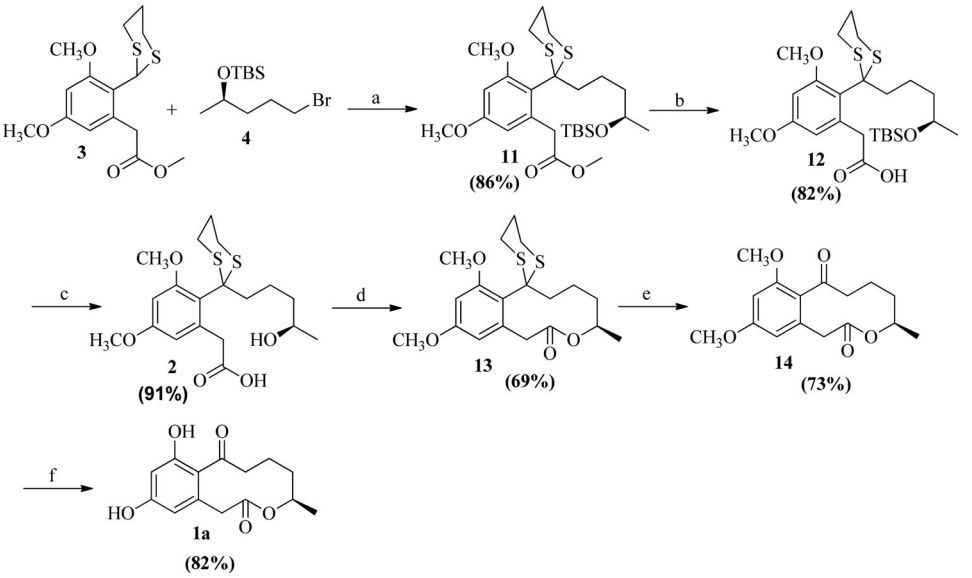
Scheme 2. *Reagents and conditions*: (a) DMS, K_2CO_3, acetone, reflux, 4h; (b) DMF, POCl3, rt to 55 °C, 12h; (c) 1,3-propanedithiol, BF_3•OEt_2, CH_2Cl_2, 0 °C to rt, 8h, 79%.

dimethyl sulfate in acetone at reflex for 4 h to afford **7** in 86% yield. The resulting ester **7** was transformed into aldehyde **8** via Vilsmeier-Haack formylation[16] (von Delius et al. 2017) using $POCl_3$ in DMF at room temperature for 20 h. Later, aldehyde **8** on treatment with 1,3-propanedithiol in the presence of $BF_3.OEt_2$ in CH_2Cl_2 at 0 °C to rt for 8 h afforded the key intermediate 1,3-dithiane **3** in 79% yield.

Synthesis of the other coupling partner **4** was commenced from known chiral epoxide **6** (Schaus et al. 2002). Accordingly, epoxide **6** on Regioselective ring-opening by allyl magnesium bromide in the presence of CuI yielded the alcohol **6a** in 78% yield. Subsequent silylation of the resulting alcohol **6a** with TBSCl and imidazole in CH_2Cl_2 gave **9** in 76% yield. Later, the terminal olefin moiety of **9** was subjected to Ozonolysis by using Ozone gas in CH_2Cl_2 at −78 °C for 15 min to furnish corresponding aldehyde, which on immediate reduction with $NaBH_4$ in MeOH at 0 °C for 6 h gave



Scheme 3. *Reagents and conditions*: (a) i) allyl bromide, Mg, CuI, dry ether, −78 °C, 2 h; ii) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (b) i) O_3, CH_2Cl_2, -78 °C, 30 min; ii) $NaBH_4$, MeOH, 0 °C to rt, 6 h; (c) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt, 3 h



Scheme 4. *Reagents and conditions*: (a) *n*-BuLi, dry THF, -20 °C, 3 h; (b) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h, 83%; (c) TBAF, THF, 0 °C to 25 °C, 3 h, 89%; (d) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, 25 °C, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 67%; (e) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), 45 °C, 3 h, 66%; (f) BBr3, CH_2Cl_2, -78 °C to r.t.

the alcohol **10** in 84% yield. Finally, treatment of alcohol **10** with CBr_4 in the presence of Ph_3P in CH_2Cl_2 afforded bromide **4** in 81% yield.

With two subunits in hand, we proceeded to couple both intermediates **3** and **4** as described in Scheme 3. Accordingly, dithiane **4** was lithiated by n-BuLi at −20 °C and then alkylated with bromide **3** to provide the desired product **11** in 86% yield (Scheme 4). Later, the resulting compound **11** was subjected to base (LiOH) hydrolysis in THF:MeOH:H_2O (3:1:1) to afford the corresponding acid **12**, which on desilylation with TBAF in THF at 0 °C to 25 °C for 3 h afforded hydroxy acid **2** in 91% yield. After successful synthesis of hydroxy acid fragment **2**, which was subjected to macrolactonisation under Yamaguchi high dilution conditions (Inanaga et al. 1979) to provide the lactone **13** in 69% yield.

Next, removal of 1, 3 dithiane group in compound **13** with $CaCO_3$ and MeI, in CH_3CN:H_2O for 3 h afforded the lactone **14** in 73% yield. Finally, the deprotection of both methyl ether groups in lactone **14** using BBr_3 in dichloromethane gave the xestodecalactone-A (**1a**) in 82% yield (Scheme 4). All the spectroscopic data of synthetic **1a** are (^{1}H and ^{13}C NMR, MS) and specific rotation fully consistent with the reported data of the natural product (Edrada et al. 2002).

3. Conclusions

Thus, in summary, we have demonstrated an efficient synthetic route for the total synthesis of xestodecalactone-A in a stereoselective manner with overall yield of 9.77%. The key steps involved in this synthesis are Grignard reaction, alkylation of 1,3-dithiane and Yamaguchi macrolactonisation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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