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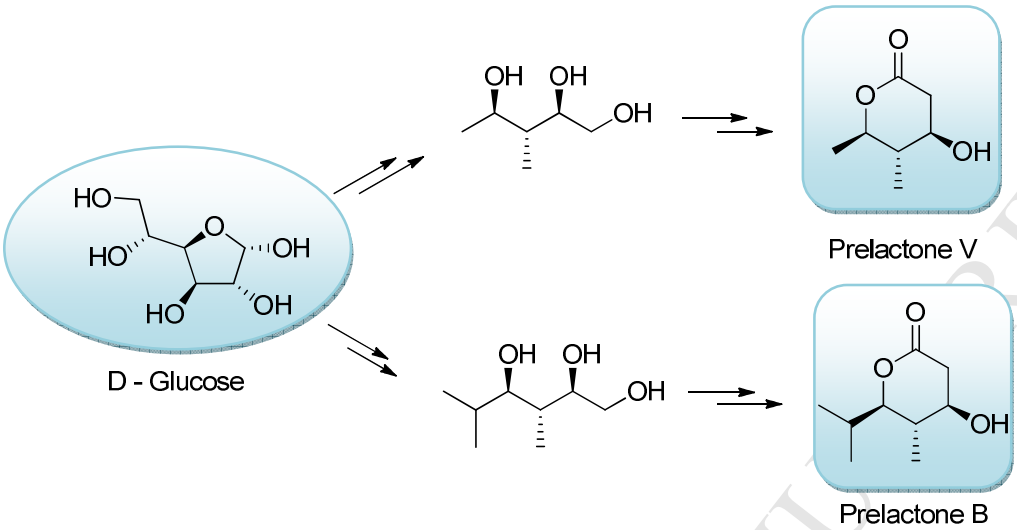

Total Syntheses of Prelactone V and Prelactone B

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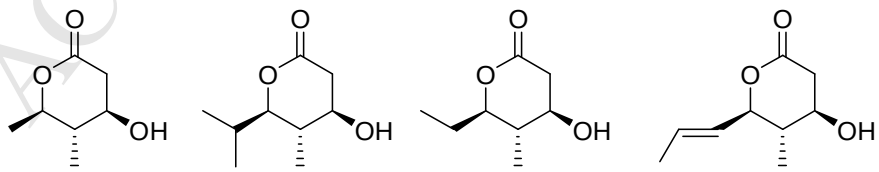
Abstract: The total syntheses of natural products Prelactone–V and Prelactone–B have been accomplished by a novel Chiron approach starting from D–glucose. The synthesis involves isopropylidene acetal formation of D-glucose using Poly(4-vinylpyridine) supported iodine as a catalyst, Tebbe olefination, Grignard reaction, Wittig olefination, selective mono deprotection of acetal using PMA/SiO_2, hydrogenation and anti-1,3-diol formation are as key steps.

Keywords: D-glucose, P(4-VPI)$^+I_3^-$, PMA/SiO_2, Wittig Olefination, Grignard reaction and Tebbe reaction and Lactonisation.

1. Introduction

Prelactones 1-4 belong to the family of polyketide macrolides with a δ-lactone, specifically a β-hydroxy-δ-lactone structure found in components of several drugs and bioactive natural products [1,2]. In addtion, they also represent useful building blocks for the synthesis of more complex structures [3-6]. Prelactones **1-5** (Fig. 1) are a subgroup of this class of natural products isolated in 1993 by Bindseil and Zeeck et al. [7] from the Streptomyces griseus. Prelactone B represents an early metabolite in the biosynthesis of polyketide antibiotics.



Prelactone V (1) **Prelactone B (2)** **Prelactone E (3)** **Prelactone C (4)**

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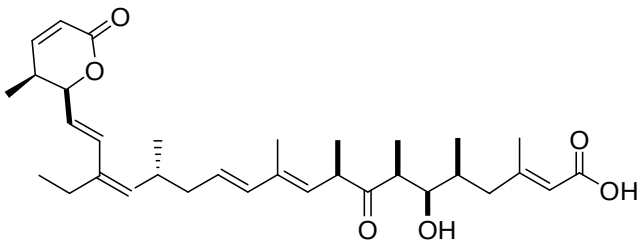


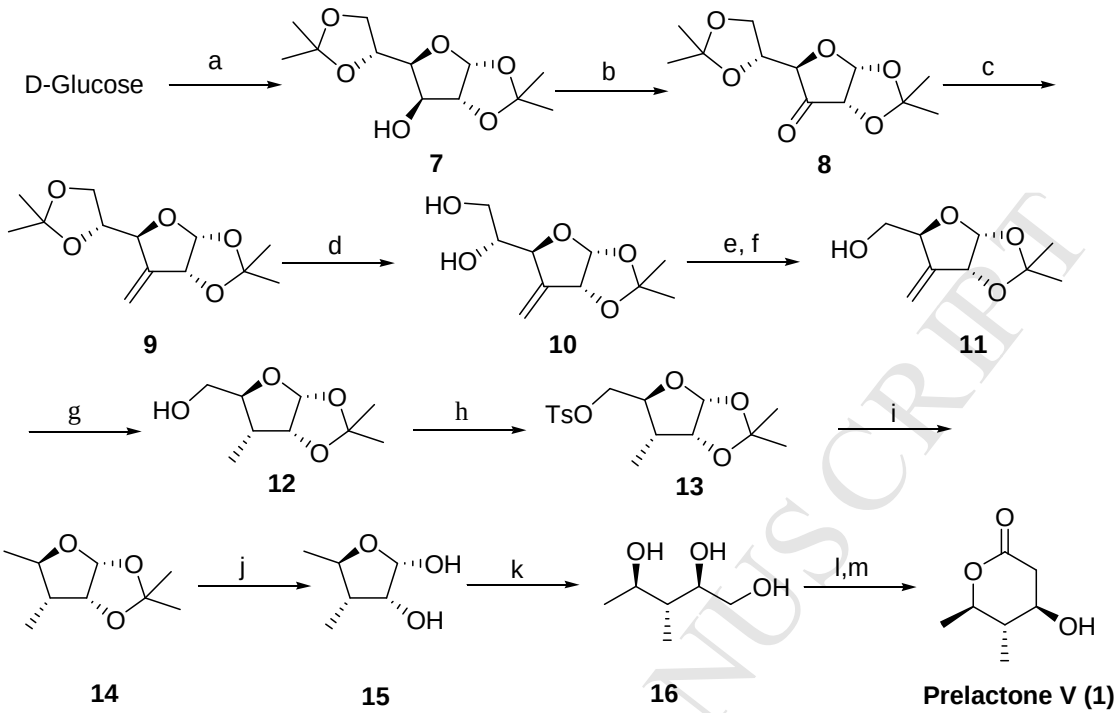
Leptomycin B
(5)

Figure 1. Chemical structures of Prelactones

It is well-known that the lactone moiety is responsible for the biological activity of Compactin and Mevinolin [8,9]. Consequently, a large number of approaches have been reported for the synthesis of prelactones [10,11,12]. Since δ-lactones are of great importance in stereo-controlled asymmetric synthesis of natural products [1], the development of modular strategy for the synthesis of these prelactones would allow the preparation of natural products as standards during mechanistic studies of polyketide biosynthesis and also provide a flexible route for the synthesis of *di-*, *tri-*, and *tetra-*substituted δ-lactones in a highly stereo-controlled manner (**Scheme 1**).

2. Results and Discussion

In continuation of our efforts towards synthesis of Leptomycin B [16, 17] (**5**), we have prepared some intermediates, from which we envisaged that prelactones can be synthesized in a highly stereo-controlled manner. We put our ideas into practice to synthesize these important lactones starting from 1,2,5,6-diisopropylidene-D-glucofuranose. We have developed a new methodology for the preparation of isopropylidene acetal from D-glucose using Poly(4-vinylpyridine) supported iodine [P(4-VPI)$^{+}I_3^{-}$] as a mild, efficient and reusable catalyst [18,19].

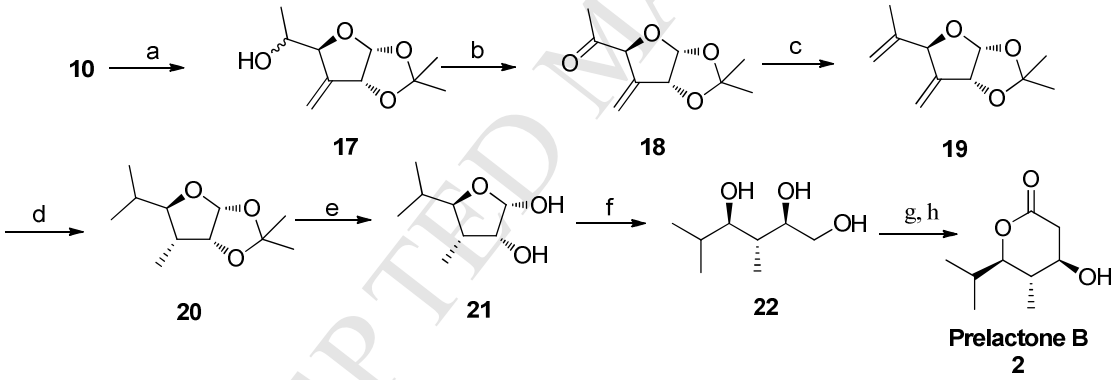


Scheme 1. Reagents and conditions: a) P(4-VPI)$^{+}I_3^{-}$, dry acetone, 3 A^{o} MS, 50 ^{o}C, 8 h, 65%; b) PDC, Ac_2O, 3A^{o} MS, CH_2Cl_2, r.t., 2 h, 85%; c) CH_3PPh_3I, *n*-BuLi, THF, -78 ^{o}C to r.t., 2 h, 95%; d) 1 mol% PMA/SiO_2, CH_3CN, r.t., 5 min, 95%; e) $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2, 1 h; f) $NaBH_4$, MeOH, 0 ^{o}C to r.t., 30 min, 94%; g) H_2, 10% $Pd(OH)_2$/C, ethyl acetate, r.t., 2 h, 95%; h) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 4 h, 95%; i) $LiAlH_4$, THF, 0 ^{o}C to reflux, 3 h, 88%; j) 30% AcOH, heat, 2 h, 72%; k) $LiAlH_4$, THF, 0 - 60 ^{o}C, 3 h, 85%; l) $NaIO_4$, cat. $NaHCO_3$ solution, CH_2Cl_2, 1 h; m) Ethyl acetate, LiHMDS, THF, -78 ^{o}C, 2 h, 62%.

Accordingly, we commenced the synthesis of prelactones from commercially available D-glucose as a starting material. Initially, 3-hydroxy-1,2,5,6-di–O-isopropylidene-α-D-glucofuranose **7** was prepared from D-glucose by using a new method which was developed by us [18] using P(4-VPI)$^{+}I_3^{-}$ a mild, efficient and reusable catalyst [19]. Oxidation of compound **7** with PDC [20,21,22] followed by one carbon Wittig olefination with PPh_3CH_3I in THF using *n*–BuLi at –78 ^{o}C afforded diacetonide olefin **9** in 95% yield. Selective mono deprotection of 5,6–isopropylidene acetal **9** was achieved by using **1** mole% phosphomolibdic acid supported on silica gel (PMA/SiO_2) in acetonitrile to furnish the diol **10** in 95% yield [23]. Oxidative cleavage of **10** using sodium periodate and aq. $NaHCO_3$ (cat.) afforded the corresponding aldehyde which *in situ* reduction with $NaBH_4$ in methanol at 0 ^{o}C provided the alcohol **11** in 94% yield. The stereoselective hydrogenation of **11** in the presence of 10% $Pd(OH)_2$/C in ethyl acetate at 60 psi resulted the compound **12** in 95% yield.

Tosylation of compound **12** with tosyl chloride in the presence of Et_3N in CH_2Cl_2 resulted the tosylate **13** in 95% yield. The compound **13** was subjected for reduction with $LiAlH_4$ under refluxing in THF to give the compound **14** in 88% yield. Cleavage of the 1,2-isopropylidene acetal **14** upon heating with 30% aq. AcOH provided the lactol **15**, which on subsequent treatment with $LiAlH_4$ in THF afforded the triol **16**. Oxidative cleavage of triol **16** with sodium periodate in the presence of aq. $NaHCO_3$ in CH_2Cl_2 gave the aldehyde which was immediately treated with organo lithium reagent which is generated *in-situ* from ethyl acetate and LiHMDS in THF at –78 ^oC to afford the anti-1,3-diol [24-30] containing β-hydroxy-ethylester in 62% yield as a major isomer, which was simultaneously underwent lactonisation to afford a six-membered (-)-Prelactone V (**1**) (**Scheme 1**).

Furthermore we focused our attention on the synthesis of Prelactone B (**2**). Thus, the synthesis of Prelactone B commenced from the key intermediate **10** which was used for the synthesis of Prelactone V (**1**) (**Scheme 1**).



Scheme 2. Reagents and conditions: a) i. $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2, 1 h; ii. MeMgI, dry ether, 0 ^oC to r.t., 2 h, 95%; b) PCC, NaOAc, CH_2Cl_2, r.t., 6 h, 89%; c) Tebbe's reagent [$Cp_2TiCH_2AlCl(CH_3)_2$], THF, 0 ^oC to r.t., 15 min, 90%; d) H_2, 10% $Pd(OH)_2/C$, ethyl acetate, r.t., 4 h, 98%; e) 30% AcOH, heat, 2 h, 72%; f) $LiAlH_4$, THF, 0 ^oC to r.t., 4 h, 85%; g) $NaIO_4$, aq. $NaHCO_3$, CH_2Cl_2, 1 h; h) Ethyl acetate, LiHMDS, THF, -78 ^oC to r.t., 62%.

Oxidative cleavage of the diol **10** using sodium periodate in the presence of aq. $NaHCO_3$ in CH_2Cl_2 provided the corresponding aldehyde, which was further subjected to the Grignard reaction i.e. with methylmagnesium iodide in dry ether at 0 ^oC. The diastereomeric mixture of alcohol **17** thus obtained was oxidized using PCC in the presence of NaOAc in CH_2Cl_2 to give the ketone **18** in 89% yield. Methylenation of the

ketone **18** using Tebbe's reagent [31] afforded the olefin **19** in 97% yield, which in turn was subjected to hydrogenation in the presence of 10% $Pd(OH)_2/C$ in ethyl acetate at 60 psi to give the compound **20** in 98% yield. Cleavage of the 1,2-isopropylidene acetal **20** by heating with 30% aq. AcOH gave the lactal **21**, which upon reduction with $LiAlH_4$ in THF at 0 ^oC afforded the triol **22**. Oxidative cleavage of compound **22** using sodium periodate in the presence of aq. $NaHCO_3$ in CH_2Cl_2 gave the corresponding aldehyde, which on subsequent treatment with organolithium reagent generated from anhydrous ethyl acetate using LiHMDS in THF at –78 ^oC to afford anti-1,3-diol [11] as a β hydroxy ethyl ester which was simultaneously underwent smooth lactonization to afford prelactone B (**2**) in 60% yield as a major isomer (**Scheme 2**). The synthesized Prelactone V (**1**) and Prelactone B (**2**) have been confirmed by the spectral studies. The spectral and physical data (melting point, specific optical rotation) of **1** and **2** were very closely matching with the reported data in the literature [32-35].

3. Conclusion

In conclusion, we have successfully demonstrated a modular strategy for the synthesis of Prelactone V and Prelactone B from 1,2,5,6-diisopropylidene-D-glucofuranose using Poly(4-vinylpyridine) supported iodine [$P(4\text{-}VPI)^+I_3^-$] as a mild, efficient and reusable catalyst for the protection of 1,2 and 5,6 hydroxy groups of-D-glucose.

Financial interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at

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The main highlights of this article are

- The total syntheses of natural products Prelactone–V and prelactone–B using a chiron approach starting from commercially available D–glucose.
- The synthesis involves isopropylidene acetal formation of D-glucose using Poly(4-vinylpyridine) supported iodine as a novel catalyst.
- The synthesis also involves the selective mono deprotection using PMA/SiO_2 catalyst.
- The synthesis also involves Tebbe olefination, Grignard addition and Wittig homologation in reasonable yields.