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Total Synthesis of Sch 725674

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ABSTRACT

A concise total synthesis of the macrolactone natural product Sch 725674 is accomplished starting from commercially available 2-deoxy-D-ribose. Pivotal reactions employed in the synthesis include the addition of 4-pentenylmagnesium bromide to the lactol derived from 2-deoxy-D-ribose, olefin cross metathesis and Yamaguchi macrolactonization.

1. Introduction

Sch 725674 (**1**) (Fig. 1) is a 14-membered macrolactone isolated by Yang and co-workers in 2005 from the culture of *Aspergillus* sp.[1] The structure of Sch 725674 was elucidated by extensive 2D NMR spectroscopy. It contains three free hydroxy groups and a *E*- α, β-unsaturated lactone. It was shown to exhibit antifungal activity against *Saccharomyces cerevisiae* and *Candida albicans* with MICs of 8 μg mL^{-1} and 32 μg mL^{-1} respectively. First total synthesis of Sch 725674 (**1**) and the confirmation of the absolute configuration was disclosed by Curran's group using their trademark fluorous tagging strategy.[2]

Following Curran's synthesis our group have reported the total synthesis of Sch 725674 starting from tartaric acid using Ley's dithiaketalization as the pivotal reaction to install the trihydroxy unit.[3] Later, many groups reported the total synthesis of Sch 725674,[4a-4f] Kaliappan and Ramakrishna[4a] reported the total synthesis of Sch 725674 starting from (S)-epichlorohydrin using Smith's Linchpin coupling of silyldithianes as key step. Reddy's synthesis of **1** originated from chiral pool D-ribose and have utilized Wacker oxidation as the key step to install the required triol fragment.[4b] Hanson et al.[4c] disclosed the synthesis of **1** based on a one pot sequential RCM/CM/hydrogenation reaction to install the triol unit. Kumar group[4d] reported the total synthesis of **1** commencing from (S)-glycidol in a multi-step sequence while Reddy and Sabitha[4e] utilized D-mannitol for the synthesis of **1**. Aggarwal's group accomplished the total synthesis of **1** using enatioselective diboration and subsequent oxidation of the chiral boronates to install the required triol.[4f] In our earlier synthesis of **1** from tartaric acid, the pivotal RCM reaction to afford the natural product suffered with a low yield. In continuation of our efforts on the use of chiral pool compounds in the total synthesis of natural products and to accomplish an improved synthesis of **1**, we undertook the total synthesis of Sch 725674 starting from commercially available 2-deoxy-D-ribose.

2. Results and discussion

We envisaged the formation of **1** from the seco acid **2** *via* Yamaguchi macrolactonization and further deprotection of the acetonide group. Formation of the seco acid **2** was anticipated from the alcohol **3**, which in turn could be obtained by olefin cross metathesis of the alkenes **4** and the masked tetrol containing alkene **5**. Addition of 4-pentenylmagnesium bromide to **6** obtained from 2-deoxy-D-ribose was chosen as appropriate transformation for the synthesis of triol containing alkene **5** (Scheme 1).

Accordingly, the synthesis commenced with the addition of 4-pentenylmagnesium bromide to the lactol **6**[5] which resulted in a separable 1: 1 diastereomeric mixture of diols **7** and **8** in 42% and 40% yields, respectively.[6] The diastereomer **7** was transformed to the required α-isomer **8** using Mitsunobu inversion in 60% yield (65% combined yield of **8** from **6**). The diol **8** was converted to the corresponding *bis*-silyl ether **5** under standard conditions in 97%

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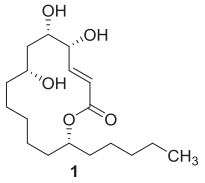
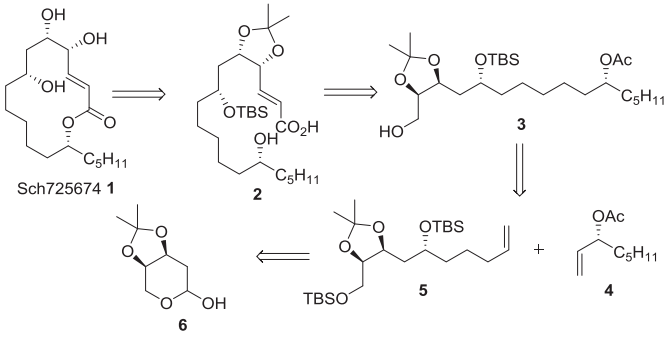


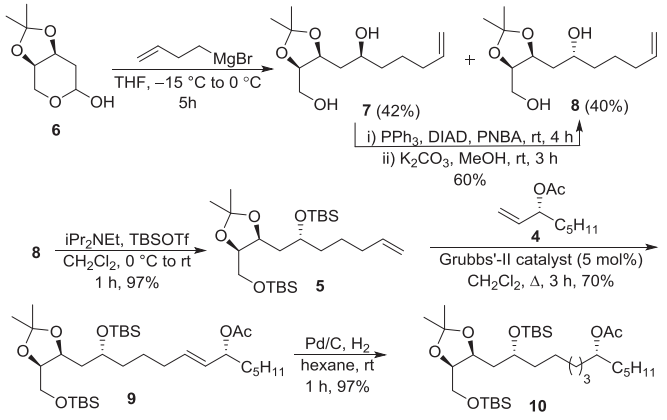
Fig. 1. Sch 725674.



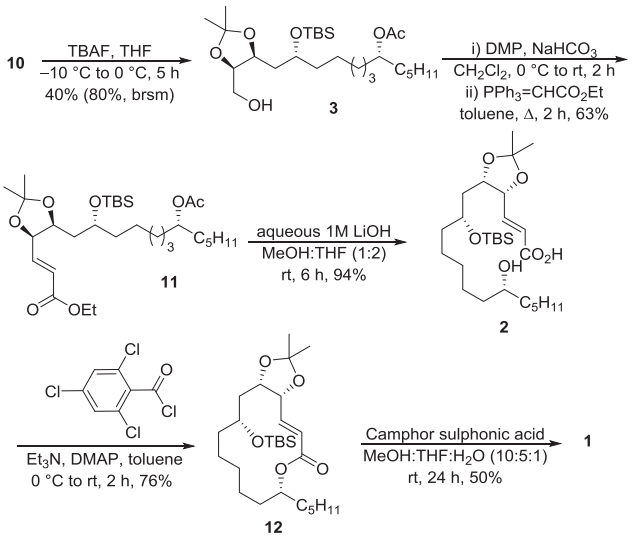
Scheme 1. Retrosynthesis for Sch725674 (**1**).

yield. Olefin cross metathesis of the alkene **5** with the allyl acetate **4**[7] in presence of Grubbs' second generation catalyst[8] furnished the product **9** in 70% yield. Hydrogenation of the olefin in **9** using Pd/C rendered the acetate **10** in 97% yield (Scheme 2).

Selective deprotection of the primary TBS group in **10** with TBAF afforded the primary alcohol **3** in 40% yield (80% based on starting material recovery). Oxidation of the primary alcohol in **3** with Dess Martin periodinane[9] followed by Wittig homologation of the resultant aldehyde furnished the conjugated ester **11** in 63% yield. Hydrolysis of both ethyl ester and acetate in **11** with 1 M aqueous LiOH provided the seco acid **2** in 94% yield, which under Yamaguchi lactonization reaction conditions afforded the 14-membered macrolactone **12** in 76% yield. Deprotection of the acetonide as well as TBS group in **12** with camphorsulphonic acid furnished the natural product Sch 725674 (**1**) in 50% yield. All the physical and spectral properties of **1** were in good agreement with that reported in the literature[3b] (Scheme 3).



Scheme 2. Synthesis of the key polyol unit **10**.



Scheme 3. Total synthesis of Sch 725674 (**1**).

3. Conclusions

In conclusion, a consise total synthesis of Sch 725674 was accomplished starting from known lactol derived from commercially available 2-deoxy-D-ribose in ~4% overall yield in 10 steps. Key reaction in the synthesis include cross metathesis and Yamaguchi lactonization to effect the macrolactonization. The reaction sequence is amenable for the synthesis of number of analogues of Sch 725674.

4. Experimental section

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz machine in $CDCl_3$ as solvent with TMS or residual solvent $CDCl_3$ or CD_3OD peak as reference. Unless stated otherwise, all the reactions were performed under inert atmosphere. All the specific rotations were determined at 24 °C.

4.1.1. Preparation of (S)-1-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-6-en-2-ol (7)

In an oven dried two neck 100 mL round-bottom flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed 4-pentenylmagnesium bromide (9.2 mmol, 18.4 mL of 0.5 M solution in THF). It was cooled to −15 °C and a solution of the lactol **6** (0.7 g, 3.6 mmol) in THF (10 mL) was added dropwise, at the same temperature. The reaction mixture was stirred for 30 min at the same temperature, slowly warmed to 0 °C and stirred for 5 h at the same temperature. After the reaction was complete (TLC), it was cautiously quenched by addition of saturated solution of aqueous NH_4Cl (20 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent gave the crude residue (as 1:1 mixture of diastereomers), which were separated by