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Synthesis of (+)-Patulolide C Using *R*-(+)-γ-Valerolactone as a Chiral Synthon.

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This article is dedicated to Prof. Simeon Arseniyadis for his valuable contribution to synthetic organic chemistry.

The total synthesis of (+)-Patulolide-C is accomplished by using enantiopure *R*-(+)-γ-valerolactone & *R*-(+)-epichlorohydrin as chiral synthons. The strategy adopted for the synthesis is a convergent approach wherein two advanced intermediates were synthesized independently using the chiral synthons and coupled to achieve the skeleton of Patulolide-C. The important synthetic steps of the synthesis are two carbon homologation of the cyclic lactol, Julia olefination of enone with sulfone in DME, DIBAl-H mediated regioselective opening of benzylidine acetal, selective oxidation of primary alcohol to aldehyde using BAIB/TEMPO and lactonization of *seco*-acid adopting Yamaguchi protocol to afford the macrolide skeleton.

Introduction

Patulolide A and C are naturally occurring 12-membered ring containing macrolides with antifungal and antibiotic activity.[1] The compounds were isolated from *Peniciliumurticae* S11R59 and characterized by Yamada and co-workers.[1,2] Its seco-acid **17** is characterized by the presence of stereogenic centers at 4- and 11- positions. Total synthesis of structurally related Patulolide has been reported in the literature.[3] γ-Lactones are important structural entities and valuable building blocks in the synthesis of natural products and biologically active molecules such as pheromones, polyketides and prostaglandins.[4] Considering the high stereoselectivity during Wittig reaction of the corresponding lactol of optically pure γ-valerolactone, the latter becomes a very good chiral synthon in the synthesis of natural products.[5] A variety of methods are in practice for the synthesis of optically pure γ-lactones that either use stoichiometric or catalytic chiral reagent systems[6] or enzymes as part of a greener approach for the asymmetric hydrogenation[7] of γ-keto esters. With a lot of progress being made in the field of asymmetric reduction of γ-keto esters using enzymes[8] it has now become quite facile to obtain the chiral alcohols that afford chirally pure γ-valerolactones in large quantities starting from γ-keto esters. The biological activity of macrolides stem from the presence of a macrocyclic ring either medium-sized (7 to 11 membered) or large-sized (12 membered and larger).[9] These lactones are important structural motifs in a wide range of biologically active natural products.[10] Few examples of simple monocyclic macrolides are, Diplodialide-A&B, Phoracantholide-I and Phoracantholide-J, Patulolide-A & C are shown in Figure 1.

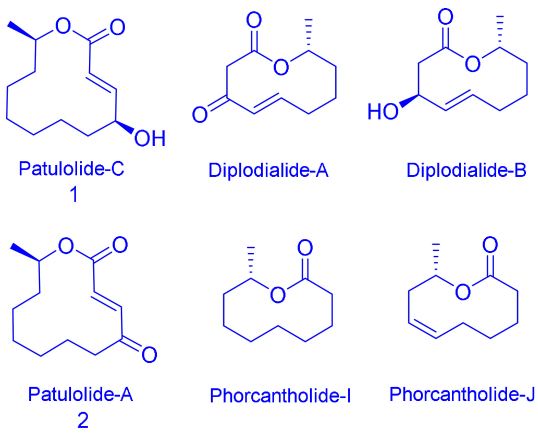

Figure 1. Monocyclic Macrolides.

In continuation of our efforts to synthesize biologically active molecules[11] beginning with chiral γ-valerolactone herein we report a facile route for the total synthesis of (+)-Patulolide-C (**1**). Further (*R*)-(+)-γ-valerolactone was synthesized in high enantiomeric purity following a literature

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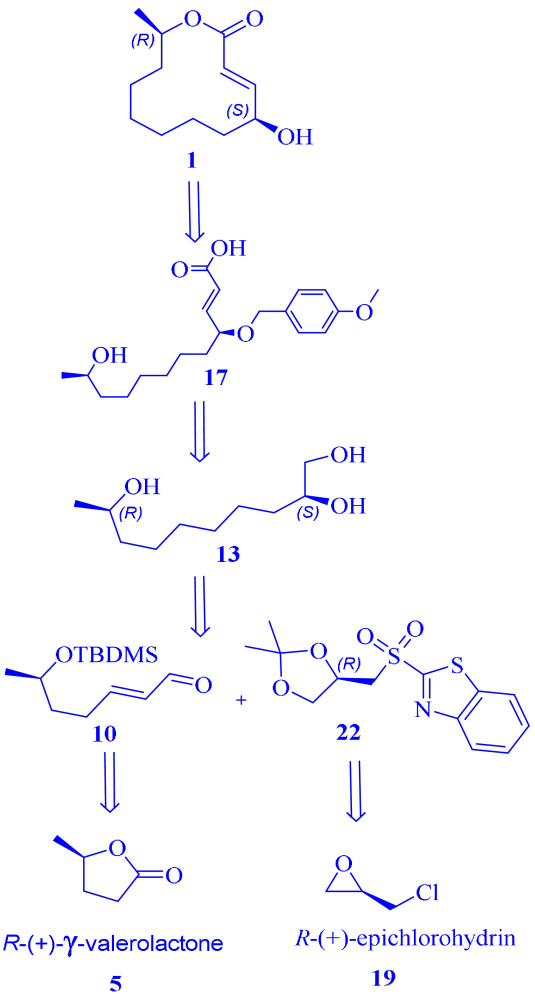
approach that uses catalytic amount of ADH enzyme for the asymmetric reduction of the keto function of commercially available ethyl levulinate.[12]

The retrosynthetic approach of title compounds **1** and **2** is described in Scheme 1. Thus **1** can be obtained by Yamaguchi

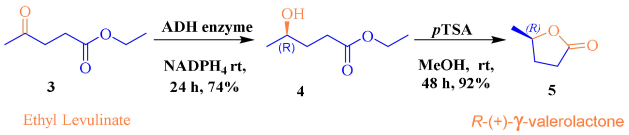


Scheme 1. Retrosynthetic approach for (+)-Patulolide-C.

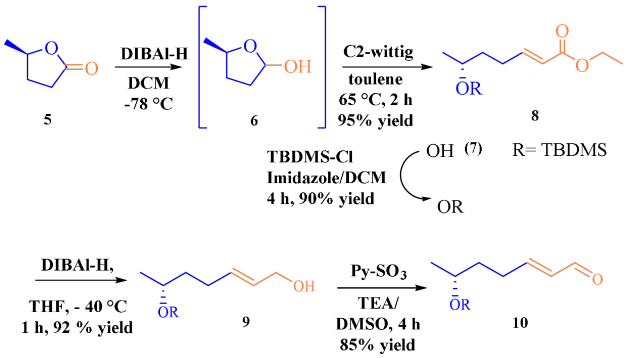
lactonization of the *seco*-acid **(17)** followed by deprotection of PMB ether using DDQ (Dichloro-5,6-dicyano-1,4-benzoquinone). The intermediate *seco*-acid **(17)** can be obtained from compound triol **13**. The latter was obtained *via* Julia olefination of fragments **10** and **22**. Compound **10** can be traced from *R*-(+)-γ-valerolactone **5** while compound **22** from *R*-(+)-epichlorohydrin **19**.

Results and discussion

As mentioned above in Scheme 2, *R*-(+)-γ-valerolactone(**5**) is synthesized from commercially available ethyl levulinate (**3**) using enzyme ADH in high optical purity (98.14% *ee* by GC)[13] Enantiopure alcohol thus obtained was subjected to lactonization on treatment with *p*TSA (*p*-Toluenesulfonic acid).



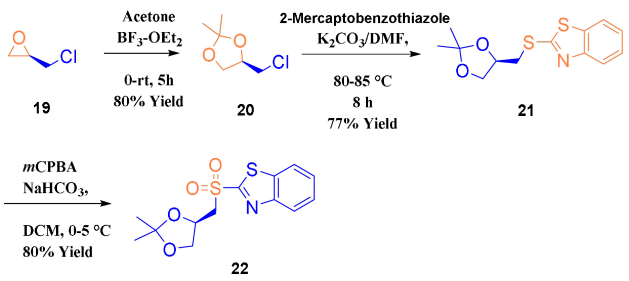
Scheme 2. Synthetic scheme for *R*-(+)-γ-valerolactone (**5**).



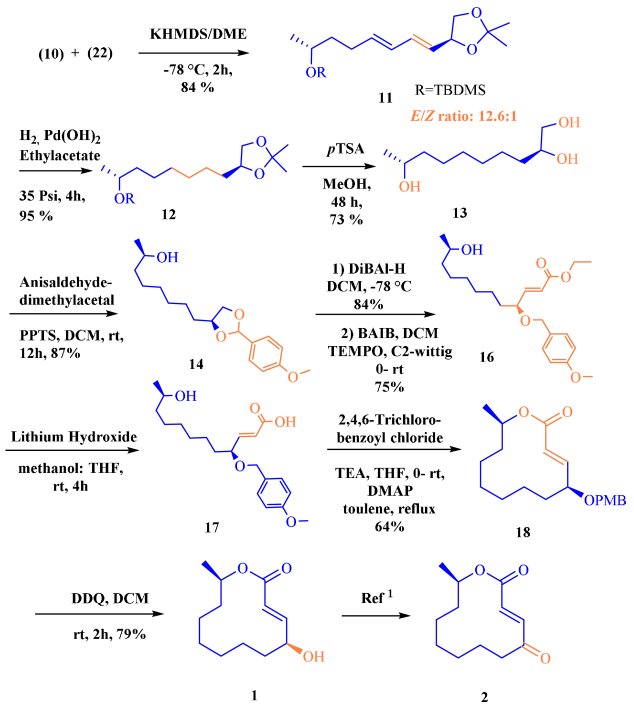
Scheme 3. Synthetic scheme for enone (**10**).

Synthesis of enone-**10** began with Diisobutylaluminium hydride (DIBAL-H) mediated reduction of *R*-(+)-γ-valerolactone at −78 °C to afford corresponding lactol.[14] The latter was treated with C2-Wittig reagent to afford **7** with an *E:Z* ratio of 95:5 as observed by ^{1}HNMR. The hydroxy function of the mixture was protected as corresponding silyl ether **8** using *tert*-Butyldimethylsilyl chloride (TBDMSCl).[15] Reduction of α,β-unsaturated ester **8** using DIBAL-H afforded allyl alcohol **9**.The allyl alcohol **9** was oxidized to enone **10** using DMSO/Py-SO_3 (Sulfur trioxide pyridine complex).[16]

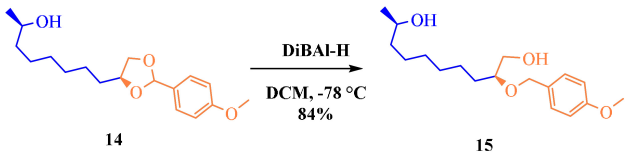
Similarly synthesis of sulfone **(22)** was initiated starting from *R*-(+)-epichlorohydrin in three steps with an overall yield of 62%. Thus *R*-(+)-epichlorohydrin **(19)** was converted to (*R*)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane **(20)** following a known procedure.[17] The latter was converted to (*R*)-2-(((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio) benzo[d] thiazole **(21)** by coupling **20** with 2-mercaptobenzothiazole in the presence of K_2CO_3 at elevated temperature. Oxidation of **(21)** was achieved using *m*-chloroperbenzoicacid (*m*CPBA) to furnish the sulfone **(22)** in good yield as depicted in Scheme 4.



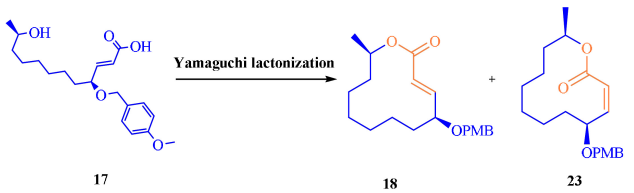
Scheme 4. Synthetic scheme for sulfone (**22**).



Scheme 5. Synthetic scheme for (+)-Patulolide A & C (2 & 1).



Scheme 6. Regioselective opening of PMB acetonide (**15**).



Scheme 7. *cis* and *trans* isomerization.

Synthesis of (+)-Patulolide-C (**1**) began with the coupling of enone (**10**) with sulfone **(22)** under Julia olefination condition[18] to afford corresponding diene (**11**) as an mixture of *E/Z isomers* with 12.6 : 1 ratio. Diene **(11)** was then subjected to catalytic hydrogenation using $Pd(OH)_2$[18d] to afford saturated compound **12**.The latter upon treatment with either *p*TSA/MeOH or methanolic HCl yield triol (**13**) as shown in Scheme 5. Several attempts targeted at the selective deprotection of acetonide of **12** in presence of TBDMS ether were unsuccessful[19] and resulted in a mixture of products.

The triol **(13)** was then protected with anisaldehyde dimethyl acetal in presence of catalytic *p*TSA to afford corresponding benzylidineacetal **(14)**. Thus obtained PMB (*p*-methoxy benzyl) acetal (**14**) was regioselectively opened with DIBAl-H to afford compound **15.**[20] as shown in Scheme 6. This step afforded the ideal structural frame work to expedite the final molecule synthesis *via* selective oxidation. Accordingly compound **15** was subjected to one pot selective oxidation and concomitant C2-ylide extension using BAIB (bis acetoxy iodo benzene)/TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) and stable 2 carbon ylide to afford **16** with good *E*-selectivity and yield.[21] Compound **16** was saponified using LiOH/MeOH in THF to provide *seco* acid **(17).**[22] Cyclization of *seco*-acid **17** was done following Yamaguchi conditions to afford corresponding lactone **(18)**.[23] During Yamaguchi lactonization we encountered the problem of *cis* and *trans* isomerization (Scheme 7) upon treatment with 2,4,6-trichloro benzoyl chloride and excess of 4-Dimethylaminopyridine (DMAP).[24] The ideal quantity of DMAP was reported to be 4 to 6 mole equivalents and addition of mixed anhydride at elevated temperature resulted in a single regio-isomeric lactone **(18)**. In the end PMB ether was deprotected using DDQ[25] to accomplish the title compound Patulolide-C **(1)**. Patulolide A **(2)** can be synthesized formally from Patulolide-C as reported in lit.[1]

Conclusions

In summary, a highly stereoselective synthesis of *R*-(+)-Patulolide-C (**1**) has been demonstrated beginning with *R*-(+)-γ-valerolactone. The route of synthesis developed for these macrolides utilized fairly inexpensive reagents and operationally friendly processes. Further, studies toward the stereoselective synthesis of other biologically active macrolides utilizing the *R*-(+)-γ-valerolactone as chiral synthon is currently underway.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Ethyl levulinate · Julia olefination · Macrolides · Patulolide · (*R*)-γ-valerolactone · Wittig reaction · Yamaguchi lactonization

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