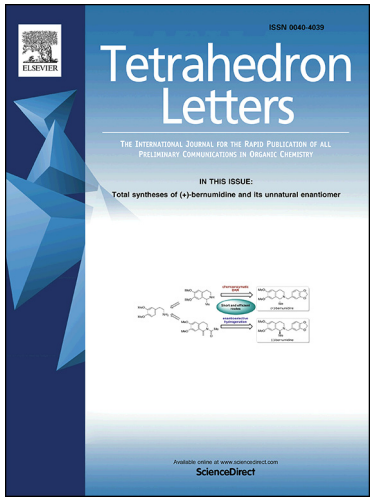

Formal synthesis of Pellasoren - A

Katta Muralikrishna, Gavireddy Chaithanya kumar, Vavilapalli Satyanarayana, R. Sudheer Kumar, Jhillu singh Yadav

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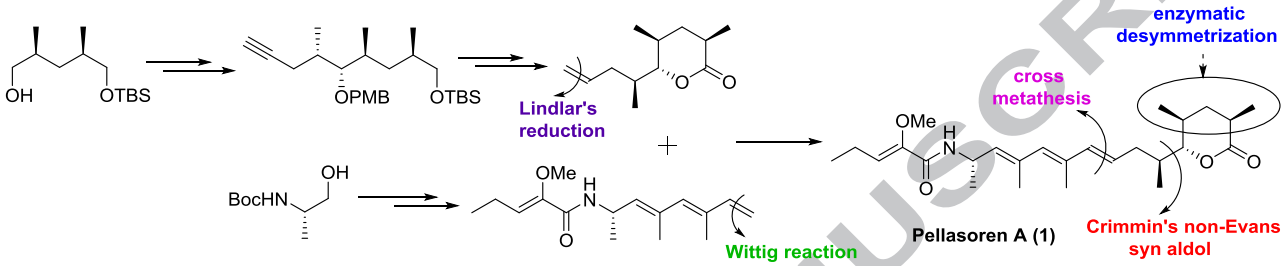

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Formal synthesis of Pellasoren - A

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ABSTRACT

A convergent and highly stereoselctive formal synthesis of Pellasoren – A is described. The salient features of the synthesis are the utilization of enzymatic desymmetrization, Crimmin's non-Evans *syn* aldol, Lindlar's and Wittig reaction.

The wide varieties of efficient secondary metabolites are produced by Myxobacteria, and the genus *Sorangium* is commonly characterized as proficient source for new, biologically active natural products.[1] In 2012, Pellasoren – A (**1**) and B (**2**) are secondary metabolites, were isolated from *S. cellulosum So ce35* by Christine Jahn, both display anticancer activity, in particular Pellasoren – A (**1**) exhibits cytotoxicity against HCT-116 human colon cancer cells at a concentration of 155 nm (IC_{50}), emphasizing the importance of the linear an all-(E) configuration. Furthermore, both pellasorens show a strong effect on lysosomes. In structural of view in interesting structural features of Pellasoren A (**1**) and B (**2**) are isobaric compounds having the same constitution, some changes in the double bond system at C10–C11 which can be rationalized by photochemical isomerization of *E*/*Z* isomers, respectively.[2]

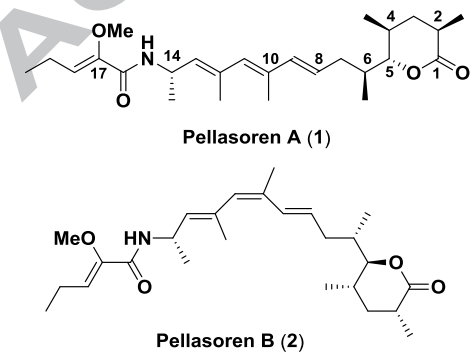
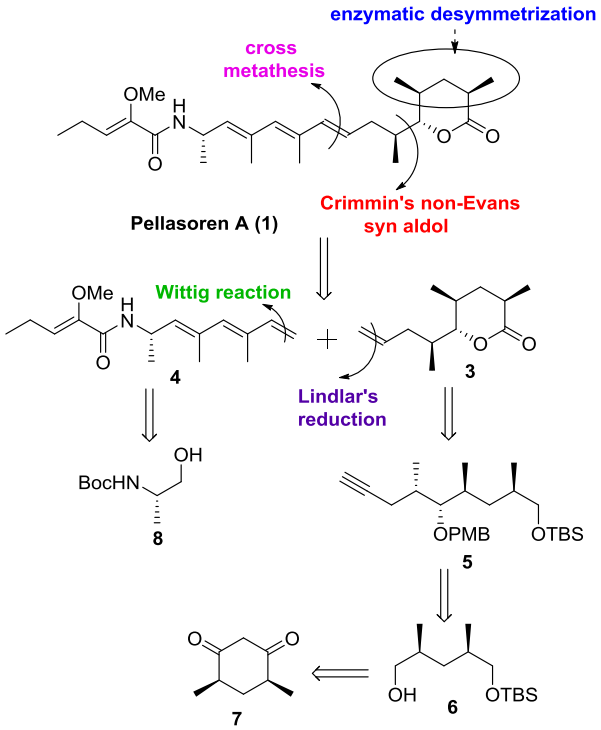


Figure 1: Structures of Pellasoren- A(1) and B(2)

Christine Jahn *et al* reported the discovery, complete structure elucidation in year 2012 and first total synthesis of pellasoren - A (**1**) through coupling of two key fragments by *E*-selective Wittig olefination. Recently Shinji Sekiya *et al* disclosed total synthesis of pellasoren – A (**1**) by Cross Metathesis *via* synthesis of stereoselective bromination of the *E,E*-vinylketene silyl N,O acetal a chiral auxiliary and applied to introduction of heteroatom at *γ* -position of *α, β* - unsaturated imide.[3] We herein present a facile and general method for the stereoselective formal synthesis of Pellasoren - A (**1**) using enzymatic desymmetrization and a Crimmins "non-Evans" *syn* aldol reaction to generate the four of the five stereogenic centres with good diastereoselectivity.

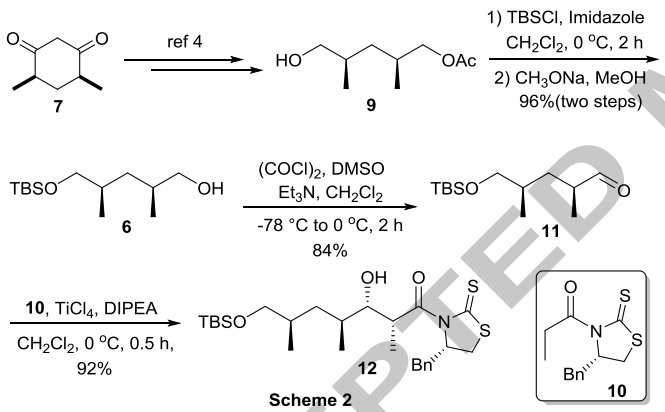


Scheme 1: Retrosynthetic analysis of Pellasoren - A (1)

Our retrosynthetic plan of Pellasoren – A (**1**) is disclosed in Scheme 1. The target molecule **1** was divided into two fragments i.e, lactone fragment **3** and amide fragment **4,** which could be combined by cross metathesis. A key objective for preparing lactone fragment **3** would be obtained from a compound **5**, which could be constructed by means of Crimmin's non-Evans *syn* aldol reaction with chiral auxiliary **10** and aldehyde **9**, which in turn to be achived from *meso*-4,6-Dimethylcyclohexane-1,3-dione **7**. Amide fragment **4** would be synthesized by coupling of carboxylic acid and amine along with the tetraene geometry in a concise manner; amine might be derived from **8**.

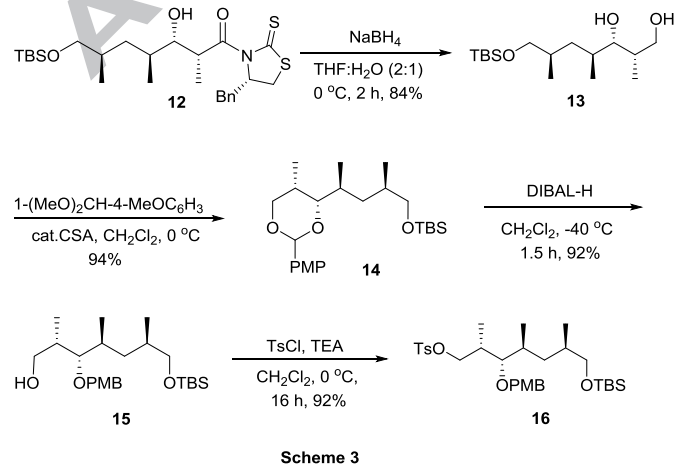
Results and Discussion:

Our synthesis began with a known precursor *meso*-4,6-Dimethylcyclohexane-1,3-dione **7** by the application of the enzymatic desmmetrization to the known diol to produce monoacetate **9** the diol commenced from compound **7** according to a literature procedure.[4] Monoacetate **9** was protected as silyl ether using TBSCl and imidazole in CH_2Cl_2 and then treated with CH_3ONa in methanol to furnish the desired primary alcohol **6** in 96% yield over two steps.[5] (Scheme 2)



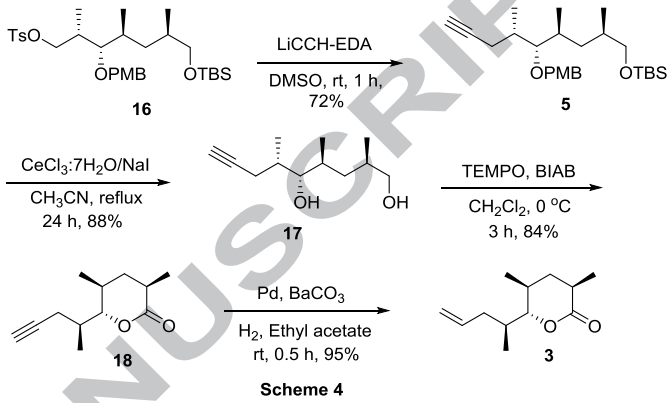
Scheme 2

At this stage primary alcohol in **6** was then oxidized to the corresponding aldehyde **11** under Swern conditions[6] with a considerably good yield. The aldehyde **11** was subjected to $TiCl_4$ mediated Crimmin's non-Evans *syn* aldol reaction[7] with Crimmin's chiral auxiliary **10** using DIPEA to produce the non-Evans *syn* aldol adduct **12** with *dr* >95:5 (Scheme 2).



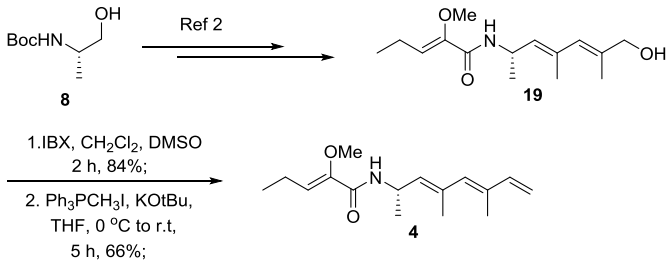
Scheme 3

The chiral auxiliary was cleaved from aldol adduct **12** by treating with sodium borohydride in THF: H_2O (2:1) to furnish diol **13** with a considerably good yield.[8] The 1, 3-diol group of **13** was protected with *p*-methoxy benzyl dimethyl acetal and catalytic amount of CSA in CH_2Cl_2 to afford the acetal compound **14** in 94% yield.[9] The regioselectively PMB acetal **14** was reduced by using DIBAL-H in CH_2Cl_2 at – 40 ^oC to afford the compound **15** in 92 % yield.[10] The primary alcohol in **15** (TsCl, TEA, 92%) was converted to its tosyl derivative **16** (Scheme 3).



Scheme 4

The tosyl derivative **16** was treatment with 5 equiv of lithium acetylide in dimethyl sulfoxide (DMSO) to furnish corresponding alkyne **5** in 72% yield.[11] The PMB and TBS groups in compound **5** were deprotected with $CeCl_3$:$7H_2O$/NaI to furnish diol **17** in 94% yield.[12] The diol **17** was converted to compound **18** by the oxidation using bis(acetoxy)iodobenzene (BIAB) in the presence of catalytic amounts of tetramethyl-1-piperidinyloxyl (TEMPO) in CH_2Cl_2 with good yield.[13] A partial reduction of alkyne functionality in compound **18** was generated using Lindlar's catalyst in the presence of quinoline under hydrogen atmosphere to give corresponding partially hydrogenated lactone **3** in 95 % yield (Scheme 4).



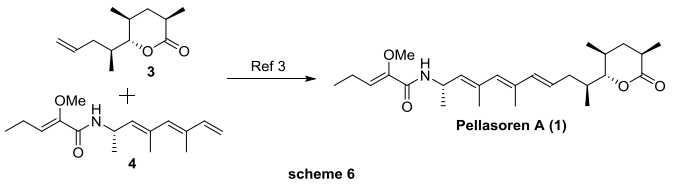
Scheme 5

The amide fragment **4** was synthesized starting from Boc-protected amino alcohol **8**. The Boc-protected amino alcohol **8** converted to required alcohol **19** prepared according to a previously reported procedure.[2] The compound **19** was oxidized with IBX in DMSO to afford corresponding aldehyde. The aldehyde which was submitted to a one carbon extension by means of Wittig reaction with Ph_3CH_3I and Potassium *tert*-butoxide as base to provide corresponding olefine **4** in 66% yield [14] (Scheme 5).

The Formal Synthesis of Pellasoren – A (1)

The compounds **3** and **4** are key advanced intermediates for the total synthesis of Pellasoren – A (**1**). Thus, we have

accomplished the formal total synthesis of Pellasoren – A (**1)** using enzymatic desymmetrization, a Crimmins "non-Evans" *syn* aldol, Lindlar's and a Wittig olefination (Scheme 6). The formal synthesis of Pellasoren – A (**1)** involved 11 steps starting from compound **8** with a 25% overall yield. Further efforts towards the completion of the total synthesis of Pellasoren – A (**1)** is currently underway.



scheme 6

Conclusions

In summary, we have successfully completed the efficient formal synthesis of Pellasoren – A (**1)**. By using a convergent strategy, we utilized an enzymatic desymmetrization for enantioselective synthesis of lactone fragment **3** from enzymatic desymmetrization of *meso*-diol by using amino lipase AK. The synthesis involved other important reactions such as a Crimmins "non-Evans" *syn* aldol reaction, Lindlar's and a Wittig olefination. The synthesis involved 11 steps starting from compound **8** with a 25% overall yield. One additional step would be required to complete a total synthesis of Pellasoren - A.

Acknowledgements

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Supplementary Material

Supplementary data associated with this article can be found, in the online version at

Highlights of The Pellasoren-A Synthesis

- **Formal synthesis of the antitumor natural product Pellasoren–A was synthesized.**
- **Four chiral centers out of five were created in this synthesis.**
- **Monoacetate 9 obtained by employing enzymatic desymmetrization.**
- **Key steps are Wittig, Lindlar'S and Crimmin's non-Evans *syn* aldol reaction.**
- **The lactone 3 was achieved in 11 steps with 25% overall yield.**