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Synthesis and biological evaluation of 12-, 13-, 14-membered macrolides and open chain 2,6-*trans*-disubstituted dihydropyran analogues for aspergillides

Srihari Pabbaraja [a,b,*,†], Naresh Gantasala [a,b], Sridhar Ydhyam [a], Hari Krishna Namballa [a,c], Subhashini Gundeboina [a], Mallikharjuna R. Lambu [a], Sanjeev Meena [d], Dipak Datta [b,d]

[a] Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
[b] Academy of Scientific and innovative Research (AcSIR), Anusandhan Bhawan, 2-Rafi Marg, NewDelhi 110001, India
[c] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, 500037, India
[d] Biochemistry Division, Council of Scientific & Industrial Research (CSIR), Central Drug Research Institute (CDRI), Lucknow, India

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ABSTRACT

Stereoselective synthesis of twenty (three 12-, five 13- and twelve 14-membered) macrolides and seventeen functionalized 2,6-*trans*-disubstituted dihydropyran derivatives have been achieved. The key reactions include an Achmatowicz rearrangement, Ferrier-type alkynylation, Yamaguchi macrolactonization and Lindlar's hydrogenation. Biological screening of the synthesised compounds showed moderate activity against human cancer cell-lines.

Marine natural products (MNP) have attracted extensive interest from chemists and pharmacologists due to their structural architecture and potent biological properties providing lead compounds for the discovery of new drugs.[1] The use of isolated MNPs as scaffold(s) for modification can be a reasonable approach for drug discovery and development. Despite many limitations associated with MNPs, the total synthesis, semisynthetic modification, SAR-based modification, occasionally even a single atom alteration, may lead to the discovery of a novel drug.[2]

Aspergillides A, B and C (Fig. 1) (three, novel, bicyclic, 14-membered macrolides with 2,6-*cis* or *trans*-fused di- or tetrahydropyan rings) are novel secondary metabolites, isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313 in bromine-modified 1/2PD culture medium.[3] Interestingly, these compounds show cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.1, 71.0, and 2.0 μg/mL respectively. The unusual structural architecture and impressive biological properties have gained significant attention from synthetic chemists with respect to their total synthesis[4,5] and have inspired medicinal chemists to synthesize diverse analogues in search for better potential molecule(s).[6]

Many a times, the chiral centers play a crucial role in biological properties.[7] Despite one isomer is biologically potent, there is always a chance that the other isomer/diastereomer may show improved potency or cause side effects. This feature has necessitated the synthetic community for stereoselective synthesis and also their other isomers towards exploring the biological properties. We have recently accomplished the total synthesis[4h,4n,5a] and analogue synthesis of aspergillide C and in continuation, as a project mode, we became interested in the synthesis of the several

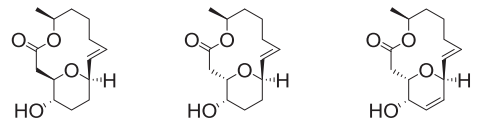

Fig. 1. Structures of aspergillides A–C.

* Corresponding author at: Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India.
E-mail address: srihari@iict.res.in (S. Pabbaraja).
† IICT communication no. IICT/Pubs./2018/081.

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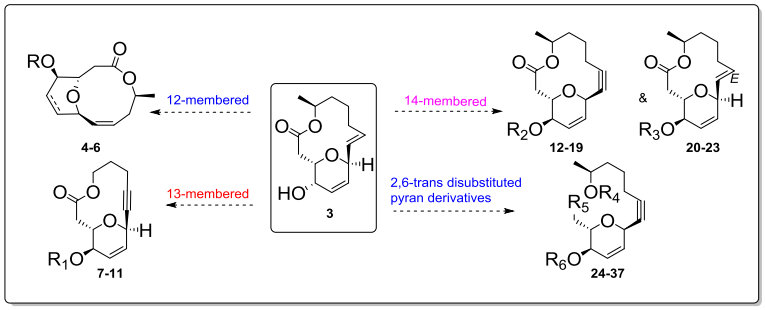


Fig. 2. Structures of proposed aspergillide-based 12-,13-and 14-membered macrolides and 2,6-*trans*-disubstituted pyran derivatives.

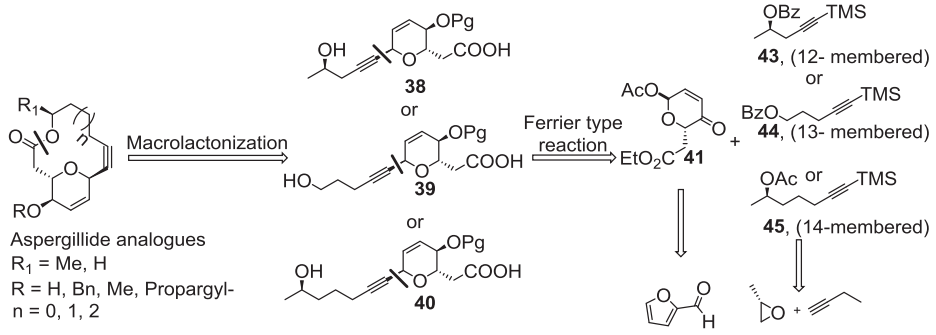


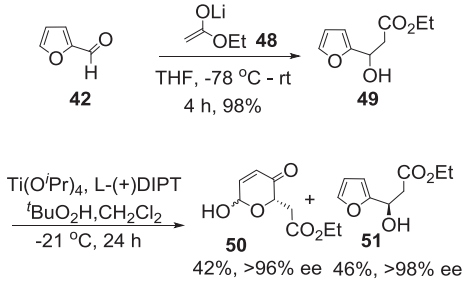
Fig. 3. Retrosynthesis.

other analogues of aspergillides to evaluate their biological activity.

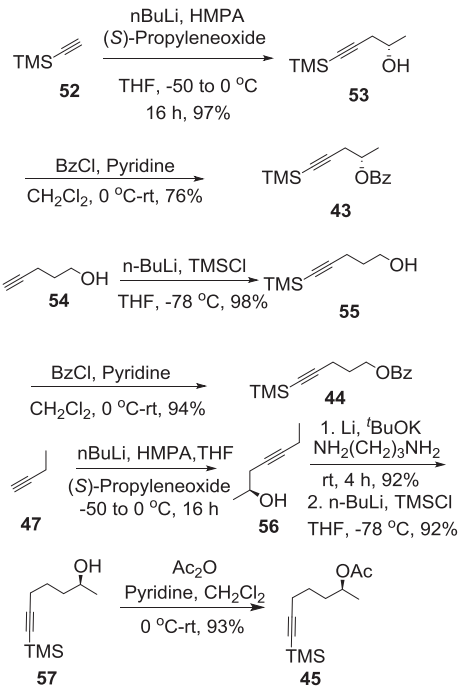
We describe herein the synthesis of 12-, 13-, and 14-membered macrolides along with the 2,6-trans disubstituted functionalized pyran derivatives for aspergillides (Fig. 2). All the synthesized analogues were screened for anticancer, antifungal, antibacterial and anti-inflammatory activities and the results pertaining to the screening are also discussed.

We envisaged that the target macrolides related to (−)-aspergillides could be prepared from the corresponding *seco* acids **38, 39** and **40** by lactonization, removal of the protective group (Pg / TBS), and alkylation of hydroxyl group at C-7. All the three *seco* acids **38, 39** and **40** could be synthesized from a common intermediate **41** through sequential reactions, that is, Ferrier type alkynylation, a chemoselective conjugate reduction of the α,β-unsaturated ketone to a allyl alcohol and protection of hydroxyl group (Pg). Compound **41** can be obtained from furfural through addition of lithium enolate of ethyl acetate and Achmatowicz oxidative rearrangement.[8] Alkyne fragment **43** can be obtained from (*S*)-propylene oxide and TMS-acetylene through an epoxide ring opening reaction and hydroxyl protection. Fragment **44** could be synthesized by the trimethylsilylation (on terminal alkyne) and hydroxyl protection (*O*-Benzoylation) of 4-pentyn-1-ol and fragment **45** can be accessed from homopropargyl alcohol through an alkyne Zipper isomerisation reaction, which in turn can be obtained from commercially available (*S*)-propylene oxide and 1-butyne (see Fig. 3) by a ring opening reaction.

Our synthesis began with an addition reaction of enolate **48** generated from ethyl acetate, to furfuraldehyde (**42**) to provide the racemic secondary furfuryl alcohol **49**. Racemate **49** was



Scheme 1. Synthesis of pyranone lactal **50**.



Scheme 2. Synthesis of alkyne compounds **43, 44** and **45**.