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An overview of macrolactone in polymer synthesis

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The article uniquely describes the ring-opening polymerization (ROP) of macrolactones. Nature is the source of information, naturally occurring macrolides could assist in monomers design and synthesis. The available approaches in the synthesis of medium-sized amphidinolides Qalong with their retrosynthetic analysis are presented. The analogues of naturally occurring biologically relevant macrolactone could be the ideal monomers for chiral polyesters for various applications.

Keywords: Macrolactones, macrolides, amphidinolides, polyolefins, polyester

INTRODUCTION

The polyolefins demand remained at 146.99 million tons in 2020 and is expected to reach at 250.43 million Tons by 2030.The polyolefins business is highly dependent on the petroleum industry. Polyolefins are not biodegradable and cause a major issue to the environment, especially to marine life [1]. Therefore, an alternative to polyolefins is needed. Two approaches could be used in the replacement of polyolefins. First, by replacing the monomer source by finding a way to monomers from feedstocks. In this regard, biopolyethylene has already been developed [2]. The other approach could be to find the way in which the properties and cost of existing polymers match the production of renewable sources. To obtain high molecular weight polymer by polycondensation reactions is challenging. The material of high molecular weight obtained from lactones *via* ring-opening polymerization (ROP) showed polyethylene-like properties [3]. In 2010, polyethylene-like polyesters have been reported through methoxy carbonylation of unsaturated fats followed by polycondensation [4]. The scope of polymers is steadily increasing in biomedical applications [5].

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ended up avoiding immunoresponse ("secrecy particles") and to extended circulation time [10]. There are various methods of ring opening polymerization of macrolactones.

Enzymatic Ring Opening Polymerization of Macrolactones

The enzyme-mediated production of polymers *via* ring lactone ring-opening polymerization is gaining an impetus. The enzymatic reactions are green reactions and provide a synthetically versatile tool for regio- and enantioselective polymers. They produce high selectivity and are environmentally friendly. The enzymatic reactions usually take place in water. The use of organic solvent offers various advantages over the aqueous media, it increases the thermal stability of enzymes and increases solubility of a range of substrates. And does not require adjustment of pH [11]. The direct enzymatic polymerization of emulsions comprising lactone nanodroplets addresses a new and helpful pathway for the combination of biodegradable polymer nanoparticles, where the compound structure and sub-atomic weight can differ in a specifically. Oligoesters totally end-covered with an alkene or diene gathering can likewise be ready by this strategy. These structure blocks broaden polyester application as they permit to grant further developed biodegradability to both siloxane and gum chemistry [12].

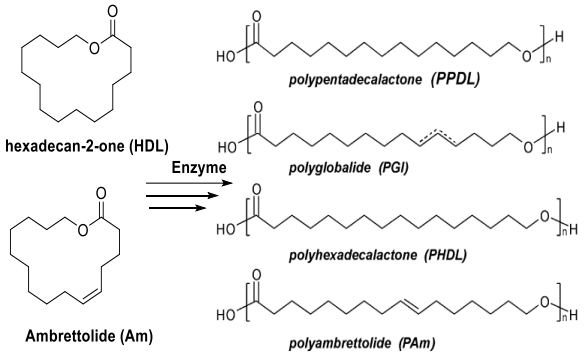


Figure 1. Enzymatic polymerization of macrolactones.

The polymers obtained from pentadecalactone, hexadecalactone, and their unsaturated analogues ambrettolide and globalide are potential biomaterials. By enzymatic ring-opening polymerization, these monomers can lead to high molecular weight materials. All these polymers are nontoxic estimated by a MTT measure for metabolic cell movement of a 3T3 mouse fibroblast cell line. The polymers are exceptionally translucent with a melting point of around 95 °C for the saturated polymers and a little lower for the unsaturated polymers (46-55 °C). It seems polymers are stable once generated because degradation was not observed under hydrolytic and enzymatic conditions. The unsaturated polymers could be crosslinked under the melt to obtain fully amorphous transparent material [13]. Albertsson *et al*. have reported enzymes as catalysed miniemulsion polymerization of PDL and HDL [14].

Acid Catalyzed Ring Opening Polymerization:

The polymer micro-nanoparticles dispersion in the water called polymer latexes, is an example of sustainable polymer science since water is safe and environmentally benign solvent. It is easy to process latexes for various applications. They are synthesized by free radical polymerization. Nonetheless, somewhat recently the development of miniemulsion polymerization has stretched out the creation of latexes to polymers which might be incorporated by polycondensation or catalytic polymerization processes prompting new kinds of polymer latexes.

A few endeavors have been conveyed to combine polyester latexes by a buildup of hydrophobic alcohols and dicarboxylic acids. In those works, Landfester and others utilized dodecylbenzene sulphonic acid (DBSA) which went about as impetuses and surfactant. The miniemulsion polymerization of macrolactones involving natural acids follows ring opening polymerization (ROP) [15]. It has been observed that polymerization at 80 ºC leads to full transformations and relatively lower polymerization time. This polymerization results in high molecular weight compounds (>10.000 g/mol). Increasing the strength of acid also increases the catalytic effect. The acid-catalyzed miniemulsion polymerization of macrolactones follows a condensation mechanism limiting the molecular weight of polymer latex [16].

ORGANOCATALYZED RING OPENING POLYMERIZATION

Organocatalyzed ring-opening polymerization of little and medium ring-sized cyclic esters, for instance, lactides, valerolactone, or caprolactone have been considered while macrocyclic lactones (macrolactones) polymerization is still in its earliest phases of studies. Metal-catalyzed ROP of lactones is an especially effective strategy to create polymers of high molecular weight, low polydispersity, and with controlled microstructure [17]. The work on lactide and ε-caprolactone has provided a mechanistic understanding of ROP [18]. The main driving force of ROP proceeding is the ring strain. Thusly, as the ring strain diminishes with expanding lactone size decreases ROP. Exceptionally productive metal-catalyzed ROP of macrolactones was reported by

Meulen *et al*. [19]. The avocation behind this is that the ROP part of these macrolactones differs from the approach to the acting of pretty much nothing or medium size cyclic lactones. Generally, the assistance of the ring sort of little lactone monomers coordinates the primary stimulus for ring-opening polymerization. In any case, the huge ring size of macrolactones is connected with low ring strain, and in this manner, polymerization reactions are driven generally by entropy. This is the explanation, a set number of catalysts have been strong for the mix of polyesters from macrolactones when appeared differently in relation to little lactones, for instance, ε-caprolactone what's more, consequently, two or three reports have been dispersed state of the art about the association of polyesters from gigantic lactones, for instance, ω-pentadecalactone (PDL) or 16-hexadecalactone (HDL)[20]. The ring-opening polymerization of macrolactones (C15-C23) empowers the creation of long-chain aliphatic polyesters which are glasslike polymers with liquefying temperatures going from 98-106 °C. The polymerization of ω-pentadecalactone (C15), nonadecalactone (C19) and tricosalactone (C23) was investigated by Myers *et al.* utilizing yttrium phosphasalen catalyst [21].

Bioactive Natural Macrolactones

Among nature's creation, macrolides are versatile and exciting natural products due to their diverse biological activities such as antibiotic, cytotoxic, or antiangiogenic. Several macrolides and polyketides have been isolated from symbiotic marine dinoflagellates [22]. Many of them show potent cytotoxicity against murine lymphoma L1210 cells. The smallest macrolactones are 8-membered (octalactins-1-2) and biggest vary upto 60-membered (quinolidomicins) (Figure 2). Erythromycin (**1**) a macrolide isolated in 1952 is widely used to treat bacterial infections, and because of its safety and efficacy, it is still a preferred therapeutic agent for the treatment of respiratory infections. Apoptolidin a 20-membered macrolide, selectively induces apoptosis in rat glia cells transformed with adenovirus E1A oncogene in the presence of normal cells and inhibits the mitochondrial F_0F_1-ATPase [23]. Actin-binding marine macrocyclic lactones, and benzolactone enamides are also possessing potent antitumor activity.

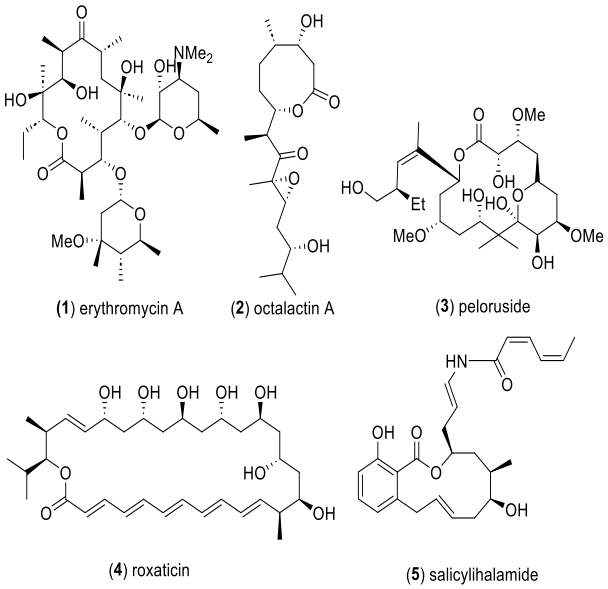


Figure 2. Examples of naturally occurring macrolactones.

A marine microorganism such as bacteria, cyanobacteria, or dinoflagellates produces toxins for their defense mechanism. That is the main source of fish and algal poisoning. Though these poisons in microgram scale can kill a person but if used in medically administered could be useful for treatment of many fatal diseases such as cancer. Many bioactive substances isolated from marine invertebrates such as sponges, tunicates, and so on have proved to be essential tools in biology for example, neurotoxins like maitotoxins helped to understand the molecular basis of cellular excitability [24]. Biologically significant secondary metabolites isolated from symbiotic marine dinoflagellates *Amphidinium* sp. called as Amphidinolides. Amp B (**6**) increased the ATPase activity of myofibrils and natural actomyosin, resulting increased in contractile responses of myofilaments. Amp H (**7**) is a novel F-actin stabilizer that covalently binds on actin [25]. It stabilizes actin similar to phalloidin (**9**) but the Amp-H-binding does not compete with phalloidin-binding to F-actin [26].

Amphidinolide W (**8**) and Q (**10**) both are 12-membered macrolides and exhibit cytotoxicity against murine lymphoma L1210 cells. Amp W is quite unique as it is the first and only macrolide in its family without an exomethylene unit.

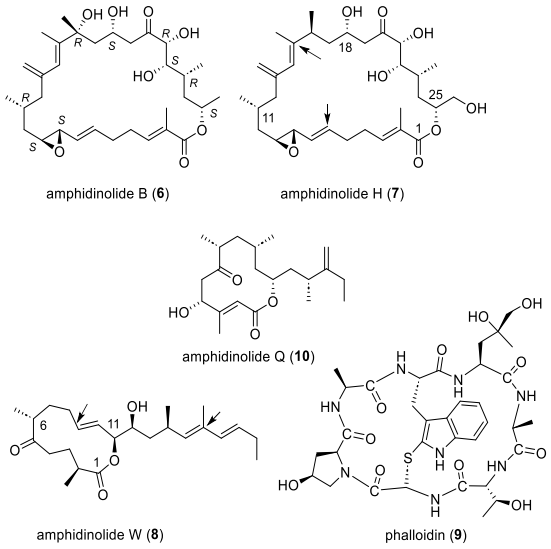
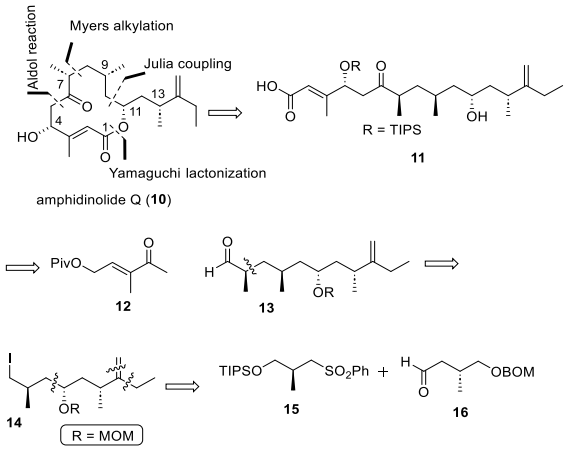


Figure 3. Structures of the 12-membered amphidinolides Q (1), W (2) and the 26-membered amphidinolide H (3).

The C9-C16 moiety of amphidinolide W compares to that of C6-C15 of amp H, which was disconnected from strain Y-42, recommending that amphidinolide W might be biogenetically connected with amphidinolide H. As of late four new polyketides, amphidinins C-F have been separated from *Amphidinium* sp of dinoflagellates [27]. They showed antimicrobial activity against bacteria and/ or fungi. Amphidinin D and F are the first glycosides related to amphidinolides. Spectral data led that amphidinins C-F are 4,5-seco-analogues of amp Q [27]. Cancer is an epidemic, related to abnormal growth of tissues. There are several techniques to treat cancer such as surgery, radiotherapy, immunotherapy, chemotherapy, etc. [28]. In chemotherapy the treatment is done by the use of a pharmaceutical product. It was found that some amphidinolides exhibits very high cytotoxicity. In this article we will discuss about the synthesis, medium sized macrolactone Amphidinolide Q known so far.

SYNTHESIS OF MEDIUM SIZED CHIRAL MACROLACTONE

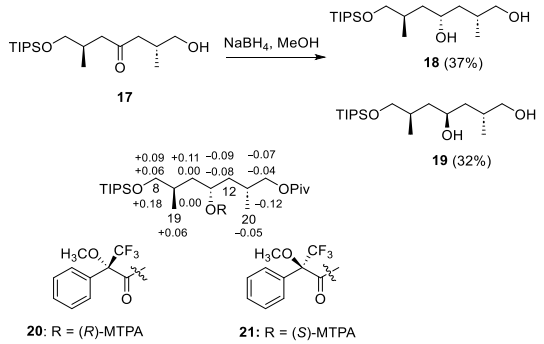
The structure of amphidinolide-Q was elucidated by NMR spectroscopy and could be proved by synthesis [29]. The retrosynthesis proposed by Hangyou *et al*. is outlined in Scheme-1. Amphidinolide Q (10) was disconnected at the lactone bond; *seco*-acid 11 was derived from ketone 2-3 and aldehyde 2-2 *via* condensation. The key aldehyde 12 containing four stereocenters was prepared from iodide 14 *via* Myers alkylation and Julia coupling of sulfone 15 with aldehyde 16 could furnish iodide 14.



Scheme 1. Retrosynthetic plan for the synthesis of Am-phidinolide Q by Hangyou *et al*.

The aldehyde obtained from alcohol (R)-2-methyl-3-((triisopropylsilyl)oxy)propan-1-ol was transformed into *β*-hydroxy sulfone *via* Julia coupling with sulfone 2-6, which after oxidation and reductive removal of the sulfone moiety provide ketone **17** [30]. The compound **17** on reduction produced a racemic alcohol (**18**&**19**). The configuration of alcohols was deduced by a modified Mosher's ester analysis [31].

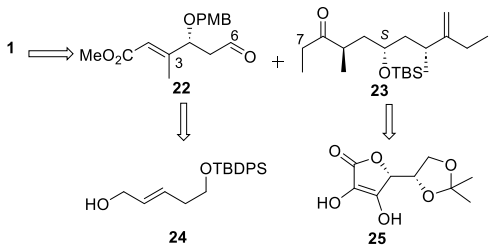
The exomethylene function was installed to **18** by a Wittig reaction followed by Appel reaction to achieve iodide **14**. The opposite end functionalization of diastereomer **19** produces desired fragment. Myers alkylation of iodide **14** with propionamide derivative essentially produces a single diastereocenter (C7) [32].



Scheme 2. $\Delta\delta$ Values [$\Delta\delta$ (in ppm) = $\delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA ester at C11 (2-13 and 2-14, respectively) of alcohol 2-11.

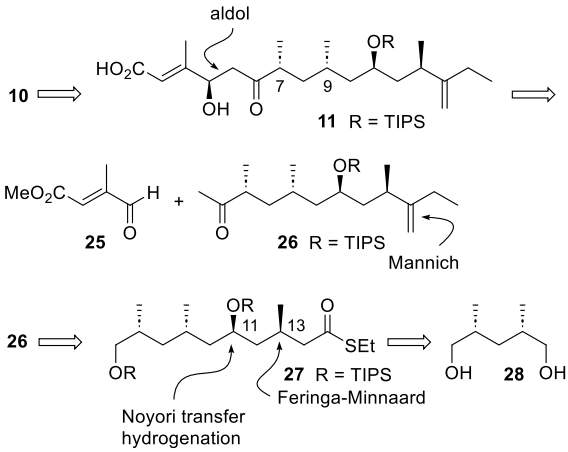
KHMDS mediated aldol reaction of the aldehyde (**13**) and ketone (**12**) produced *β*-hydroxy ketone. That after Luche reduction of ketone produced a diastereomeric mixture of allyl alcohol. Pinnick oxidation of the aldehyde to *seco*-acid **11**, followed by Yamaguchi

macrolactonization and TBAF mediated cleavage of silyl ether furnished amp Q.



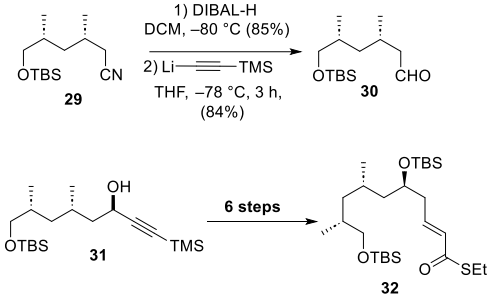
Scheme 3. Retrosynthetic plan for the synthesis of Amphidinolide Q by Nishiyama *et al.*

The synthetic strategy described by Nishiyama *et al.* (Scheme 3) outlines the possibility of constructing amp Q by joining segment **22** and **23** followed by macrolactonization [33]. The synthesis of fragment **22** began with the epoxidation of alcohol **24** obtained from 1,3-propanediol. *E*-selective methylation of the propiolic ester part using a PhS group as an auxiliary [34], afforded the *α,β*-unsaturated ester **22**. The synthesis of ethyl ketone **23** was initiated from the ascorbic acid derivative. Ascorbic acid derivative (**25**) was cleaved, oxidized to corresponding carboxylic acid. The introduction of the Evans auxiliary in acid, followed by methylation leads to the C9 stereocenter. Parikh-Doering oxidation and a Horner-Wadsworth-Emmons reaction and after routine functional group manipulation and Peterson's olefination introduced the *exo*-methylene function [35]. The Aldol reaction of both fragments **22** and **23** under acidic condition gave undesirable elimination whereas under basic conditions the reaction suffered from moderate yield [33]. Moreover, the keto function at C8 still has to be removed. The retrosynthetic approach Mishra *et al.* followed is shown in Scheme 4. They have envisioned to fragment the seco-acid **11**. Into two unequal size fragment considering the aldehyde function *a,b*-unsaturated aldehyde **25** and ketone **26**. The *meso*-diol **28** was converted to alcohol via enzyme-mediated desymmetrization as key step [36]. Chain extension on the derived tosylate led to nitrile **29** [37]. Further the nitrile was reduced to aldehyde using DIBAL-H, following the reaction with lithium trimethylsilylacetylide led the delivery of propargylic alcohol **31** as a mixture of C11 diastereomers. That on, after oxidation with Dess-Martin periodinane, followed to reduction with a Noyori transfer hydrogenation using (*R*,*R*)-Ru catalyst, produced essentially one diastereomer[38]. Further steps, continuing with the synthesis, to chain extension with *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene) ethanethioate gave unsaturated thioester **32** [39].



Scheme 4. Retrosynthetic plan for the synthesis of Amphidinolide Q by Mishra *et al.*

The asymmetric methyl cuprate additionin presence of (*R*)-Tol-BINAP provided thioester (C6-C15 fragment) on gram scale. Further, chemical transformation led to seco-acid [40-42].



Scheme 5. Conversion of nitrile 29 to thioester 32.

CONCLUSION

In conclusion, the demand for polyethylene is rising day by day and the disclosure of sustainable sources is demanding. Macrolactones are natural compounds, their polymerization could give a material with comparable properties to polyethylene. To plan different polymers for various applications, the idea of monomers is necessary. Various macrolactones could give idea on monomers. Biologically relevant macrolactones have been explored along with the various approaches of ring opening polymerization of macrolactones. The idea on various monomers will open a new dimension in polymer synthesis and in the application such as drug delivery, implants, and tissue engineering. The retrosynthetic analysis and their synthesis will trigger in the discovery of new monomers for chiral polymers. The enzyme-catalyzed uncontrolled polymerization issue was handled using metal catalyzed controlled ring opening polymerization.

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