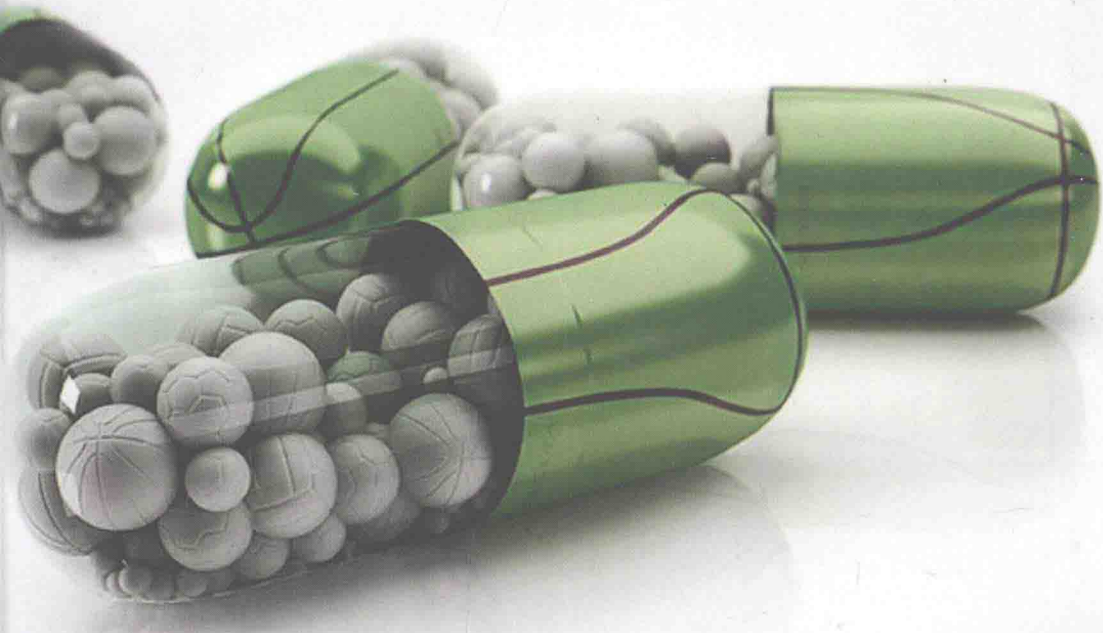
Drug Carrier Systems Handbook



Erica Helmer

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Edited by **Erica Helmer**

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Preface

In my initial years as a student, I used to run to the library at every possible instance to grab a book and learn something new. Books were my primary source of knowledge and I would not have come such a long way without all that I learnt from them. Thus, when I was approached to edit this book; I became understandably nostalgic. It was an absolute honor to be considered worthy of guiding the current generation as well as those to come. I put all my knowledge and hard work into making this book most beneficial for its readers.

This book compiles contributions of prominent experts and researchers in the multidisciplinary arena of novel drug delivery systems. It gives insights into the ongoing and recent potentialities of various drug delivery systems. Emergence of analytical approaches and capabilities to determine particle sizes in nanometer ranges has focused interest towards nanoparticles for more effective methods of drug delivery. The book assesses and reviews procedures involved in the drug carrier systems to prepare and apply, along with the methodologies necessary to design, develop and characterize them. Some of the important topics are oral delivery of insulin, novel mucoadhesive polymers for nasal drug delivery, amphiphilic cyclodextrins, synthesis, utilities and application of molecular modeling.

I wish to thank my publisher for supporting me at every step. I would also like to thank all the authors who have contributed their researches in this book. I hope this book will be a valuable contribution to the progress of the field.

Editor

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Miscellaneous

Amphiphilic Cyclodextrins, Synthesis, Utilities and Application of Molecular Modeling in Their Design

Atena Jabbari and Hamid Sadeghian

Additional information is available at the end of the chapter

1. Introduction

Drug delivery systems that traditionally are used by the patient do not respond the drug delivery's needs of the world. According to the large number of the hydrophilic and hydrophobic drugs, design and synthesis of new drug delivery system seems to be necessary. With the traditional drug delivery systems practically there is no control over the time, location and rate of drug release, in addition to the drug concentration was fluctuated in the blood frequently and may even go beyond the therapeutic dose and less effective and cause more side effects. With the new drug delivery systems that called controlled released drug delivery system, we will be able to control and determine the rate, time and location of drug release. CDs are potential candidate for such a role, because of their ability to change physicochemical and biological properties of guest molecules through the formation of inclusion complexes (Uekama et al,1998). The most common pharmaceutical application of cyclodextrins is to increase the stability, solubility and bioavailibity of drug molecules and other pharmacological benefits,such as the reduction of unwanted side effect (Hedges, 1998).

Cyclodextrins (CD) are macrocyclic oligosaccharides composed of D-(+)-glycopyranosyl units linked α (1→4). CDs are classified as α-,β- and γ-CD according to the number of glucose units: six, seven and eight, respectively. Cyclodextrins have a truncated cone shape with a hydrophilic exterior and a hydrophobic cavity. A guest molecule of appropriaty size and shape is incorporated into hydrophpbic cavity in aqueous media (Szejtli, 1998).

However, the potential use of CDs in biological system needs amphiphilic properties because natural CDs have relatively low solubility both in water and organic solvents, thus limits their uses in pharmaceutical formulations. Amphiphilic or ionizable cyclodextrins can

modify the rate or time of drug release and bind to the surface membrane of cells, that may be used for the enhancement of drug absorption across biological barriers.

Amphiphilic cyclodextrins can be obtained by the introduction of lipophilic groups at primary and or secondary face of the CD. Amphiphilic CDs have been shown to form monolayers at the air-water interface (Parot-Lopez, 1992; Greenhall et al, 1995) and micelles in water (Auze´ly-Velty et al, 2000). Different self-organized amphiphilic CDs, such as nanospheres (Skiba et al, 1996), solid-lipid nanoparticles (Dubes, 2003) , liquid crystals (Ling et al, 1993) and vesicles (Ravoo & Darcy, 2000) were prepared with varying length of hydrophobic chains for their promising properties for farmaceutical applications.

Hydrophilic-hydrpphobic balance, molecular shape and solvation have all been enunciated as important criteria for formation of distinct lyotropic assemblies (Israelachvilli, 1985; Fuhrhop & Koning, 1994).

A particulary interesting example of self-assembly of amphiphilic CDs in water is bilayer vesicles. CDs vesicles consist of bilayers of CDs, in which the hydrophobic "tails" are directed inward and the hydrophilic macrocycle"head groups" are facing water, thereby enclosing an aqueous interior. Recently, vesicles composed entirely of nonionic, anionic, and cationic amphiphilic CDs was described (Falvey et al, 2005).

Nano capsules and nanospheres were prepared using amphiphilic β-and γ-CDs modified on the secondary face by nanoprecipitation and emulsion/solvent evaporated techniques avoiding the use of additional surfactant (Woussidjewe et al, 1996).

The first amphiphilic cyclodextrin were synthesized in 1986 by Kwabata et al. The primary OH-groups of β-CD were made lipophilic with alkyl sulfunyl groups with various length. This amphiphilic CD could form monolayer at the air-water interface (Kawabata et al, 1986).

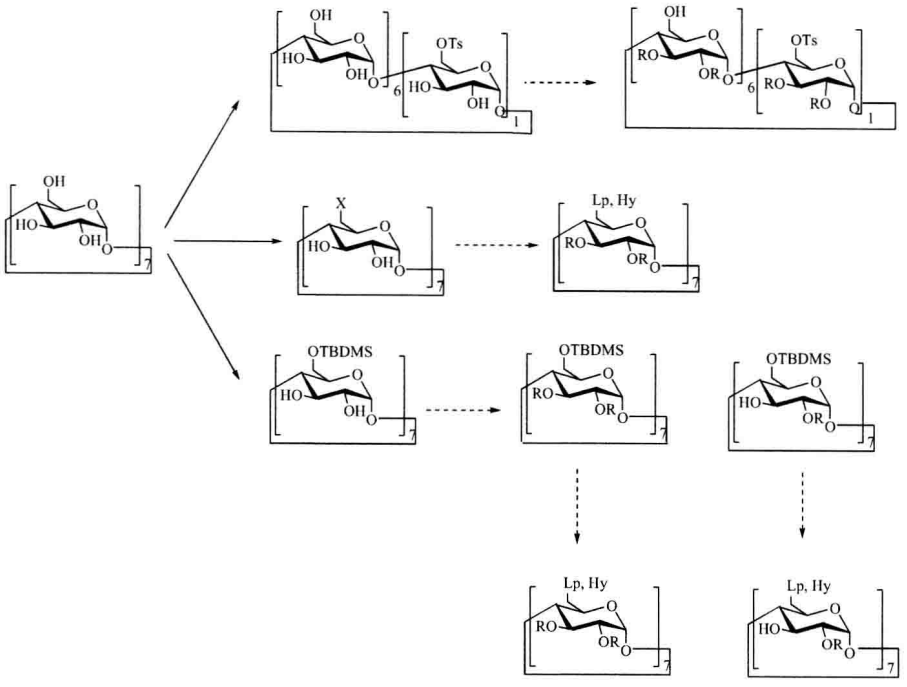
2. Synthesis of amphiphilic cyclodextrins

β-CDs in synthesis of amphiphilic cyclodextrins was used more than α- and γ CDs. Common synthetic path to amphiphilic cyclodextrins was shown in Fig. 1.

2.1. Alkylated, arylated and lipid –Conjugated CDs

Synthesis of alkylated α- and β-CDs and their treatment at air –water interface, have been described by Jurczak et al (Wazynska et al, 2000). Silyl-protected α- or β-CDs was alkylated then desilated to achievement amphiphilic per-(2,3-di-O-alkyl)-CDs (5) (Fig. 2).

Compound (10) which contain amphiphilic chains, was synthesized from per-amino-β-CD using peptide chemistry (Imamura et al, 2002) (Fig. 3). Reason of suitable complexation of anilinonaphthalene sulfonic acid can ralativ to presence of Adipic-glucamine chains that enhance extension of the cavity in this structure. γ-CDs derivatives of this family, can complex with two molecules of anthraquinone-2-sulfonate (Ling & Darcy, 1993) (Fig. 4).



Lp=lipophile, Hy=hydrophile; for Lp,R, is hydrophilic; for Hy ,R ,is lipophilic

Figure 1. Common synthetic path to amphiphilic cyclodextrins

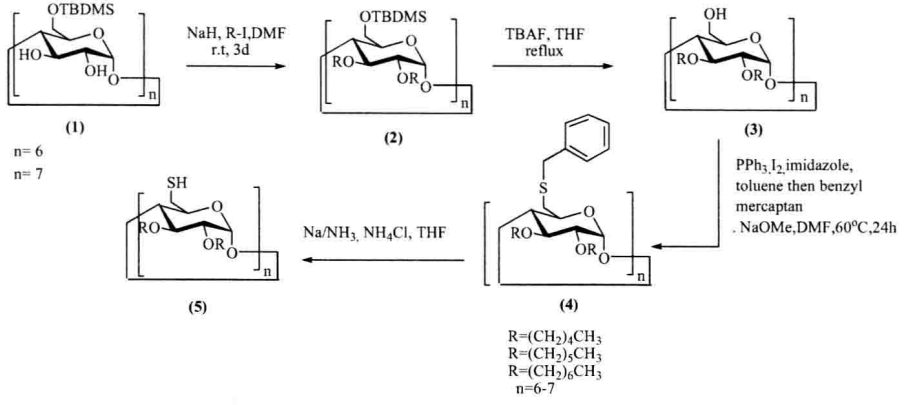


Figure 2. Synthesis of alkylated cyclodextrins

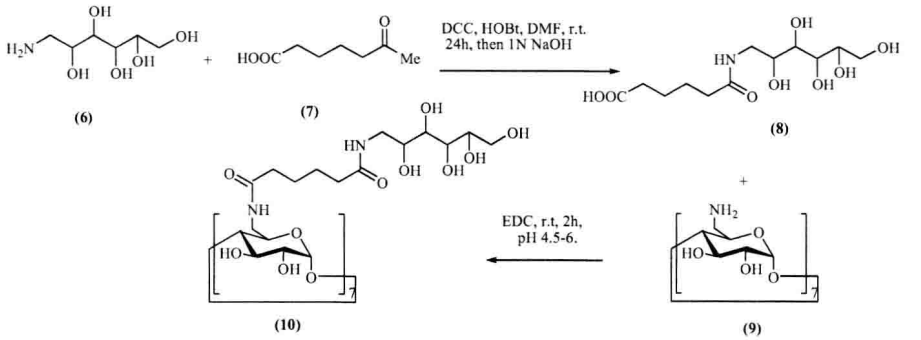
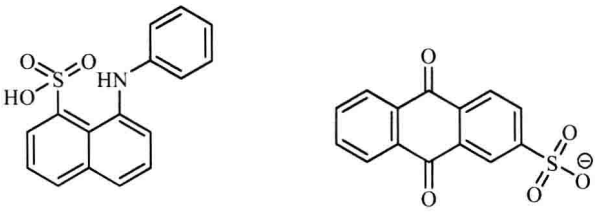


Figure 3. Peptide chemistry was used for synthesis of amphiphilic cyclodextrins



8-Anilino-1-naphtalenesulfonic acid (11)

Anthraquinone-2-sulfonate (12)

Figure 4. Structures of two guest molecules for complxation with compound (10)

Wu and coworkers in 2010 reported the synthesis of new amphiphilic biodegradable β-cyclodextrin/poly (L-leucine)(β-CD-PLLA) copolymer by ring-opening polymerization of N-carboxy-L-alanine anhydride in N,N-dimethylformamide(DMF) initiated by mono-6-amino-β-cyclodextrin (Zhang et al, 2010). These compound could self- assemble into nano-micelles in water and could be expected to find application in drug delivery systems (Fig. 5).

A novel thiolated carboxymethyl chitosan-g-β-cyclodextrin (CMC-g- β-CD) drug delivery carrier was synthesized by Gong et al (Prabaharan & Gong, 2008).

Thiolated CMC-g- β-CD was prepared using two steps. First ,carboxymethyl- β-CD (CM β-CD) was grafted onto carboxymethyl chitosan (CMC) using water-soluble 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS) as the condensing agents. Next, the resultant product was further grafted with cycteine methyl ester hydrochloride (CMEH) (Fig. 6).

The drug release showed that thiolated CMC-g- β-CD tablets provided a slower release of the entrapped hydrophobic model drug, ketoprofen, than the chitosan control, and the release behavior was influenced by the amounts of thiol groups present on the polymer chains. These results suggest that thiolated CMC-g- β-CD with improved mucoadhesive

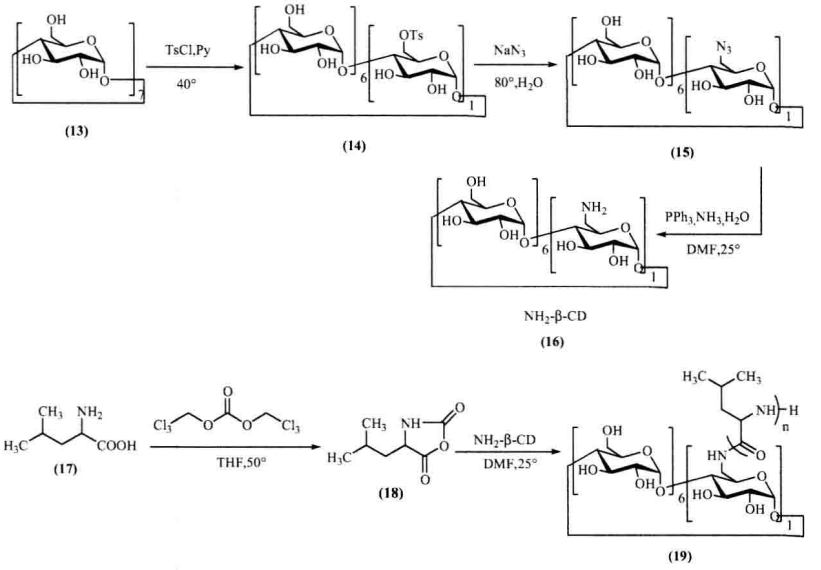


Figure 5. Synthetic pathway to amphiphilic biodegradable β-cyclodextrin/poly (L-leucine)(β-CD-PLLA) copolymer

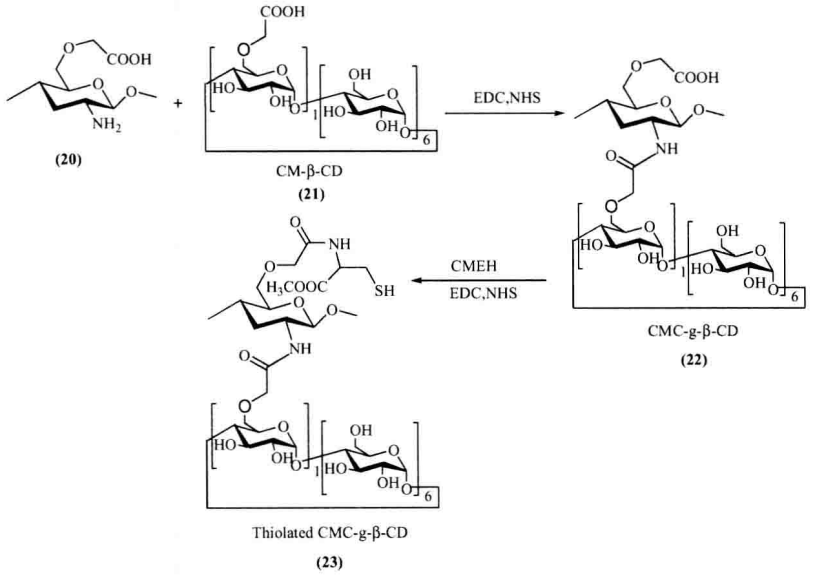


Figure 6. Preparation of thiolated CMC-g- β-CD

properties may potentially become an effective hydrophobic drug delivery system with controlled drug release capability.

Chitosan-cyclodextrin nanosphere were prepared by in situ formation through Michael addition between N-maleated chitosan (NMC) and per-6-thio- β-cyclodextrin sodium salt in an aqueous medium (Wang et al, 2011). This facil preparation method did not involve any organic solvent and surfactant. Through adjusting the preparation conditions, the nanosphere with a relatively narrow size analyzer. Doxorubicin hydrochloride (DOX-HCl), a water soluble anticancer drug, was loaded in the nanosphere with a high encapsulation efficiency (Fig. 7).

Chloesteryl derivatives of CDs were mostly investigated by Pilard and coworkers. Synthetic pathway of one of them was shown below (Auze'ly-Velty et al, 1999) (Fig. 8).

In 2007, Mallet and coworkers synthesized new derivatives of amphiphilic CDs (Collat et al, 2007). These compound were obtained from reaction between carboxylic acid that derivative of chlosterol with di-amino CDs in presence of DCC and 1-hydroxy benzo tri azol(HoBt). These compounds can act similar to biological membrans (Fig. 9).

2.2. Oligo(ethylene oxide) amphiphilic CDs

The first Amphiphilic CD to form bilayer vesicles were reported by Ravoo and Darcy in 2000 (Ravoo & Darcy, 2000; Mazzaglia et al, 2001; Falvey et al, 2005). Synthesis of them initiated from per-6-bromo and at the result of nucleophilic substituation with the sodium or potassium salt of alkyl thiols, per-alkyl thio CDs were prepared then hydroxyl groups that bind to C-2 of these compounds reacted with an excess of ethylene carbonat and finally average of two units of ethylene glycol were located in this position (C-2 of the CD) (Ravoo & Darcy, 2000; Mazzaglia et al, 2001) (Fig. 10).

This reaction was performed with α- and γ-CD subsequently (Falvey et al, 2005). In these derivatives, the cavity size and hydrophilic of the cyclodextrin headgroup increase. Oligo(ethylene oxide) amphiphiles can form bilayer, vesicoles, and nanoparticles.

2.3. Cationic CD amphiphiles

Donohue and coworkers reported the synthesis of CDs in which hydroxyl groups of oligo(ethylene oxide) were substitude with amine groups and their hydrochloride salts were used in gene delivery studies (Donohue et al, 2002) (Fig. 11).

2.4. Anionic CD amphiphiles

With alkylation of CDs by Declercq and coworkers (Leydet et al, 1998), achievement to versatile groups and so new structures were possible. For example Kraus et al with oxidation by osmium tetroxide in presence of 4-methyl morpholine prepared novel alcoholic stractures of mentioned allylic derivatives (Kraus et al, 2001). They converted the resulting diastreoisomeric diols to carboxylated CDs with oxidation (Fig. 12).

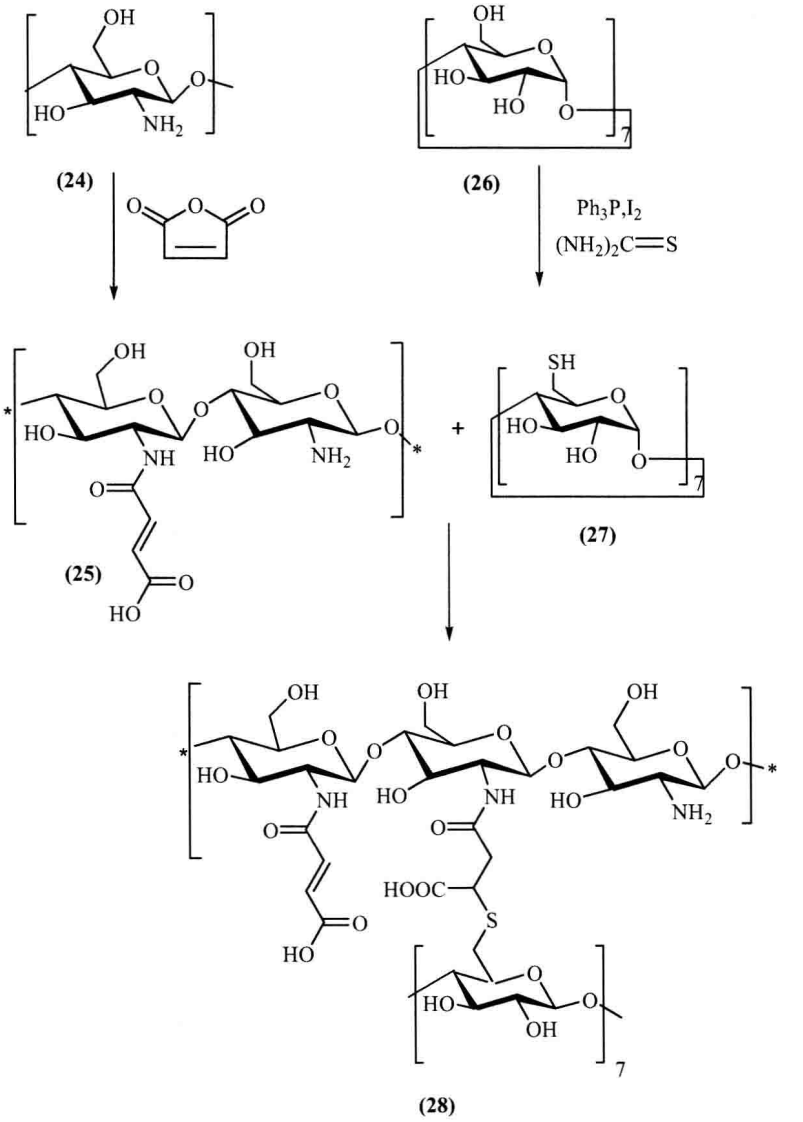


Figure 7. Synthetic path to Chitosan-cyclodextrin nanosphere

The first sulfated amphiphilic CD synthesized by Dubes (Dubes et al, 2001, 2003). They produced compound (48) via esterification of silyl-protected CDs (45) with hexanoic anhydride at position 2 and 3. After removal of the silyl groups, the primary hydroxyl groups were sulfated by SO_3.pyridine complex (Fig. 13).

2.5. Flurinated CD amphiphiles

Granjger and coworkers prepared the per tri fluromethyl thio-β-CD derivative (Granger et al, 2000), which formed monolayer at the air-water interface despite the short hydrophobic chains that applicable in oxygen delivery. Mono- di and per fluoro alkyl thio-CDs (Péroche et al, 2003, 2005) were made subsequently and demonstrated to self-organise into nanosphere in aqueous media, unlike their analogous alkylated derivatives that formed flat particle under same condition (Fig. 14).

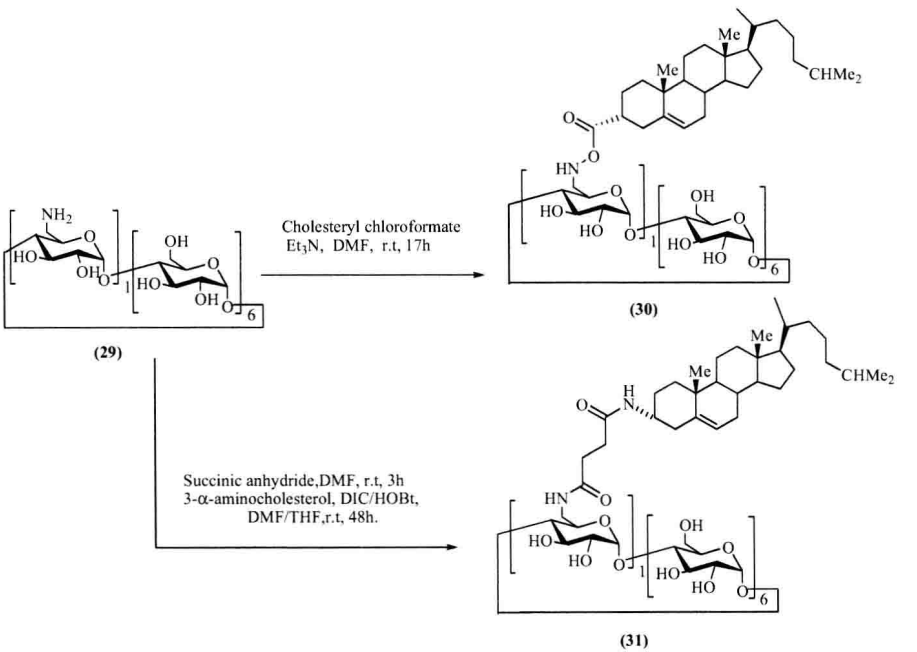


Figure 8. Synthesis of one of chlosteryl derivatives