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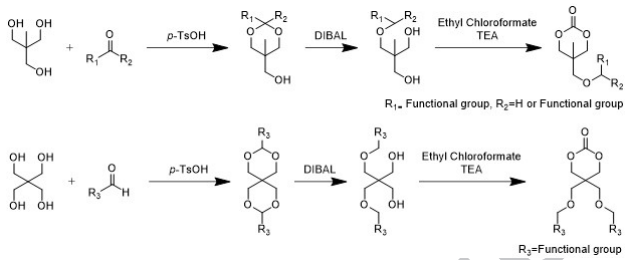

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Novel synthesis method of ester free trimethylene carbonate derivatives

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ABSTRACT

Ester free poly(trimethylene carbonate) (PTMC) derivatives show biocompatibility and biodegradability and do not generate any acidic compounds after decomposition. Their syntheses methods are limited however, hampering their material application. Herein, we established a novel synthesis route of ester free trimethylene carbonate (TMC) derivatives. The novel synthesis route was described using six aldehydes and one ketone as starting compounds. The key reaction is the selective deprotection from two protected hydroxyl groups in the cyclic acetal structure by diisobutylaluminium hydride. This novel synthesis route means that it is possible to convert aldehyde group to ether groups in the side chain of TMC. Conventionally, only a substituent derived from a primary alcohol was introduced into the side chain. We therefore succeeded in decreasing the number of reaction steps from five to three, compared with the conventional route. Furthermore, the development of a novel synthesis route enabled the introduction of substituents derived from secondary alcohols, anticipating the creation of further types of ester free TMC derivatives.

Introduction

Recently, the aging society has become a world-wide problem, making the development of various medical materials such as scaffolds for tissue engineering an urgent issue.[1,2] In particular, biodegradable materials have attracted attention for medical application.[3] The biodegradable property of materials used in medical implant devices allows them to degrade gradually in the body. Therefore, there is no need to perform further surgery after implantation, which helps to reduce the mental and physical burden on the patient.[4]

Poly(lactic acid) (PLA) is well-known as a biodegradable medical material. PLA has attracted attention because it can be synthesized from renewable plant resources, but it is sometimes difficult to use in biomedical applications due to its hardness and brittleness.[5,6] It has also been pointed out that it changes pH in the body and is thought to be a source of inflammation,[7,8] since it generates acidic compounds after decomposition. On the other hand, poly(trimethylene carbonate) (PTMC) obtained by polymerization of trimethylene carbonate (TMC) which is a six-membered ring carbonate is also widely known as a biocompatible and biodegradable compound.[9-13] Flexibility is one of the properties of PTMC.[14] Furthermore, it is possible to design the TMC derivatives by introducing substituents into the side chain in order to add functionality. Many potential applications have been reported such as DNA delivery systems for gene therapy[15], suppression of platelet adhesion by surface modification of the substrate,[16] and application to biodegradable hydrogels incorporating antibodies.[17]

However, most of the currently known PTMC derivatives have a structure with an ester bond in the side chain.[18-21] In this case, acidic compounds are generated upon decomposition. As a result, we believe that this feature of ester free PTMC weakens the polymer main chain. Thus, we were motivated to develop ester free PTMC derivatives with functional groups at the side chain. In fact, there are some examples available for the syntheses of TMC derivatives. This is a technique of introducing a substituent by ether linkage into the side chain of TMC. For example, there is a synthesis method using *Candida antarctica lipase B*[22] and another method using a four-membered ring as an intermediate.[23] However, the structures and methods are limited to the specific compounds.

Previously, we have also reported on ester free TMC derivatives, resulting in functional polymers with ether linkages in the side chain. Firstly, we have reported on thermoresponsive ester free PTMC derivatives bearing oligoethylene glycol (OEG) in the side chain.[24] Secondly, photoresponsive PTMC derivative coumarin derivatives have been synthesized.[25] The analysis of the degradation behaviors of PTMC derivatives with OEG in the side chain[26] and the formation of nanoparticles by amphiphilic copolymer with PLA and PTMC derivatives have also been reported.[27] Since they do not generate any acidic compounds at the time of disassembling, treatment could be carried out without

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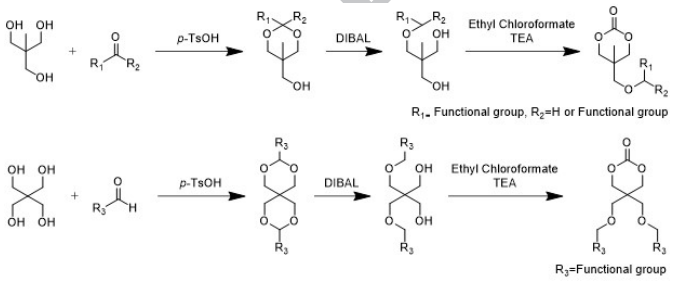
changing the pH in the body. However, the starting compound for their monomer is limited to the primary alcohol, as well as requiring many synthesis steps, usually five. This could therefore be one of the reasons why there are not so many ester free TMC derivatives.[14]

In this study, we have developed a novel synthesis route to make ester free TMC derivatives, using more common materials. The novel synthesis route introduces the aldehyde compound as the starting material and converts it to the TMC side chain by ether bond. The key reaction uses diisobutylaluminium hydride (DIBAL) which is a reducing agent.[28] By using DIBAL, it is possible to cut off only one side of the acetal structure.[29-32] Several compounds were synthesized to confirm the usefulness of the novel synthesis route.

Results and discussion

The novel synthesis method differs from the conventional method in the number of reaction steps. In the conventional synthesis method, two hydroxyl groups are protected and the remaining hydroxyl group and the sulfonyl protected substituent are coupled. Then, deprotection of two hydroxyl groups is carried out, and the TMC derivative is synthesized by the carbonation reaction. Hence, there are five reaction steps.[10] Also, since it is the S_N2 reaction, a steric effect is caused, and it has been a problem that only limited substituents can be introduced. Therefore, in order to synthesize the ester free type TMC derivative more easily, it was proposed to directly introduce the compound used for protecting the hydroxyl group into the side chain. In the novel synthesis method, however, two hydroxyl groups are protected with the substituent to be introduced and only one side of the cyclic acetal structure is deprotected using DIBAL (Scheme 1). Using this method, it was possible to synthesize a diol into which a substituent, which is a precursor of the TMC derivative, was introduced after protecting the hydroxyl group. Thereafter, the carbonation reaction was carried out, and a TMC derivative was synthesized by three-step reaction using a novel synthesis method. This method was applied to six aldehydes and one ketone to successfully synthesize eight TMC derivatives.



Scheme 1. Novel synthesis of ester free type trimethylene carbonate derivatives.

Figure 1 shows ^{1}H NMR spectra when benzaldehyde was used as the starting material. Since the peak of the methylene proton at 5.44 ppm in compound **1** shifted to the low magnetic field of 4.52 ppm in compound **2** by the deprotection reaction by DIBAL, formation of the diol compound **2** was confirmed (Figures 1a and 1b). Also, since the peak of the hydroxyl group of 2.37 ppm in compound **2** disappeared and the peak of the methylene proton at 3.58 to 3.74 ppm shifted to a high magnetic field of 4.07 to 4.38 ppm in compound **3**, the formation of the TMC derivative was confirmed (Figures 1b and 1c).

Figure 2 shows FT-IR spectra when benzaldehyde was used as a starting material. Since the peak of the hydroxyl group at 3,485 cm^{-1} in compound **1** was changed to 3,271 cm^{-1} in compound **2**, formation of the diol compound **2** was confirmed (Figures 2a and 2b). Also, since the peak of the hydroxyl group at 3,271 cm^{-1} in compound **2** disappeared and the peak of the carbonate at 1,746 cm^{-1} in compound **3** was observed, the formation of the TMC derivative was confirmed (Figures 2b and 2c).

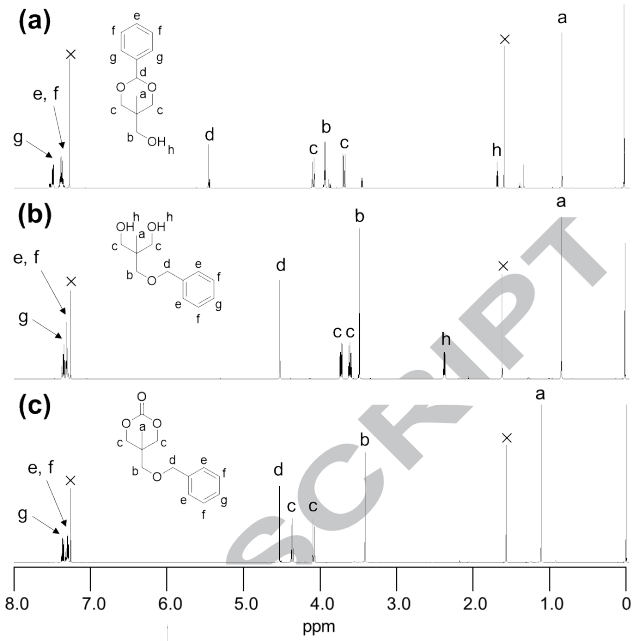


Figure 1. ^{1}H NMR spectra of compound **1** (a), **2** (b) and **3** (c) (500 MHz, $CDCl_3$).

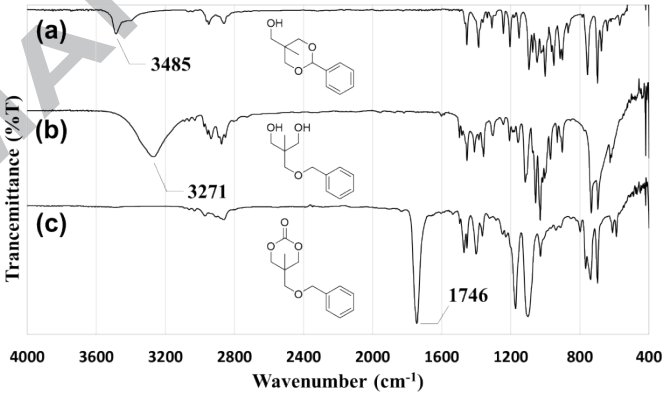
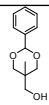
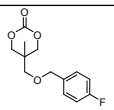
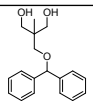
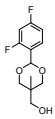
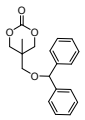
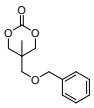
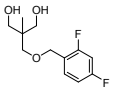
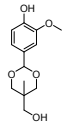
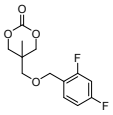
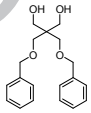
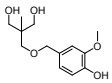
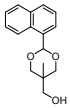
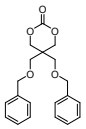
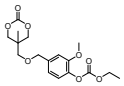
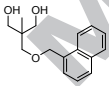
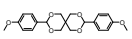
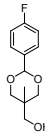
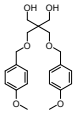
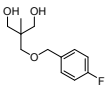
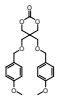


Figure 2. FT-IR spectra of compound **1** (a), **2** (b) and **3** (c).

A series of synthesized TMC derivatives are shown in Table 1. Eight TMC derivatives were synthesized, seven derivatives are novel compounds (Table 2, entries 2-8). All currently known ester free type TMC derivatives are liquid, while compounds **12**, **18**, **21** and **24** are solid TMC derivatives. Compounds **3**, **18** and **21** in which no substituent was attached to the aromatic ring were obtained with relatively high yield. However, compounds **6**, **9**, **12** and **24** with substituents attached to the aromatic ring were obtained at relatively low yield. This result suggests that when DIBAL reduces the acetal structure, the deprotection reaction is inhibited by steric bulkiness. It is also suggested that the electronic effect of the substituent is affected. The yield of each intermediate compound is shown in Table 1. Diol compounds **2**, **14**, **17** and **20** in which no substituent was attached to the aromatic ring were obtained with relatively high yield. Compared with the compounds **2**, **14**, **17**, and **20**, the diol compounds **5** and **23** having an electron donating substituent on an aromatic ring have a lower yield. In particular, the diol compound **8** and **11** having an electron withdrawing substituent have the lowest yield. Therefore, selective deprotection by DIBAL was determined to be affected by steric and electronic effects. Compound **15** had a low yield in the acetal reaction, so that the overall yield was low. This is due to side reactions occurring during the acetal reaction, resulting in a decrease in yield.

Comparisons of compounds **3**, **9** and **12** showed almost no change in T_g and T_{10}. Compounds **3** and **9** were liquid and **12** was

Table 1. The yield of each intermediate compound.

Compound	Product	Yield (%)	Compound	Product	Yield (%)	Compound	Product	Yield (%)
1		89	**9**		44	**17**		62
2		75	**10**		72	**18**		76
3		67	**11**		31	**19**		97
4		34	**12**		73	**20**		71
5		54	**13**		7	**21**		75
6		70	**14**		64	**22**		69
7		87	**15**		82	**23**		43
8		5	**16**		73	**24**		65

solid. It was thought that this was due to the fact that benzaldehyde and 4-fluorobenzaldehyde were liquid and 2,4-difluorobenzaldehyde was solid. Likewise, compound **15** was a liquid because 1-naphthaldehyde was a liquid, and compound **18** became a solid because benzophenone was a solid. Although vanillin was a solid, compound **6** became a liquid. This is due to the fact that the ethylchloroformate reacted with the hydroxyl group of the aromatic ring, and the intermolecular bond via the hydroxyl group disappeared. In compounds **21** and **24**, the product became a solid despite the fact that benzaldehyde and *p*-anisaldehyde were liquid. As a result, if the starting material is a liquid even if it has a rigid structure, the possibility of solidification should be considered. Compared with compounds **18** and **21** having no substituent on the aromatic ring, the T_g and T_m of compound **18** using ketone as a starting material was higher than that of compound **21** in which the aldehyde was used as a starting material. It is derived from the side chain structure. Compound **18** is in a form in which a secondary alcohol is introduced into the side chain, and compound **21** is in a form in which a primary alcohol is introduced. Therefore, because compound **21** could move relatively freely compared with compound **18**, it was considered that there was a difference in thermal properties.

Conclusion

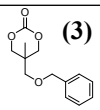
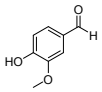
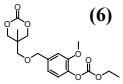
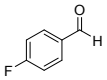
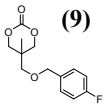
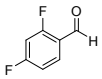
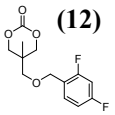
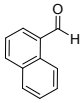
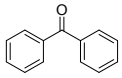
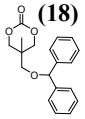
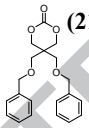
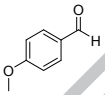
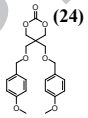
In conclusion, we succeeded in developing a novel synthesis route for ester free TMC derivatives. By developing this novel synthesis route, it became possible to introduce a substituent in the side chain in the form of an ether bond using aldehyde or ketone as a starting substance. This made it possible to introduce a substituent derived from a secondary alcohol into the side chain. In addition, compared with the conventional synthesis method, it was possible to reduce the number of reaction steps from five to three, enabling time and cost reductions.

It was suggested that the state of the TMC derivative could be controlled by the selection of starting material and structure. Thermal analysis showed that T_{10} was more than 200 ℃ in all TMC derivatives. This makes it possible to conduct dry heat sterilization allowing it to be used as a medical material. This novel synthesis method opens the possibility of a wide range of new ester free type TMC derivatives.

Supporting Information

Experimental details; Figures S1−S48 (^{1}H NMR and FT-IR).

Table 2. Ester free type trimethylene carbonate derivatives were synthesized.

Entry	aldehyde or ketone	Product	appearance	T_g [a] (℃)	T_m [a] (℃)	T_{10} [b] (℃)	Yield (%)
1		 (3)	Liquid	-50	-	239	45
2		 (6)	Liquid	-24	-	291	13
3		 (9)	Liquid	-50	-	252	3
4		 (12)	Solid	-51	85	240	16
5		 (15)	Liquid	-22	-	276	4
6		 (18)	Solid	-7	75	279	34
7		 (21)	Solid	-33	53	288	52
8		 (24)	Solid	-39	76	257	19

[a]Determined by DSC. [b]Determined by TGA. T_{10} is the temperature which 10% of the weight loss.

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- Novel synthesis method is shown for ester free trimethylene carbonate derivatives.
- Six aldehydes and one ketone compounds converted to monomers
- It requires only three steps.
- The selective deprotection by diisobutylaluminium hydride is key reaction.
- This method would provide variety of functional biodegradable polymers.