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Chemical Synthesis of Cyclodextrins by Using Intramolecular Glycosylation

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Received May 1, 2002

An efficient synthesis of cyclodextrins (CDs) by using the intramolecular glycosylation is demonstrated. α-CD, an α(1→4)linked hexaglucoside, was prepared via a block condensation of three maltose units. A modified key maltose intermediate as a precursor to both glycosyl donor and acceptor components was prepared in 6 steps starting from maltose. All the glycosylation for chain elongation and cyclization of saccharides was carried out after tethering the donor to the acceptor by the phthaloyl bridge to give the desired saccharides in good yields with complete α-selectivity. δ-CD composed of 9 glucose units was synthesized by the same manner from three maltotriose units.

Introduction

Stereoselective glycosylation has been an important issue for the efficient synthesis of oligosaccharides. Recently, various studies on stereo- and regiocontrol of glycosylation have been reported by using intramolecular reaction of a glycosyl donor and a glycosyl acceptor linked together with an appropriate bridge.[1−3] Intramolecular glycosylation is classified into two categories. One is so-called "intramolecular aglycon delivery".[2] In this method, the glycosyl acceptor is delivered to the donor via a linker attached to the donor moiety. In the other category, a stable bridge is used as a "molecular clamp" that controls the spatial arrangement of a donor and an acceptor to kinetically accelerate the glycosylation and allows a stereo- and regioselective reaction.[3]

We reported the first application of the latter method to the synthesis of the glucosaminylmuramic acid residue, which was not formed by direct glycosylation using the oxazoline method without a molecular clamp, in 1986, and termed it the molecular clamp method.[3a] Recently, the stereoselective glycosylation reaction using this method has been reported by several groups, especially by the intensive works of Ziegler et al and Schmidt et al.[3] We previously reported that α(1→4) and β(1→4) glycosidic linkages were formed in good yields with high stereoselectivity by the use of phthaloyl and silyl bridges bound to the 6-position of a donor and an acceptor, respectively (Figure 1).[4]

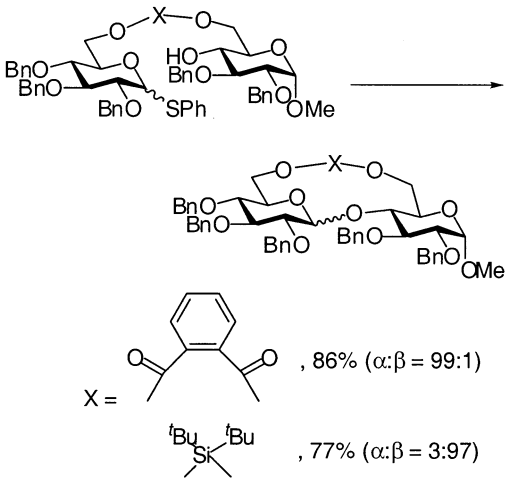

FIGURE 1. Stereoselective glycosylation by using the molecular clamp method.

In the present study, the molecular clamp method was applied to the synthesis of cyclodextrins (CDs) to demonstrate the utility of the "molecular clamp" method for oligosaccharide synthesis via segment condensation leading to efficient synthesis of CDs.

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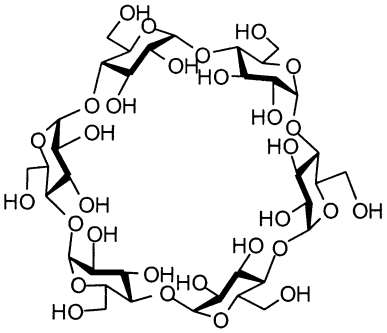
10.1021/jo025887r CCC: $22.00
Published on Web 10/25/2002

CDs are cyclic oligosaccharides consisting of D-glucopyranosyl units connected by α(1→4) glycosidic linkages. The natural CDs which consist of 6, 7, or 8 glucose units are well-known as α-, *β*-, and *γ*-CD, respectively.[5] CDs have a hydrophobic cavity that can include a variety of chemical substances. CDs have been widely used in foods and cosmetics, as well as pharmaceutical, environmental, and industrial chemistry.[6,7] Chemical modifications of CDs have been reported not only for the biomimetic studies but also for the improvement of the physicochemical properties of their complexes such as solubility and bioavailability.[8] Many studies of de novo synthesis of CDs and their analogues have also been reported.[9,10] Structurally diverse CD analogues can be readily obtained by de novo synthesis, though substantial time and efforts are required for the synthesis. As a pioneering work, the chemical syntheses of α-CD and *γ*-CD were reported by Ogawa and Takahashi in 1985.[9b,c] By employing a similar synthetic strategy, a new member of the CD family, namely, cyclo(1→4)-α-D-glucopentaoside, was synthesized by Nakagawa et al.[9d] Kuzuhara et al. succeeded in the synthesis of "chimera cyclodextrin", which has the D-glucosamine residue in place of a glucose residue in the CD skeleton.[9e−g] The function of CDs having larger ring system is also of interest. CDs having more than 9 glucose units are obtained by enzymatic digestion of starch by using cyclodextrin glucanotransferase (CGTase) only in tiny amounts.[11]



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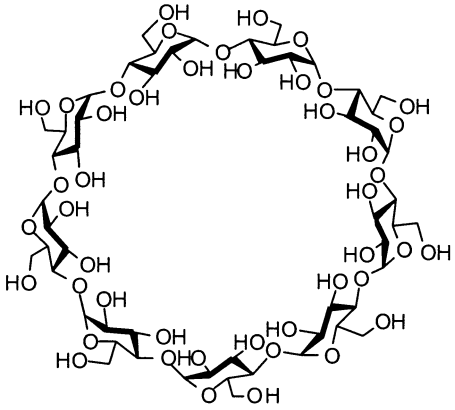

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FIGURE 2. Structures of α-CD **1** and *δ*-CD **2**.

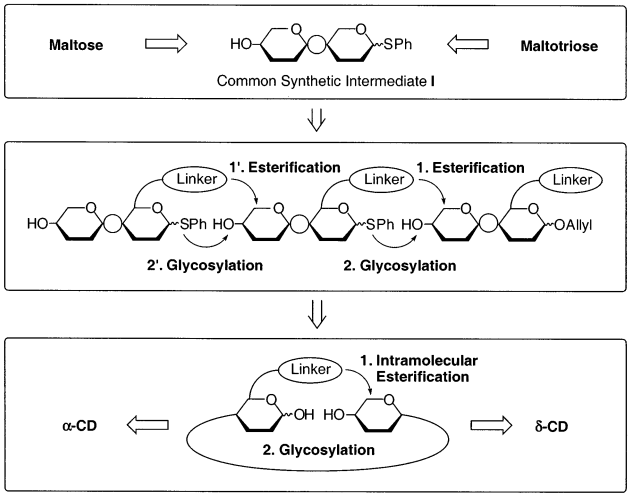

FIGURE 3. Synthetic strategy for CDs.

In the present study, the molecular clamp method using the phthaloyl bridge was applied to the synthesis of α-CD (**1**) and *δ*-CD (**2**) (Figure 2). This was the first success in the chemical synthesis of CDs having more than 9 glucose units.

Result and Discussion

The synthetic strategy for CDs is shown in Figure 3. CDs have a highly symmetric structure composed of only

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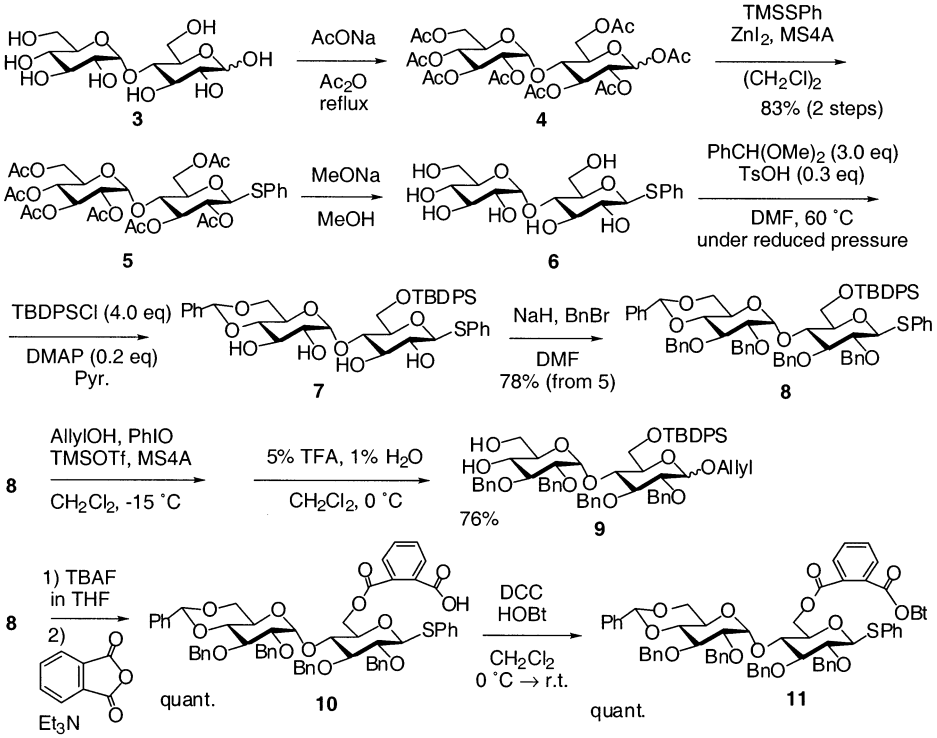
SCHEME 1



D-glucose units connected by α(1→4) linkages. Commercially available maltooligoglucosides are thus used as starting materials to reduce the synthetic steps. For the synthesis of α-CD, maltose [α(1→4) linked diglucose] is selected as a starting material and α-CD was thus constructed with three maltose units. Maltose was first converted to the corresponding thioglycoside **I** as a common synthetic intermediate for both donor and acceptor. An acceptor moiety was derived from this intermediate by conversion to the allyl glycoside. Elongation of the saccharide chain was effected by stepwise glycosylation. The molecular clamp method using phthaloyl linker was employed for each glycosylation step. Macrocyclic esterification was then carried out to bring the donor part close to the acceptor part in order to suppress the undesired oligomerization at the cycloglycosylation step, since macrocyclic esterification was expected to afford better yields than the direct cycloglycosylation. In addition, stereocontrol for the glycosylation was also expected by the molecular clamp. Cleavage of the terminal allyl group of the cyclic ester and cycloglycosylation afforded α-CD. The δ-CD was synthesized in a similar manner by using maltotriose [α(1→4) linked triglucose] as a starting material.

The liner hexasaccharide **17** was prepared as shown in Schemes 1 and 2. The disaccharide thioglycoside **8** was prepared from maltose as a common synthetic intermediate. Maltose **3** was treated with sodium acetate (AcONa) in acetic anhydride (Ac_2O) to give the octaacetate **4**. Treatment of **4** with phenylthiotrimethylsilane (TMSSPh) in the presence of ZnI_2[12] afforded the thioglycoside **5** in 83% yield from **3** (2 steps). After all acetyl groups of **5** were removed, the 4′- and 6′-hydroxy groups of **6** were protected with a benzylidene group using benzaldehyde dimethylacetal [$PhCH(OMe)_2$] in the presence of *p*-toluenesulfonic acid in DMF under reduced pressure (15 mmHg).[9e,f] The primary 6-hydroxy group of the product was then selectively protected with a *tert*-butyldiphenylsilyl (TBDPS) group using *tert*-butyldiphenylsilyl chloride (TBDPSCl) to afford the tetraol **7**. Benzylation of all the hydroxy groups of **7** gave the synthetic intermediate **8** in 78% yield from **5** (4 steps). The disaccharide thioglycoside **8** was coupled with allyl alcohol (AllylOH) by using iodosobenzene (PhIO) and trimethylsilyl trifluoromethansulfonate (TMSOTf) as a promoter in CH_2Cl_2.[13] We previously reported that combination of PhIO and TMSOTf activated thioglycosides chemoselectively in the presence of allyl glycoside. The benzylidene group of the product was then removed with 5% trifluoroacetic acid (TFA) to give the diol **9** in 87% yield (α:β = 7:1). After a TBDPS group of **8** was removed with tetrabutylammonium fluoride (TBAF), the resulting free 6-hydroxy group of the disaccharide was reacted with phthalic anhydride to give the phthaloyl half ester **10**, which was treated with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) to give activated ester **11**.

The coupling reaction of the donor part with the acceptor part **9** was first carried out by using 1.3 equiv of **10**, 1.5 equiv of DCC, and 0.1 equiv of 4-(dimethylamino)pyridine (DMAP) against **9** to give the product **12** in

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(12) Hanessian, S.; Guindon, *Carbohydr. Res.* **1980**, *86*, C3.

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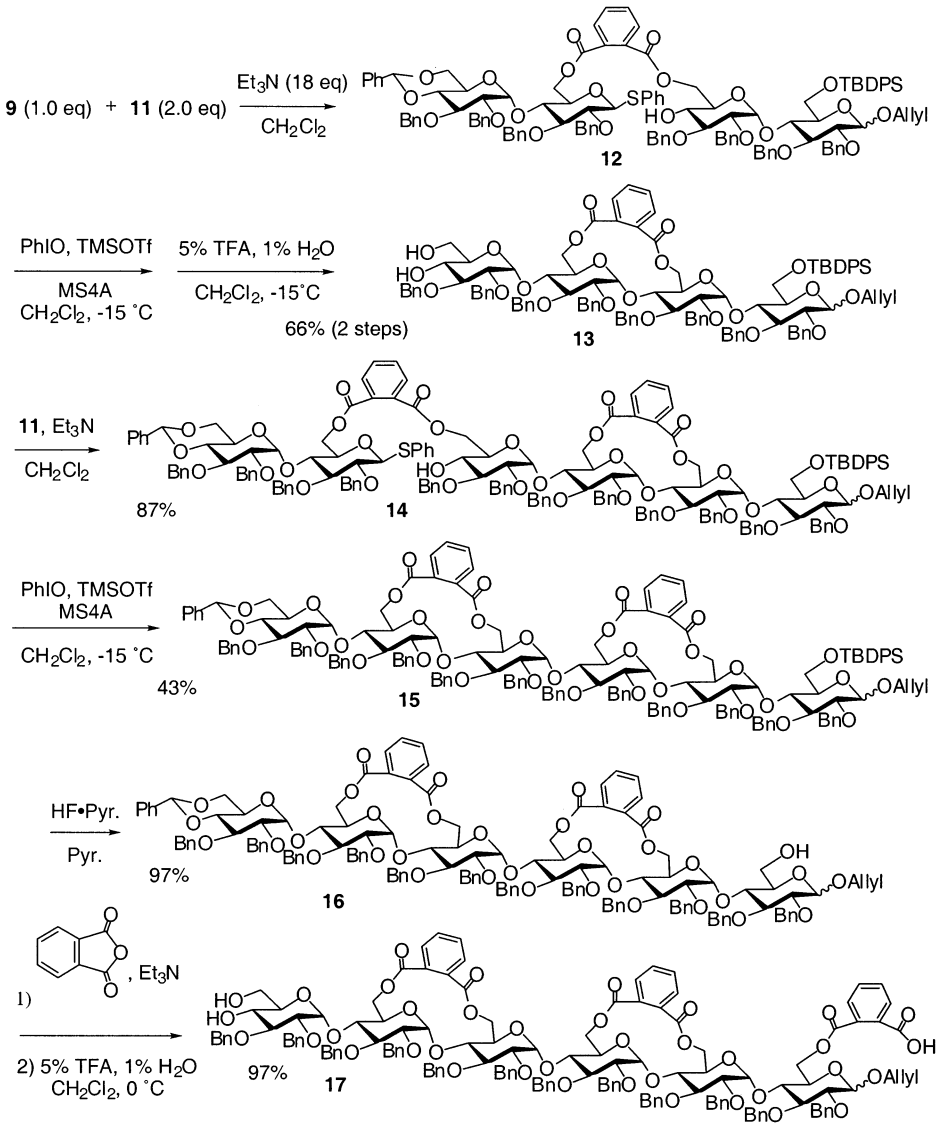
SCHEME 2



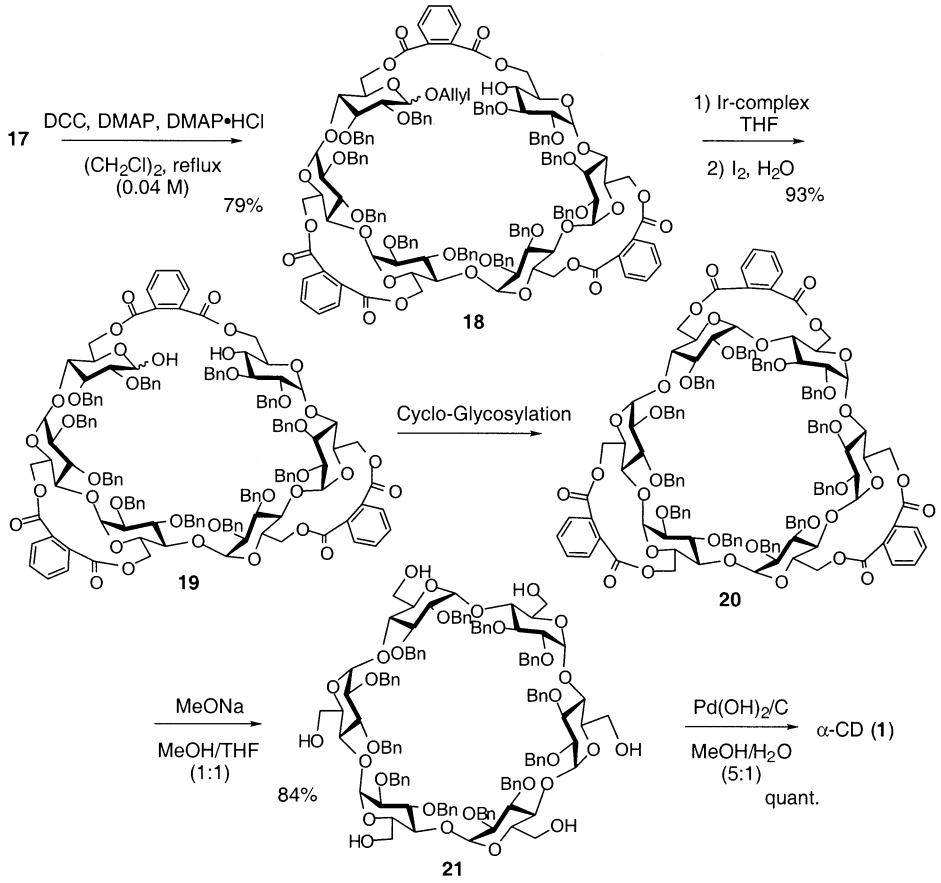
55% yield (data not shown). The same product **12** was regioselectively obtained in 90% yield when 2.0 equiv of the activated ester **11** and 18 equiv of triethylamine (Et_3N) were used.

The intramolecular glycosylation reaction of bridged precursor **12** was then carried out by using 1.1 equiv of PhIO and 0.5 equiv of TMSOTf in CH_2Cl_2 under N_2 atmosphere. Subsequent debenzylidenation of the product with TFA afforded the desired tetrasaccharide **13** in good yield with complete α-selectivity. The present glycosylation method in CH_2Cl_2 without molecular clamp generally gives corresponding glycosides with low stereoselectivity.[13] In a method similar to the synthesis of bridged precursor **12**, the linear tetrasaccharide **13** was treated with the activated ester **11** in the presence of Et_3N to give the bridged precursor **14** for the hexasaccharide in 87% yield. After the intramolecular glycosylation of **14**, the linear hexasaccharide **15** was obtained in 43% yield with complete α-selectivity. The major side reactions at this step were hydrolysis of the thioglycoside moiety and debenzylidenation. To introduce the linker, the TBDPS group of the linear hexasaccharide **15** was cleaved with hydrogen fluoride−pyridine (HF·Pyr) to afford the desired compound **16** in 97% yield. The condensation of the 6-hydroxy group of **16** with phthalic anhydride followed by treatment with TFA/H_2O/CH_2Cl_2 afforded the product **17**.

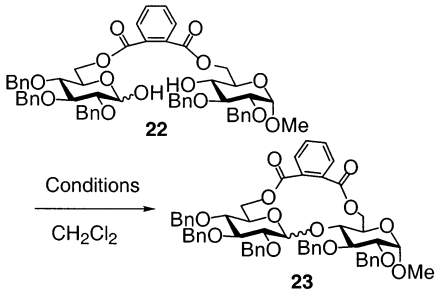
The synthesis of α-CD (**1**) was performed as shown in Scheme 3. The macrocyclic esterification was performed according to the method reported by Keck and Boden.[14] The macrolactonization of **17** with DCC, DMAP, and DMAP·HCl proceeded regioselectively in refluxing 1,2-dichloroethane [$(CH_2Cl)_2$] under high dilution (0.004 M) conditions to give the cyclic ester **18** in 79% yield. In the case where a hexasaccharide lacking the interresidual two phthaloyl groups was used, the desired cyclic ester was obtained only in 47% yield (data not shown). Thus, the phthaloyl bridges proved to be important to maintain a favorable conformation for the facile cyclization. For the final cycloglycosylation, the 1-*O*-allyl group of the macrocyclic ester **18** was removed via isomerization of the allyl group to the 1-propenyl group with a cationic

(14) Boden, E. P.; Keck, G. *J. Org. Chem.* **1985**, *50*, 2394.

SCHEME 3



SCHEME 4



iridium complex followed by treatment with I_2.[15] The cyclic ester **19** was thus obtained in 93% yield.

To find out the best reaction conditions for intramolecular cycloglycosylation, the glycosylation of bridged disaccharide **22** was first examined (Scheme 4, Table 1). As a novel method for activation of a 1-hydroxy sugar, the authors have already reported "dehydrative glycosylation".[16] This method is especially effective for construction of the α(1→4) glycosidic linkage and allows α-preferential glycosylation. This dehydrative glycosylation was first tested for the present substrate **22** (Table 1). Trifluoroacetic anhydride [$(CF_3CO)_2O$] and trimethylsilyl perchlorate ($TMSClO_4$) prepared from trimethylsilyl chloride (TMSCl) and silver perchlorate ($AgClO_4$) were used as a dehydrative reagent and a promoter, respectively. The reaction proceeded slowly in CH_2Cl_2 to give the desired disaccharide **23** with a complete α-selectivity (Table 1, entry 1), but the yield (61%) was not satisfactory. In this case, the major side reaction was 4-*O*-acylation of the acceptor component. To suppress the 4-*O*-acylation, TMSOTf, which has a lower reactivity than $TMSClO_4$, was used as a promoter. The reaction yield, however, was not improved (entry 2). To improve the yield, glycosylation by using a glycosyl imidate,[17] which is considered to be the most reactive glycosyl donor, was then tested (entry 3). Glycosyl imidate was prepared by treatment of **22** with trichloroacetonitrile (CCl_3CN) in the presence of cesium carbonate (Cs_2CO_3). The formation of the 4-*O*-imidate was not observed under these conditions. Without purification of the resulting imidate, glycosylation was performed in CH_2Cl_2 in the presence of TMSOTf to give the desired disaccharide **23** in 97% yield α-pref-

TABLE 1. Intramolecular Glycosylation of Bridged Saccharide 22.

entry	conditions	yield/%	α:β
	dehydrative glycosylation		
1	1.2 equiv $(CF_3CO)_2O$, 0.2 equiv $TMSClO_4$	61	100:0
2	1.5 equiv $(CF_3CO)_2O$, 0.2 equiv TMSOTf	63	100:0
	glycosylation via imidate		
3	(1) 1.0 equiv Cs_2CO_3, 10 equiv CCl_3CN (2) 0.1 equiv TMSOTf	97	89:11

(15) Oltvoort, J. J.; van Boeckel, C. A. A.; de Koning, J. H.; van Boom, J. H. *Synthesis* **1981**, 305.

(16) Wakao, M.; Nakai, Y.; Fukase, K.; Kusumoto, S. *Chem. Lett.* **1999**, 27.

(17) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731.

SCHEME 5

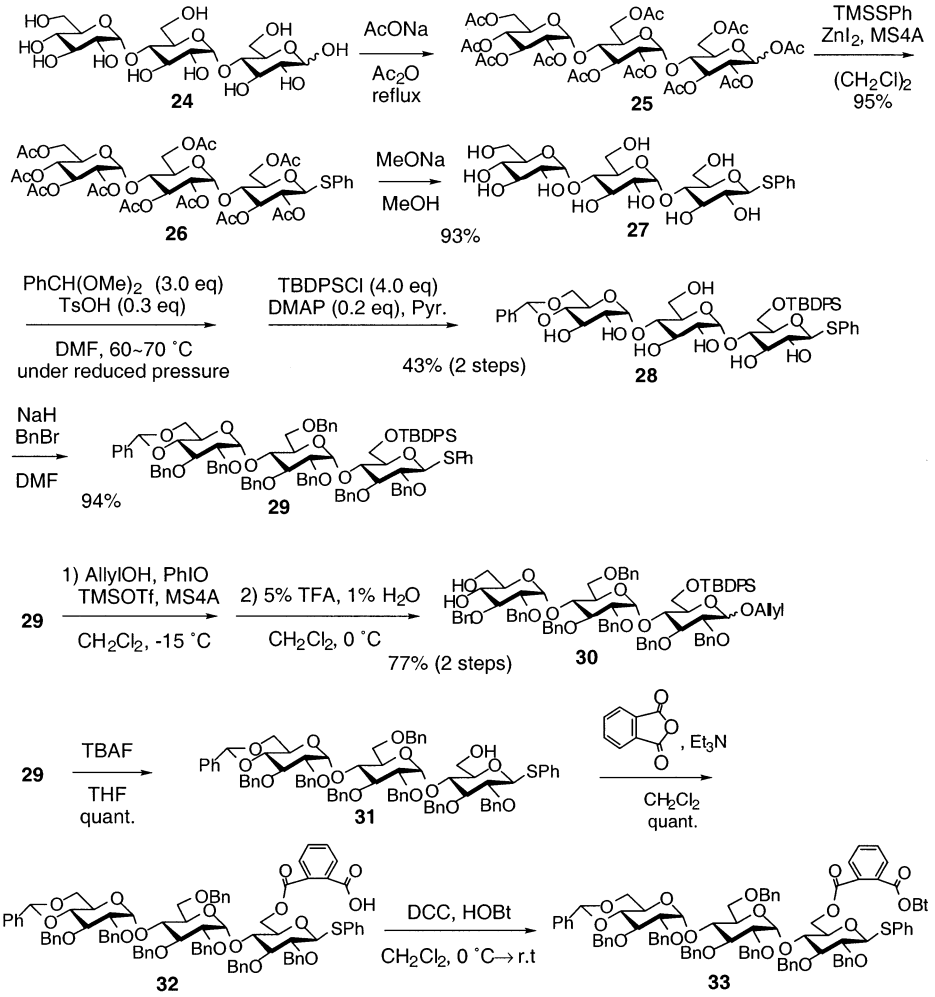


TABLE 2. Examination of Cycloglycosylation of 19

entry	conditions	yield/% (recovery)	α:β
	dehydrative glycosylation		
1	1.2 equiv $(CF_3CO)_2O$, 0.2 equiv $TMSClO_4$	15 (69)	100:0
2	2.0 equiv $(CF_3CO)_2O$, 0.2 equiv $TMSClO_4$	18 (30)	100:0
	glycosylation via imidate		
3	(1) 1.0 equiv Cs_2CO_3, 10 equiv CCl_3CN (2) 0.1 equiv TMSOTf	66	100:0

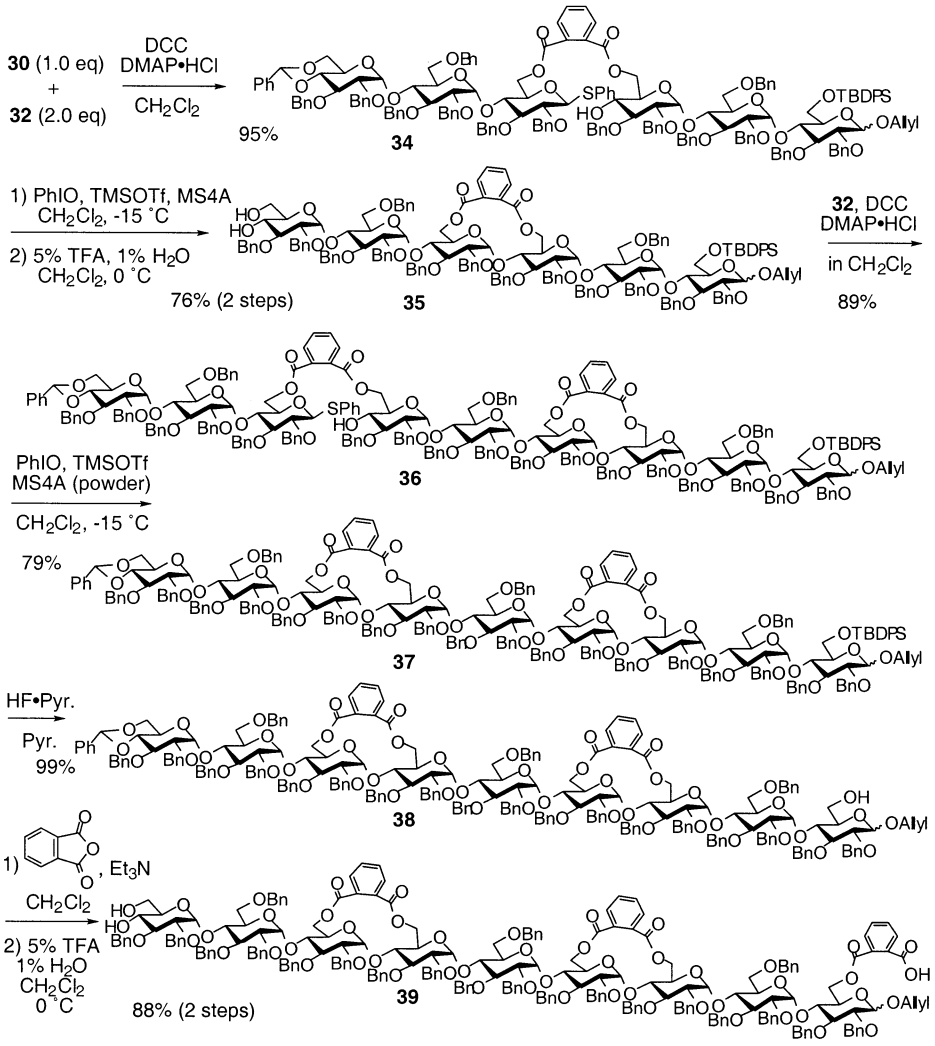
erentially (α:β = 89:11). Thus, a high α-promoting effect of the phthaloyl bridge at the 6,6′-positions was also observed here since glycosylation with 2-*O*-benzylated trichloroacetimidates without the phthaloyl bridge gave corresponding glycosides with no selectivity under the present glycosylation conditions.

The above results indicated that the dehydrative glycosylation method is excellent in the α-selectivity and the imidate method is so with regard to the yield. Thus, both of the methods were applied to the cycloglycosylation (Table 2). In the case of the dehydrative glycosylation, the desired product **20** was obtained with complete α-selectivity but in very low yields (entries 1 and 2). Most of the starting material **19** was recovered. Thus, the reactivity of the 1-hydroxy group of compound **19** was considered to be significantly low. By contrast, application of the imidate method to cycloglycosylation dramatically improved the yield of the desired glycosylation reaction. The reaction proceeded smoothly in the presence of TMSOTf to give **20** only in the α-form in 66% yield. Stereoselectivity of glycosylation was controlled by a combined effect of the property of the linker and the structure of the substrate.

For the synthesis of α-CD, the protected cyclic hexasaccharide **20** was smoothly methanolized by treatment with 0.5 M NaOMe to give the hexaol **21** in 84% yield (Scheme 3). Finally, hydrogenolysis of all the benzyl groups followed by purification by reversed-phase column chromatography using HP-20 furnished the desired α-CD **1** (quantitative yield). The structure of **1** was confirmed by NMR and ESI-MS spectra. In fact, the NMR data of synthetic **1** were identical with that of commercially available α-CD.

To synthesize δ-CD composed of nine glucose units, the common synthetic intermediate **29** was first prepared from maltotriose **24** as shown in Scheme 5. Maltotriose **24** was converted via the undecaacetate **25** to the thioglycoside **26** in 95% yield (2 steps). Methanolysis of all the acetyl groups furnished the undecanol **27** in 93% yield. The 4^{III}- and 6^{III}-hydroxy groups of **27** were protected with a benzylidene group and the primary 6^{I}-hydroxy group with a TBDPS group to afford the desired product **28** in 43% yield from **27** (2 steps). All the remaining hydroxy groups of **28** were protected with

SCHEME 6



benzyl groups to provide the synthetic intermediate **29** in 94% yield. The total yield of **29** from maltotriose **25** was satisfactorily 36% for 6 steps.

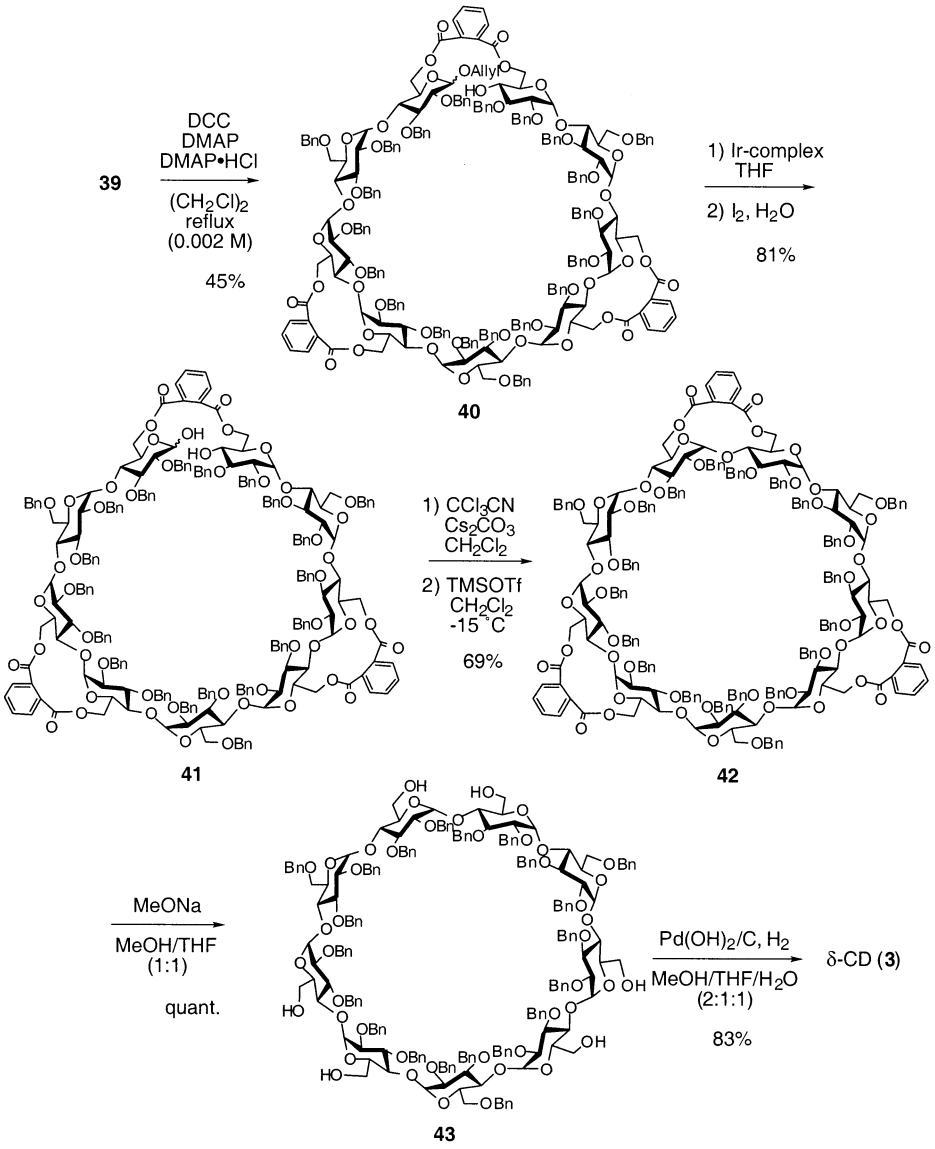
In the same manner as the synthesis of α-CD, the common synthetic intermediate **29** was converted to the acceptor moiety **30** and the donor moiety **32** and **33**. The coupling of **29** with AllylOH followed by removal of the benzylidene group with TFA furnished the allyl glycoside **30** in 77% yield ($\alpha:\beta = 7:1$) Cleavage of the TBDPS group at the 6^I-position of **29** with 1 M TBAF (in THF) proceeded smoothly to give **31** in a quantitative yield. The resulting free 6^I-hydroxy group of **31** was acylated with phthalic anhydride to give **32** in a quantitative yield. Treatment of **32** with DCC and HOBt provided the desired product **33**, which was used without purification for the next reaction.

The coupling reaction of **30** and **33** with 20 equiv of Et_3N under conditions similar to the synthesis of **12** was not completed. Even with 60 equiv of Et_3N, the reaction was not completed either, giving the desired product **34** in 54% yield with 38% recovery of the starting material. The coupling reaction with use of DCC was next investigated with DMAP·HCl, which has a lower basicity than DMAP, as a promoter to suppress the formation of *N*-acylurea under basic condition. The coupling of **30** and **32** in the presence of DMAP·HCl provided the desired product **34** in 95% yield (Scheme 6).

For the elongation of the saccharide chain, the glycosylation and acylation were repeated (Scheme 6). The glycosylation of the bridged precursor **34** with PhIO in the presence of TMSOTf followed by debenzylidenation with TFA afforded the desired hexasaccharide **35** in 76% yield with complete α-selectivity. From this experiment, the molecular clamp method was found to secure α-selectively even in the condensation between trisaccharides. The coupling of **32** and **35** with DCC in the presence of DMAP·HCl provided the desired bridged product **36** in 89% yield. The glycosylation of **36** gave the linear nonasaccharide **37** in 79% yield with complete α-selectivity. The structure of nonasaccharide **37** was confirmed by NMR and ESI-MS spectra. The TBDPS group of the linear nonasaccharide **37** was deprotected with hydrogen fluoride−pyridine to afford the desired compound **38** in 99% yield. Treatment of the 6-hydroxy group of **38** with phthalic anhydride followed by the removal of the benzylidene group with TFA afforded the product **39**.

The synthetic pathway for the cyclic nonasaccharide **42** is illustrated in Scheme 7. The macrocyclic esterification of **39** was then performed by a method similar to the synthesis of α-CD with DCC, DMAP, and DMAP·HCl

SCHEME 7



in refluxing $(CH_2Cl)_2$ under high dilution conditions (0.002 M). The reaction occurred selectively at the 6^{IX}-position to give the macrocyclic ester **40** in 45% yield. Although the reaction yield became lower with increasing chain length and flexibility of the saccharide, the yield of the desired product **40** was satisfactory (see below). After cleavage of the allyl group of the cyclic ester **40** in 81% yield, glycosyl imidate was prepared by treatment of the product **41** as above. The resulting imidate was employed without purification to the final glycosylation reaction performed in the presence of TMSOTf to provide the cyclic nonasaccharide **42** in 69% yield with complete α-selectivity. Thus, the cycloglycosylation by the molecular clamp gave the desired product **42** in high yield and perfect stereoselectivity despite of the large ring size: direct cyclization of a nonasaccharide has never been reported. Total yield of cyclic esterification and cycloglycosylation was significantly high even in comparison with direct cycloglycosylation reported for the synthesis of α- to γ-CDs.[9a−c] The structure of the nonasaccharide **42** was confirmed by NMR and ESI-MS spectra. The NMR spectrum represents quite simple trisaccharide peaks owing to the C_3-symmetric structure.

The protected cyclic saccharide **42** was converted to δ-CD according to the method employed in the synthesis of α-CD (Scheme 7). Methanolysis of phthaloyl groups of **42** in MeOH/THF/H_2O (2:1:1) provided the octadecabenzyl ether **43** in a quantitative yield. Final hydrogenolysis of all the benzyl groups with $Pd(OH)_2$/C followed by purification by reversed-phase column chromatography with HP-20 furnished δ-CD (**2**) in 83% yield. The structure of the obtained δ-CD (**2**) was confirmed by NMR and ESI-MS spectra.

As described, both α- and δ-cyclodextrins were efficiently synthesized by the use of the molecular clamp method. The present study demonstrated that the molecular clamp method using the phthaloyl bridges attached to the 6-positions of the donor and the acceptor is particularly useful for the formation of an α(1→4) glucosidic linkage. The method also proved to be useful for oligosaccharide synthesis via segment condensation with high yield and high selectivity. Cyclic oligosaccha-

ride structures were also efficiently constructed by the same method, i.e., intramolecular glycosylation of the oligosaccharide macrolactonized via a phthaloyl bridge. This method is expected to be useful for the synthesis of other cyclic oligosaccharides.

Acknowledgment. The present work was financially supported in part by "Research for the Future" Program No. 97L00502, a Grant-in-Aid for JSPS Fellows No. 01798 from the Japan Society for the Promotion of Science to M.W., and by Grants-in-Aid for Scientific Research No. 09044086 from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental synthesis details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025887R