ORGANIC LETTERS

2012
Vol. 14, No. 6
1612–1615

First Per-6-*O*-tritylation of Cyclodextrins

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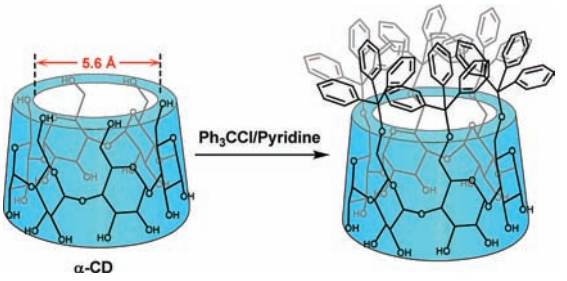
Received February 14, 2012

ABSTRACT



Because of the large dimension of the trityl group and the truncated conical geometry of cyclodextrin (CD) molecules, it is unclear if there is enough space at the narrower end of CDs to permit a per-6-*O*-tritylation. This work demonstrates that it is indeed possible to simultaneously install a trityl group at the O6-position of every glucopyranosyl unit in a CD. A novel per-6-substitution method has been developed for CD chemistry.

Triphenylmethyl, or the trityl group, is a common and important protecting group for alcohols and other functional groups.[1] In carbohydrate chemistry, the trityl group's large size and superior stability toward bases have been extensively exploited to achieve regioselectivity in protecting primary alcohols in the presence of more hindered secondary and tertiary alcohols. In the history of cyclodextrin (CD) chemistry, the 6-*O*-tritylation has been studied by several groups since 1969.[2,3] Recently, Matt and co-workers have designed another even bulkier version of the trityl group called "super trityl"[4] along with some capped tritylating reagents for the O6-protection of CDs.[5] To date, a number of 6-*O*-mono-,[2b–d] di-,[2e,f,4a] tri-,[2c,3a] and tetratritylated[3,4b] CD derivatives have been reported; these tritylated products have played a crucial role in accessing different multisubstituted CD scaffolds for various applications.[6] Interestingly, despite a long history of performing 6-*O*-tritylations, functionalizations

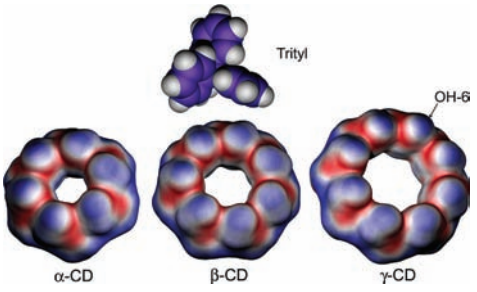


Figure 1. CPK model of the trityl group in a propeller conformation and a surface model to illustrate the primary rims (front) of CDs.

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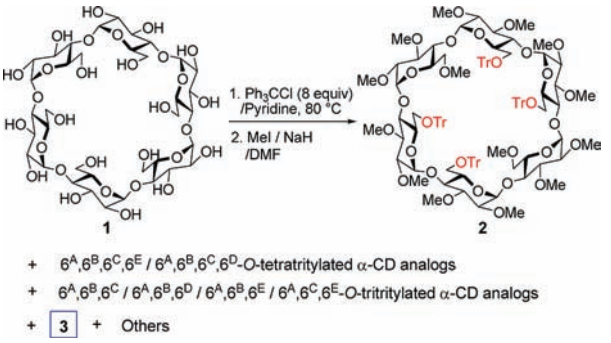
10.1021/ol300358u
Published on Web 03/06/2012

Scheme 1. Selective Tritylation of α-CD



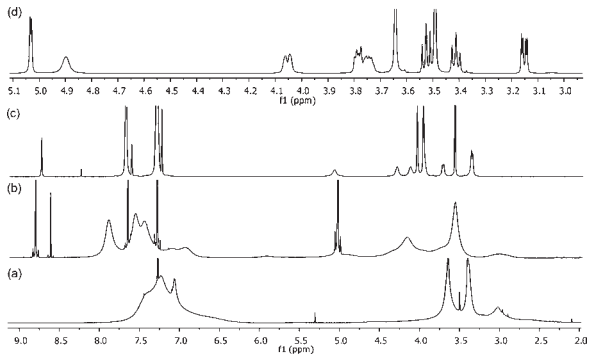


Figure 2. The ^{1}H NMR (600 MHz) spectra of (a) **3** in $CDCl_3$ (298 K); (b) **3** in pyridine-d_5 (298 K); (c) **3** in pyridine-d_5 (360 K); and (d) **4** in $CDCl_3$ (298 K).

of CDs with more than four trityl groups have not been reported, even by using forcing conditions. Since all three common CDs (α, β, and γ) have a similar truncated cone-shape,[7] such geometry arranges all primary hydroxyl groups (6-OH groups) of the glucopyranosyl units to the narrower end (primary rim) of the cone (Figure 1); consequently, between OH-6 groups of the adjacent pyranose units, there is only limited amount of space available. Thus some fundamental questions need to be asked, i.e., whether it is physically possible to introduce more than four trityl groups at the primary face of a CD. Even further, does a CD molecule have enough space to allow for the installation of a trityl group at the O6-position of all the α-D-glucopyranosides at the same time? Here, we report our finding, which can unambiguously answer these questions.

One of our projects required synthesis of the symmetrical $6^A,6^B,6^D,6^E$-*O*-tetratritylated α-CD **2**.[3] We thought that we could improve the overall yield by carrying out modifications on previously published conditions.[3a] Compound **2** was obtained in 25% yield after two steps: first, a selective 6-*O*-tetratritylation of α-CD in pyridine (0.03 mol·L^{-1}) with trityl chloride (4.5 equiv) at 70 °C for

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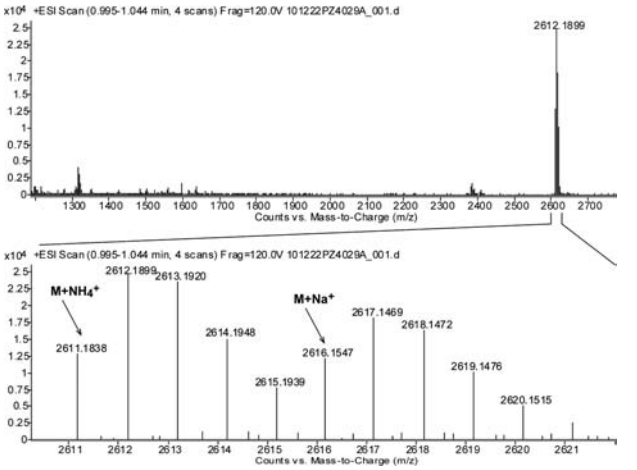
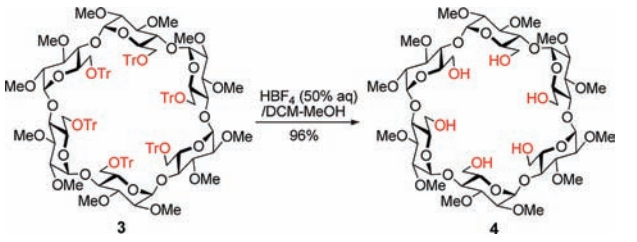


Figure 3. The ESI-HRMS spectra of the isolated compound **3**.

Scheme 2. Acid-Mediated Detritylation of **3** to Provide **4**



48 h, and second, a per-*O*-methylation of the obtained reaction mixture (MeI/NaH/DMF). Since all previous work[2a,3,4b] indicated that it was difficult to functionalize CDs with more than four trityl groups, we thought that we could improve the overall yield of **2** at the first step by carrying out the reaction at a higher temperature under higher substrate concentrations, using more reagent, and prolonging the reaction time; in doing so, we could force the conversions of all mono-, di-, and tritritylated intermediates to the most desired tetratritylated compounds (Scheme 1); the per-*O*-methylation step usually proceeds in excellent yields. Thus, we carried out an experiment by treating trityl chloride (8 equiv) with α-CD (**1**) in anhydrous pyridine (0.13 mol·L^{-1}) at 80 °C; after 5 days, the reaction mixture was precipitated out from water and directly per-*O*-methylated as before.[3a] However, this did not significantly alter the yields of **2** (<20%). The majority of the reaction was converted to a less polar compound **3**, isolated in ~35% yield.

From the recorded ^{1}H NMR spectrum of compound **3** in $CDCl_3$ (Figure 2a), it appeared to be an unattractive compound; indeed, it was initially regarded as a mixture of aromatic byproduct because no apparent proton from the α-CD was observed; some signals of aromatic protons and possibly some peaks correlating to methoxy groups were observed. In general, the spectra of **3** appeared to be very broad.

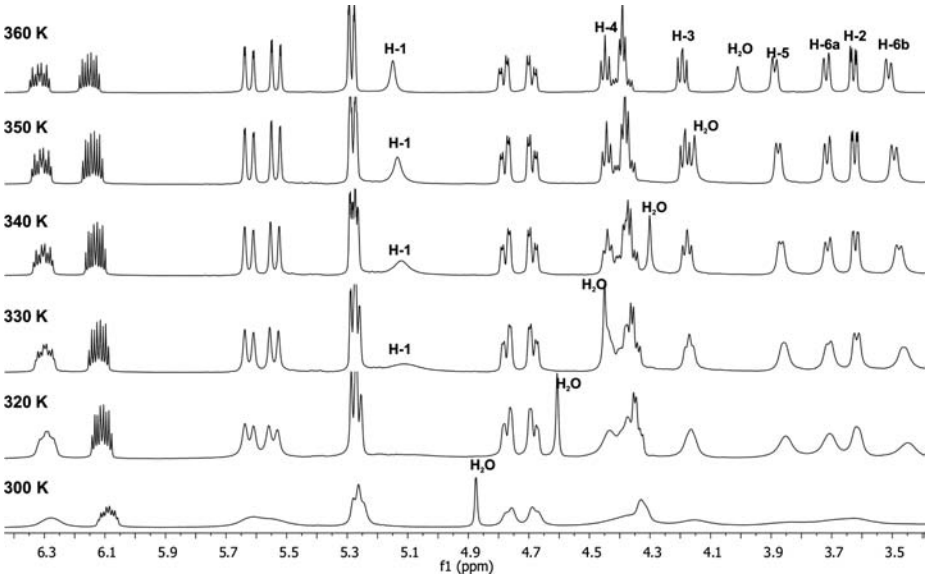


Figure 4. The variable temperature experiments of ^{1}H NMR (600 MHz) spectra of compound **12** in pyridine-d_5.

One thing that definitely troubled us was that the total mass of obtained 6-*O*-tetratritylated α-CD derivatives did not reasonably account for the initial amounts of α-CD invested in the reaction; when **3** was charred with 5% sulfuric acid on TLC, it was first turned into a bright-yellow spot, which is characteristic for the trityl group; however, the same spot finally turned dark black, suggesting that compound **3** could contain some carbohydrate components. We thus decided to characterize it by electrospray high-resolution mass spectrometry (ESI-HRMS); the result was surprising, as we observed many peaks at the *m*/*z* 2612 regions. By expanding the region, we discovered peaks at *m*/*z* 2611.1838 and *m*/*z* 2616.1546, which matched perfectly the $M + NH_4^+$ (expected: 2611.1964) and $M + Na^+$ (expected: 2616.1518) isotope peaks of a per-*O*-methylated α-CD derivative containing six trityl groups (Figure 3). However, the ESI-HRMS could not confirm the positions of all trityl groups. The initial consideration was that since the primary face of the α-CD is the smallest among all three CDs, the forced tritylation condition could have affected the secondary face, producing a mixture of positional isomers.

Further investigation of compound **3** by NMR spectroscopy revealed that its ^{1}H spectra in pyridine-d_5 at room temperature remained extremely broad (Figure 2b). However, when we raised the temperature to 360 K (Figure 2c), a dramatic improvement in resolution was observed; although the spectrum was still somewhat broad, we could confirm that the obtained compound **3** was indeed a tritylated α-CD with surprisingly simple patterns. Other NMR studies from 1D ^{13}C, 2D ^{1}H−^{1}H GCOSY, and ^{1}H−^{13}C HSQC experiments (see the Supporting Information) further revealed that, remarkably, compound **3** has an axial C6 symmetry. Combined with the ESI-HRMS data, we concluded that compound **3** must be the unexpected per-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-CD (Scheme 2). To further ascertain the structure of **3**, we carried out a per-detritylation by treating **3** with a solution of HFB_4 (50% aqueous) in a mixture of dichloromethane and methanol; the reaction afforded the previously known per-2,3-di-*O*-methyl-α-CD **4**;[8] further analysis of the ^{1}H NMR spectrum of **4** (Figure 2d) unambiguously established the positions of all methyl groups, thus once again confirming the chemical structure of its precursor compound **3**.

Next, we were interested in obtaining the per-6-*O*-tritylated α-CD (**7**) in pure form. We also wondered if the same reaction could be applied to β- and γ-CDs (**5** and **6**). Thus starting from α-CD (**1**), we carried out a series of tritylating experiments by optimizing the amounts and addition method of the reagent. The best yield of compound **7** (62%) was obtained when we first allowed **1** to react with 6 equiv of trityl chloride at 80 °C for 24 h, and during the subsequent 5 days, we added an additional 1 equiv of the reagent each day (total: 11 equiv). Compound **7** was isolated by chromatography (10% methanol−dichloromethane). Interestingly, unlike other undertritylated products that had a poor solubility in common organic solvents, compound **7** was very soluble in chloroform, ethyl acetate, and acetone; obviously, the lipophilicity of the six trityl groups makes the compound much easier to handle. Unlike compound **3**, the ^{1}H NMR spectrum of **7** in deuterated chloroform was reasonably resolved at room temperature (albeit slightly broad). For example, the six H-1's appeared as a doublet at 4.62 ppm ($J_{1,2} \sim 2.6$ Hz), while the other protons have the expected coupling patterns; the H-6a and H-6b protons were observed at slightly shielded region (3.09−3.18 ppm). The subsequent

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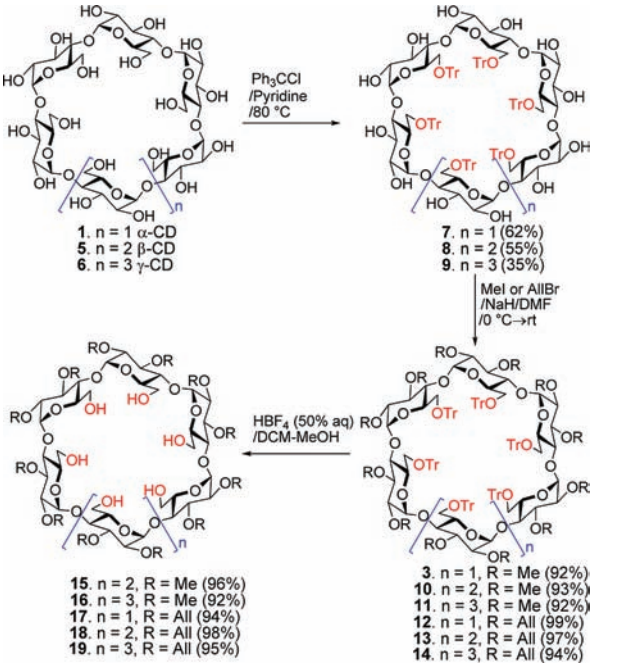
Scheme 3. Per-6-*O*-tritylations of α-, *β*-, and *γ*-CDs as an Efficient Methodology for Per-6-*O*-protections



per-2,3-*O*-methylation proceeded very efficiently to afford **3** in 92% yield.

In an analogous manner, similar per-6-*O*-tritylation conditions were applied to *β*- (**5**) and *γ*-CD (**6**) to afford the desired compounds **8** and **9** in 55 and 35% yield, respectively (Scheme 3). Both compounds were per-2,3-di-*O*-methylated in excellent yields (93% for **10** and 92% for **11**). Additionally, we performed a per-2,3-di-*O*-allylation on compounds **7**–**9** to provide compounds **12**–**14** in excellent yields (94–99%).

Like in the case of compound **3**, the ^{1}H NMR spectra of both per-2,3-*O*-methylated *β*- and *γ*-CD derivatives **10** and **11** were extremely broad at room temperature (see the Supporting Information). This observation was also true for all per-2,3-*O*-allylated compounds **12**–**14**. As an example, Figure 4 shows the variable temperature experiments of per-2,3-*O*-allyl-6-*O*-trityl-α-CD (**12**) recorded at 600 MHz field in pyridine-d_5. At 300 K, the NMR signals of all CD protons were practically unrecognizable, as they all disappeared into the baseline because of severe line broadening; however, when we heated up the same sample, the carbohydrate signals gradually showed up and intensified. At 360 K, the spectra became very well resolved, which showed almost all expected coupling patterns. We attributed the observed line broadening of the ^{1}H NMR spectra of all compounds **3**, **10**–**14** to the extreme crowding at the primary rims, resulting in slow bond rotation in solution; full alkylations at the secondary rim introduced more steric crowding to the molecule, which further restricts the flexibility of the CD macrocycles.

Again, the structures of compounds **10**–**14** were further confirmed by deprotecting their trityl groups using HBF_4 (50% aqueous solution) in a mixture of dichloromethane and methanol (Scheme 3). All detritylated compounds **15**–**19** were obtained in excellent yields (92–98%).

In conclusion, despite the large physical dimension of the trityl group, this work unequivocally provides answers to previous unanswered questions on the numbers of trityl groups that one can introduce to the primary face of CDs. Further structural and molecular modeling studies might help us understand how the trityl groups are fitted into a CD. We also demonstrated that per-6-*O*-tritylations can be carried out in gram quantities and in moderate to good yields for all CDs. Considering the superior stability of the trityl group, we think that the per-6-*O*-tritylation will prove to be a valuable method in CD chemistry that complements the only few methodologies available for per-6-functionalizations.

Acknowledgment. We thank the Alberta Glycomics Centre and the University of Calgary for the financial support of current project. C.C.L. thanks the Canadian Foundation for Innovation and the Government of Alberta for the Leadership Opportunity Fund.

Supporting Information Available. General experimental procedures and related analytical data for compounds **3**–**4** and **7**–**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.