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Polymer supported calixarene derivative useful for solid-phase synthesis application

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ABSTRACT

A calix[4]arene derivative has been anchored to carboxyl CPG and TentaGel supports by an easily cleavable ester bond and DMT groups allow a simple loading evaluation via UV–vis spectroscopy. The loading of the calixarene on TentaGel resin has also been estimated by HR-MAS NMR experiments. The potential of the polymer supported calixarenes (**9** and **10**) in solid phase synthesis has been tested by condensation of four thymine nucleotide units onto the upper rim of the calix[4]arene skeleton.

1. Introduction

Solid-phase synthesis in organic chemistry has provided enormous advantages in terms of separation and purification of materials and unique opportunities in controlling organic reactions.[1] Now, the solid phase synthesis has become a central feature in the synthesis of organic materials with repetitive units. It is an attractive approach for the rapid preparation of a large number of compounds and for discovering new active molecules.[2]

Synthetic versatility and the presence of a complexing cavity make calixarene macrocycles as interesting platforms for multiple applications ranging from biochemical to environmental fields.[3] Relevant interest has been addressed to the anchoring of calixarene macrocycles on a solid support in order to develop functional systems with varied applications, including those as electrochemical and luminescent sensors in ion detection,[4] as devices for selective extraction of ion and neutral molecules,[5] as HPLC stationary phases[6] and GC open-tubular capillary coating,[7] and as catalysts and enzyme mimics.[8] Cu, Au, or Si surfaces,[9] and a variety of polymers[10] have been used to anchor calixarene derivatives through non covalent or covalent linkages.

Differently, a very few Letters have focused on the application of anchored-calix[4]arene in solid-phase synthesis.[11] They described calix[4]arenes grafted on aminomethyl polystyrene resin,[11a–c] amino-methylated NoveSyn™ TG resin,[11d] or Argopore-NH_2 beads[11e] useful for developing peptido-calix[4]arene libraries and discovering host molecules for guest peptides or catalysts for ester hydrolysis.

To the best of our knowledge, no example of calix[4]arene anchored to Controlled Pore Glass (CPG) has been reported, whereas some anchorage on TentaGel S NH_2 resin via amide bond has been described.[12] The extraction performance against heavy metals of TentaGel supported calix[4]arenes has been investigated, but no application of these calixarene-resins for solid-phase synthesis of calixarene derivatives has been focused.

Since CPG and TentaGel supports are widely used for the solid-phase synthesis of biologically relevant oligomers,[13] in this Letter we wish report a new synthetic approach for anchoring a calix[4]-arene derivative to these two polymers via an easily cleavable ester bond, and prove the potential of the supported calixarenes in solid-phase synthesis by obtaining a nucleotide–calixarene derivative.

2. Results and discussion

Calix[4]arene derivative **8** bearing a terminal OH group at the lower rim and DMT protected OH groups at the upper rim was designed to be covalently bound to CPG-COOH and TentaGel S-COOH supports via an ester bond. Compound **8** was synthesized in very good yield starting from tripropoxy-calix[4]arene derivative **1**[14] and following the synthetic route depicted in Scheme 1. Compound **1** was reacted with 2-bromoethyl acetate in the presence of NaH to give compound **2** (87%), which was subjected to

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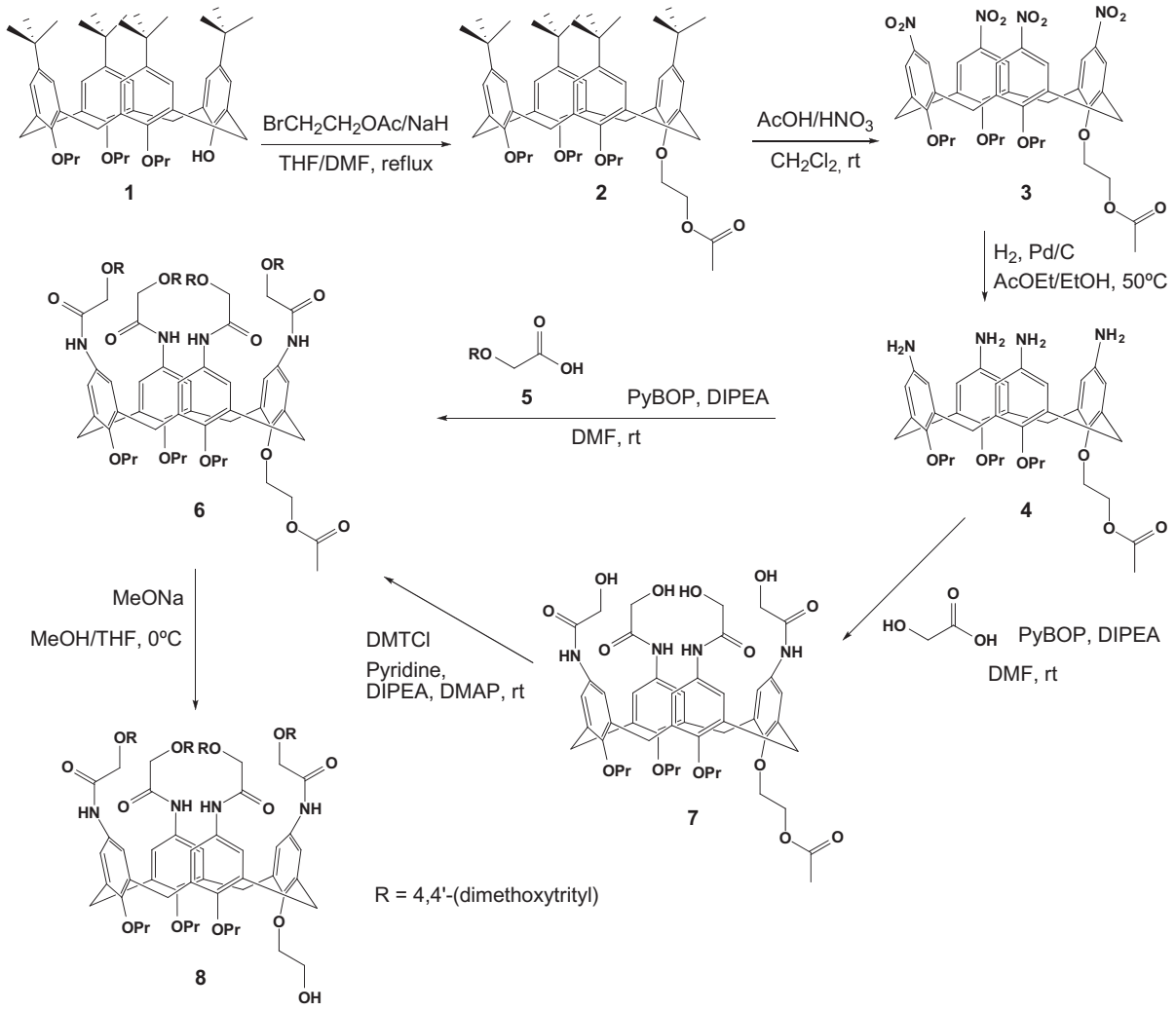


Scheme 1. Synthetic route to obtain compound **8**.

ipso-nitration (compound **3**, 72%) and subsequent reduction (compound **4**, 97%). Treatment of the amino-calixarene derivative (**4**) with properly prepared *O*-(4,4′-dimethoxytrityl)glycolic acid **5**[16] in dry DMF and in the presence of PyBop and DIPEA afforded compound **6** in good yield (82%).[15]

Compound **6** was obtained in lower yield (20%), when compound **4** was reacted with glycolic acid in the presence of PyBop and DIPEA to give compound **7** (92%), whose terminal hydroxyl groups were subsequently protected by treatment with 4,4′-dimethoxytrityl chloride, DIPEA, and a catalytic amount of DMAP.[15]

Deacetylation of **6** by treatment with MeONa provided the target compound **8** in 91% yield.[15]

All synthesized compounds were characterized by ^{1}H, ^{13}C, and 2D NMR spectra, which clearly confirmed the expected structures.

The linkage of the calixarene derivative **8** to the COOH groups of purposely prepared CPG-COOH support[17] or commercially available TentaGel S-COOH resin was accomplished by using DMF as the solvent and HATU, DIPEA, and DMAP as coupling agents (Scheme 2). The coupling reaction provided the polymer supported calixarenes **9** and **10**.[15]

After removal of the DMT groups from **9** and **10** by acid treatment, absorbance measurements at 504 nm showed a loading of calixarene units on the support of 18 μmol g^{-1} (13%) and 71 μmol g^{-1} (32%) for **9** and **10**, respectively.

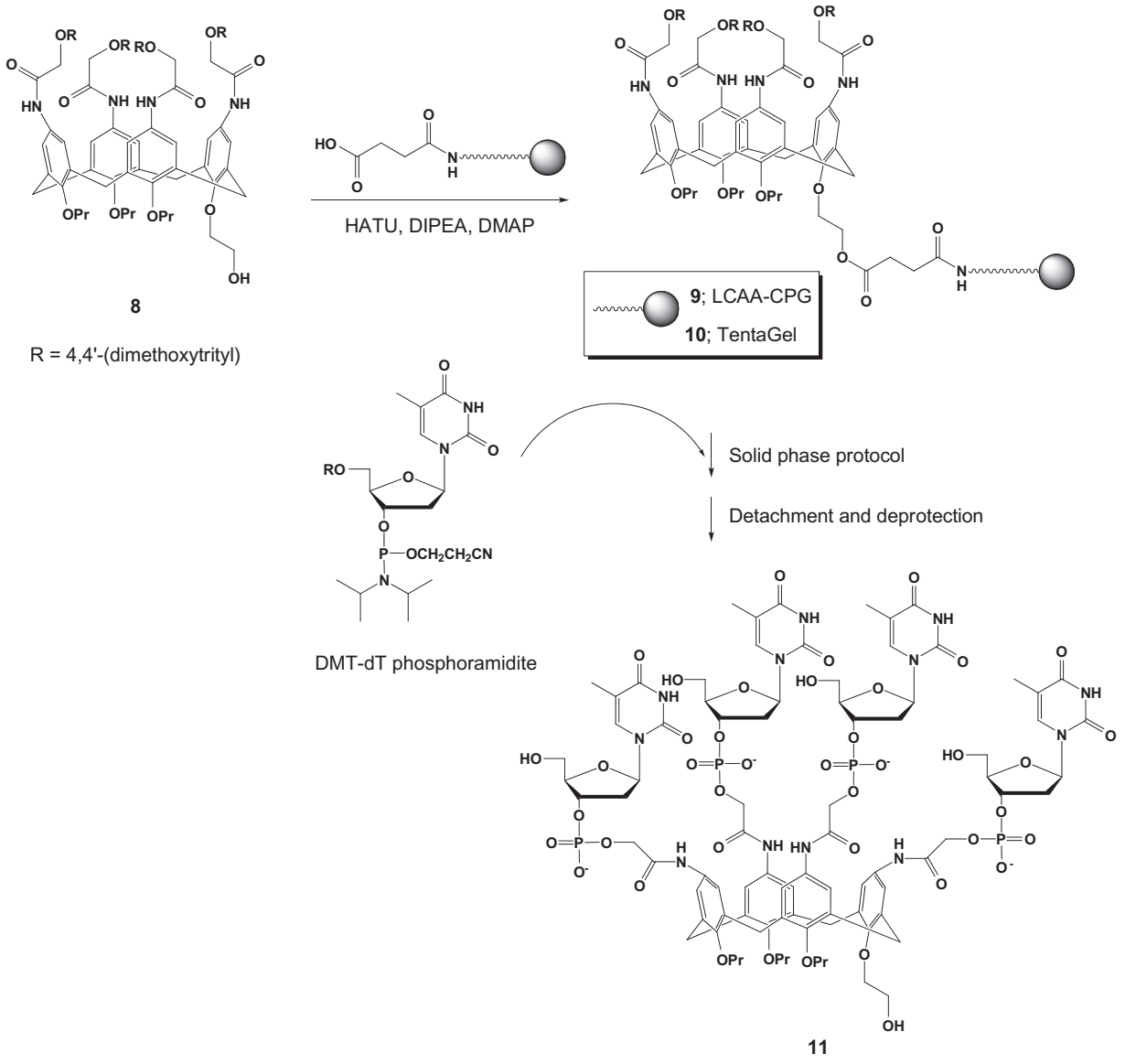
Considering that a capacity of about 220 μmol g^{-1} is provided for commercial TentaGel S-COOH resin and that each calixarene molecule anchored to the resin leads to four DMT-protected OH groups, an increasing in resin capacity up to 284 μmol g^{-1} was obtained in the case of calixarene-resin **10**.

The higher loading of calixarene on TentaGel resin compared to the nonswelling CPG support could be related to the easier diffusion of the calixarene molecules into the less dense aggregate regions of this resin (high swelling volume).[10b]

The loading value calculated for **10** was confirmed by HR-MAS NMR spectrum that provided a normalized integral ratio of 1:3 between the propyl CH_3 protons of the calixarene and the succinyl CH_2–CH_2 protons of the resin.[15]

Previously, our group has reported the synthesis in solution of mono-, di-, and tetra-nucleotide calixarene derivatives bearing nucleotide units at the calixarene lower rim,[18] and Kim and Kim have described the solid-phase synthesis of an oligonucleotide–calixarene in which the calixarene scaffold was condensed during the stepwise elongation sequence;[19] but the solid-phase synthesis of a nucleotide–calixarene starting from a polymer supported calixarene has not yet been investigated.

At the view of this, to prove the efficiency of **9** and **10** in solid-phase synthesis, we decided to carry out a single coupling cycle with 5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxythymidine



Scheme 2. Synthesis of polymer supported calixarenes **9** and **10**, and nucleotide–calixarene **11**.

phosphoramidite on Cyclone DNA synthesizer. Detachment of the condensation product from the support column by treatment with concentrated ammonia and pyridine at room temperature provided compound **11** in 63% and 82% yield from **9** and **10**, respectively.

Compound **11** was characterized by NMR experiments; the presence of two AX systems for the $ArCH_2Ar$ groups clearly indicated that compound **11** retained the single Ar–Ar symmetry plane of the parent compound **8**. The exhaustive tetrafunctionalization of the macrocycle was corroborated by the integral ratio between the nucleotide and calixarene protons (i.e., 1:2 for ribose H-1 and calixarene ArH).

3. Conclusion

In conclusion, we have reported a new synthetic approach for anchoring a calixarene macrocycle to CPG and TentaGel supports, in which for the first time an easily cleavable ester bond and DMT groups drive the linkage and loading evaluation, respectively.

The efficiency of the polymer supported calixarenes **9** and **10** in solid phase synthesis has been demonstrated through obtaining the first example of nucleotide–calixarene tetrafunctionalized at the upper rim.

Our results suggest that the calixarene scaffold of **9** and **10** might be a valid template for symmetrical assemblage of linear oligomers or in combinatorial chemistry for the development of libraries of symmetrically or asymmetrically functionalized calixarenes. Work is in progress in this direction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.082.

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