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Improved synthesis of 1,5-dinaphtho[38]crown-10

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ABSTRACT

We have devised a method of achieving the much-used macrocyclic polyether, 1,5-dinaphtho[38]-crown-10, in three steps by a route that is more efficient and requires fewer purification procedures than those reported in the literature to date. The strategy can also be extended to the synthesis of asymmetric crown-10 ether derivatives with one 1,5-dinaphtho ring system.

Over 40 years ago, Pedersen's groundbreaking discovery[1] of the crown ethers opened up an entirely new field of research called host–guest chemistry by Cram[2] and supramolecular chemistry by Lehn.[3] The observation that these crown ethers can act as ligands for the complexation of metal (Groups Ia and IIa in particular) and organic cations have inspired the investigation of a lot of molecular recognition processes[4] and self-assembly phenomena.[5] The ability of crown ethers containing fused (π-electron rich) aromatic rings to act[6] as receptors for π-electron deficient substrates, for example, Paraquat and Diquat, has led to the development of templation[7] as an efficient means to synthesize mechanically interlocked molecules (MIMs) such as catenanes and rotaxanes.[8] Of all the aromatic crown ethers employed as templates in the synthesis of MIMs, 1,5-dinaphtho[38]crown-10 (DN38C10) is amongst the most popular ones[9] because of (i) the π-electron-donating characteristics[10] of the 1,5-dioxynaphthalene (DNP) units and (ii) the ability of these units in appropriate settings in catenanes to support planar chirality.[11]

DN38C10 has already appeared as a compound in almost 100 different publications in the chemical literature. One reason it has been employed in the synthesis of MIMs is its ability to act as an efficient template for the assembly of a range of π-electron deficient cyclophanes,[12] and at the same time, have its DNP units express their dynamic chirality in the catenated products.[11] The DNP units can also participate in the functioning of bistable MIMs[13] as a recognition site. It is for all these reasons and more that DN38C10 is going to remain a key synthon when it comes to the chemistry of MIMs and other supramolecular precursors and analogues. Since all the current methods for the synthesis of DN38C10 were less than ideal for our purposes, we were prompted to develop a new synthetic route for the preparation of this compound, which is reported herein.

The three methods for the preparation of DN38C10 that are currently reported in the literature are characterized by the number of steps detailed in Scheme 1. The first method reported[9a] in 1987 is a four-step one (Method 1) involving the monobenzylation of 1,5-dihydroxynaphthalene (DHNP) to afford 5-(benzyloxy)naphthalene-1-ol (MBNP), followed by reaction with tetraethylene glycol bistosylate (BTTEG) and a subsequent deprotection (catalytic hydrogenolysis) before performing a ring closure with BTTEG. In 1998, Sanders and co-workers[9b] reported a protocol (Method 2) which avoided the use of protecting groups by simply reacting DHNP with a large excess of BTTEG to form 1,5-bis[2-[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]ethoxy]naphthalene bis(4-methylbenzenesulfonate) (BTEEEEN) which was subjected to ring closure with DHNP. In the same year, we reported[9c] a single-step approach (Method 3) using cesium ions to template the formation of DN38C10 directly from DHNP and BTTEG. Methods 2 and 3 both had isolated yields of 16% representing a considerable improvement over the original synthesis with its overall yield of 4%.

While we have verified that these overall yields hold to a first approximation, this criterion is not the only one to take into consideration in evaluating a synthetic strategy. Taking into consideration other criteria, all three methods (Methods 1–3 in Scheme 1) come with significant limitations. While Method 1 is tedious and very low yielding, Methods 2 and 3 come at a price because of challenging purification steps. Method 2 requires the use of hot petroleum ether in order to achieve a reasonable chromatographic separation of BTTEG from BTEEEEN in the first steps of the synthesis. In our hands, BTEEEEN could not be isolated in yields in excess of 40% without resorting to the inconvenience and danger of using

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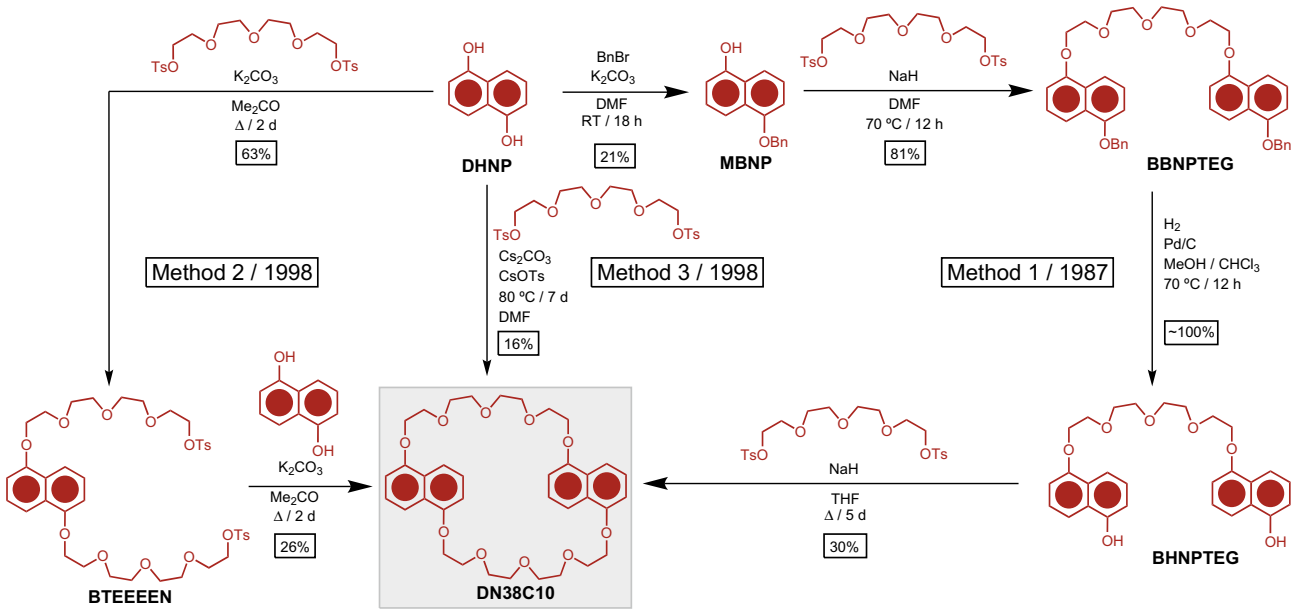
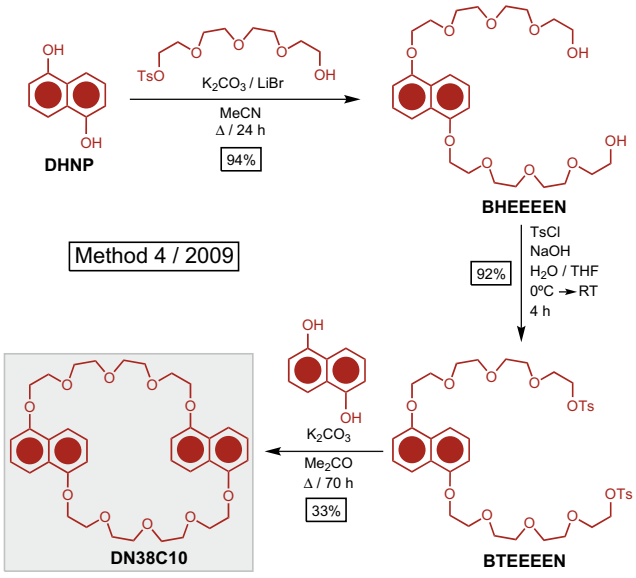


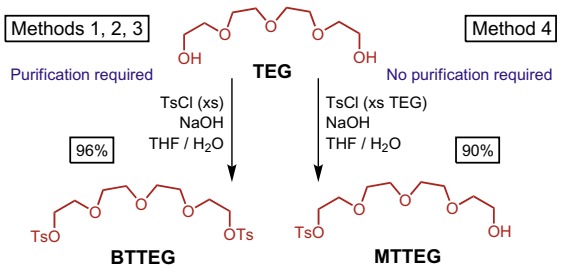
Scheme 1. Different methods employed to date in the synthesis of DN38C10.

hot petroleum ether as the eluant in accordance with the recommendation in the literature.[9b] Method 3 also calls for a long reaction time and an equally challenging separation of DN38C10 from higher and lower cyclic and acyclic oligomers using flash column chromatography (FCC) as well as the troublesome requirement to remove large volumes of *N*,*N*-dimethylformamide (DMF) during the workup.

We now report (Scheme 2) another alternative method (Method 4) for the preparation of DN38C10. Not only does it offer an improvement over all the other previous methods (Methods 1–3) in terms of overall yield (28%), but it also offers the advantage of being much easier to perform from start to finish than the other three methods. It strikes a good balance between the painstaking purification steps required in Methods 2 and 3, and the tedious low-yielding steps that characterize Method 1. Each step in the new synthesis will now be discussed critically.



Scheme 2. New synthesis of DN38C10 in three steps.



Scheme 3. Tosylation of TEG.

Firstly, the tosylation (Scheme 3) of tetraethylene glycol (TEG)—a step which is 'hidden' in all four methods—works in favor of Method 4. It is the only one to utilize tetraethylene glycol monotosylate (MTTEG) in the glycolation of the dinaphthol, that is, DHNP. Although the yields are comparable, the preparation[14] of MTTEG in high purity is less demanding than that of BTTEG[15] simply because the production of pure BTTEG requires FCC in order to separate the excess of tosyl chloride and/or MTTEG. By contrast, the isolation of pure MTTEG using an excess of TEG proceeds with an aqueous workup in 90% yield without the need for any further purification.

The first step in the new synthesis is the glycolation of DHNP with exactly 2.0 equiv of MTTEG in MeCN containing sub-stoichiometric amounts of LiBr. We have found that filtration of the crude reaction mixture, followed by careful workup using a brine/10% NaOH solution (3:1) affords (94% yield) BHEEEEN of sufficient purity to be employed in the next step and with an efficiency that has already been reported in the literature.[16]

The second step in Method 4 is the tosylation of BHEEEEN in THF/H_2O with NaOH as base to give BTEEEEN. If 2.2 equiv of tosyl chloride are used then this step can also be performed without purification by chromatography to obtain a product that is sufficiently pure to be able to continue on to the next step. Again we followed the literature procedure reported[16] for this reaction, the only minor difference being that the product was filtered as a solution in CH_2Cl_2 through a plug of silica. If a sample of high purity is required, then FCC on the crude product is a facile procedure

compared to the purification of the same compound after the first step in Method 2. In this case, the impurities are much easier to separate using FCC (SiO_2, EtOAc/hexanes), which avoids the inconvenience and danger of using a heated solvent as the eluant.

The final ring-closing step[17] is similar to that of Method 2, the only modifications being a slow addition of reactants by syringe pump injection and the precipitation of the final product from CH_2Cl_2/MeOH. We found that injecting BTEEEEN and DHNP over the course of 48 h improved the yield by 7% in comparison with the reported yield in the literature,[9b] affording DN38C10 in an overall yield of 28%. In summary, we have found this three-step method (Method 4) for the synthesis of DN38C10 to be the most facile, practical, and high-yielding route to DN38C10. Method 4 exemplifies that subtle differences in synthetic protocol can correspond to relatively large differences in overall yield and difficulty. A comparison between the four methods is drawn in Table 1.

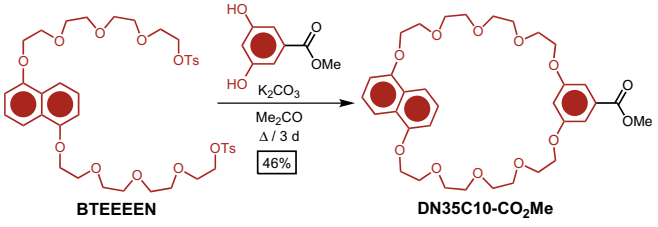
Method 4—the new proposed method—has an added advantage that is only shared with Method 2: it is that constitutionally asymmetric crown ethers can be prepared in a modular fashion from the penultimate product, namely BTEEEEN. Indeed, it is surprising that Method 4 has not been described already in the literature since it is replete with examples[12b,18] of other crown-10 ethers synthesized from BTEEEEN. We have also assessed the use of Method 4 in the preparation of asymmetric crown ethers by carrying out a ring-closing reaction (Scheme 4) between methyl 3,5-dihydroxybenzoate and BTEEEEN. We found that DN35C10-CO_2Me is formed in 46% yield, an 11% improvement over the literature reports.[18d,19] This crown ether could be modified to be employed in procedures to immobilize, polymerize, and coordinate MIMs to metals.

In conclusion, we have developed a straightforward three-step procedure to make 1,5-dinaphtho[38]crown-10 which requires purification only in the final step of the reaction sequence. The purification-free route to BTEEEEN, combined with the slow injection ring-closure procedure gives the new method of synthesis a unique advantage when it comes to preparing asymmetric crown-10 ethers in better yields than those previously reported in the literature. Given the status of 1,5-dinaphtho[38]crown-10 and its analogues, preparing them easier and faster means that applications of MIMs can be brought into sharper focus.

Table 1
Comparison between literature methods (Methods 1–3) and Method 4 by number of steps, overall yield, FCC purifications, and reaction time

Method	Steps[a]	Yield[b] (%)	FCC[c]	Time[d] (days)
1	4	4	4	5
2	2	16	3	4
3	1	16	2	7
4	3	28	1	4

[a] Number of steps from DHNP as starting material.
[b] Total yield over the number of steps in column two (Steps).
[c] Number of purifications by FCC including tosylation in Scheme 3.
[d] Total reaction time (workups and purifications not considered).



Scheme 4. Synthesis of a functionalized asymmetric crown-10 ether from BTEEEEN.

Acknowledgment

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17. A typical ring-closing procedure is described. DHNP (160 mg, 1.0 mmol) and BTEEEEN (820 mg, 1.0 mmol) were dissolved in Me_2CO (40 mL) and injected into a suspension of K_2CO_3 (7 g, 51 mmol) in Me_2CO (200 mL) under reflux at a

rate of 0.8 ml/h and the reaction proceeded for 70 h. The reaction mixture was cooled to ambient temperature, filtered, and washed with $CHCl_3$ (50 mL). The solvent was evaporated from the filtrate and the residue was partitioned between H_2O (100 mL) and $CHCl_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2×75 mL). The organic extracts were combined and the solvent was evaporated to afford a brown oil, which was purified by FCC (SiO_2, $Et_2O/CHCl_3$/MeOH 69:30:1). All fractions containing the product were concentrated and precipitated from CH_2Cl_2/MeOH (1:6) to afford DN38C10 as a white powder. (210 mg, 33%) ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 7.79 (d, 4H, J = 8 Hz), 7.19 (t, 4H, J = 8 Hz), 6.50 (d, 4H, J = 8 Hz), 4.06 (m, 8H), 3.93 (m, 8H), 3.78 (m, 8H), 3.75 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 154.1, 126.6, 125.0, 114.4, 105.4, 70.9, 69.7, 67.7; HRMS (APPI-TOF-MS): m/z calcd for $C_{36}H_{45}O_{10}$ $[M+H]^+$: 637.3007; found: 637.3012.

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