



# Improved conditions for the addition of alkoxides to di(ethylene glycol) di-*p*-tosylate: application to the stereospecific synthesis of the *trans*-isomers of dicyclohexano-18-crown-6<sup>†,‡</sup>

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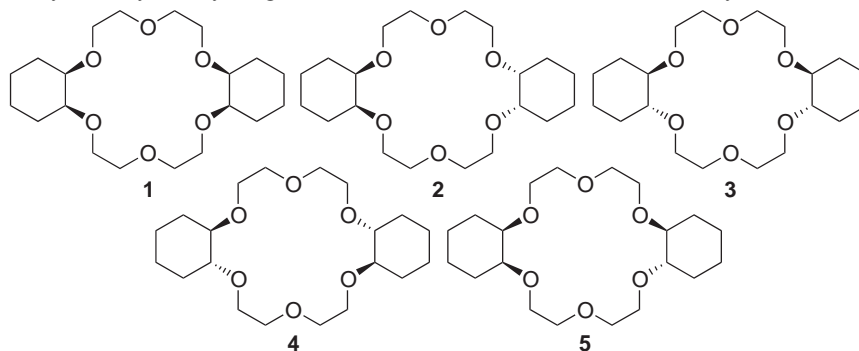
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**Abstract**—Conditions are defined for the efficient preparation of polyethers by direct condensation of ditosylates and alkoxides, and this approach is shown to provide a facile method for the synthesis of the *trans-syn-trans* (C) and *trans-anti-trans* (D) isomers of dicyclohexano-18-crown-6 (DCH18C6), one which both provides significantly improved yields and avoids the difficult separations required by certain previously described synthetic methods. © 2001 Elsevier Science Ltd. All rights reserved.

The complexation properties of crown ethers have been intensely studied<sup>1–3</sup> since their initial identification by Pedersen.<sup>4</sup> Of the numerous crown compounds now known, dicyclohexano-18-crown-6 (DCH18C6) has been among the most thoroughly investigated.<sup>1–3</sup> This compound can exist in five distinct isomeric forms (1–5), each varying with respect to *cis-trans* isomerism at the point of ring fusion and *syn-anti* isomerism between cyclohexano substituents across the macrocyclic cavity. Two of these stereoisomers, the *cis-syn-cis* (A) and *cis-anti-cis* (B) forms (1 and 2, respectively), are readily obtained by catalytic hydrogenation of

dibenzo-18-crown-6.<sup>5</sup> These two isomers have attracted considerable interest as metal ion complexants or extractants, and it is now well established that they can differ significantly in both complexation and extraction behavior for a given metal ion.<sup>2,6–8</sup> Analogous investigations of the *trans-syn-trans* (C) and *trans-anti-trans* (D) stereoisomers (3 and 4, respectively), among them our own studies of the influence of steric and stereochemical factors on the magnitude of synergistic interactions between crown ethers and various organophosphorus ligands,<sup>9,10</sup> have been hampered by the lack of satisfactory methods for their preparation.

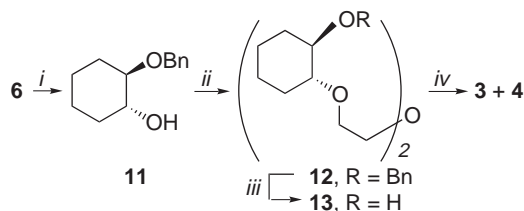


**Keywords:** crown ether; stereospecific synthesis.

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**Scheme 1.** (i) BnBr, NaH, DMSO, 65%. (ii) See Table 1. (iii) 10% Pd/C, H<sub>2</sub>, MeOH, rt, 48 h, quantitative. (iv) 60% NaH, DMSO, 13, rt, 16 h, 64% (3+4).

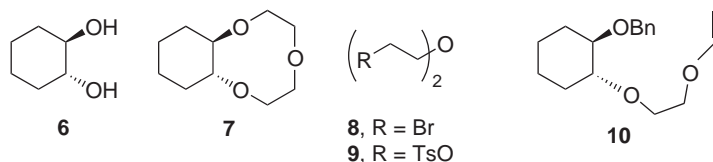
Prior syntheses of these isomers have been effected using a variety of strategies.<sup>11–13</sup> While elegant, these methodologies either lead to complex product mixtures or afford yields insufficient for extended study. Generally, the C isomer (**3**) is more readily obtained; in one instance,<sup>12</sup> it crystallized from the crude product mixture, while in a second,<sup>13</sup> it was the predominant isomer obtained, even when racemic *trans*-1,2-cyclohexanediol was employed as the starting material. In contrast, the isolation of the D isomer (**4**) has proven problematic. In fact, only a chiral synthesis of (+)-**4** using a ‘half crown’ strategy,<sup>14</sup> bridged through the western cyclohexyl moiety, starting from (+)-(*1R,2R*)-*trans*-1,2-cyclohexanediol ((+)-**6**) has been shown to give the compound in a meaningful yield (12%).<sup>13</sup> The yields of both isomers were likely affected negatively by the poor addition of alkoxides to ditosylates,<sup>15–20</sup> and in some cases, the formation of 1,4,7-trioxa[4.7.0]bicyclo-tridecane (**7**), which tends to co-crystallize and co-elute with **4**.<sup>12</sup>

We envisioned a straightforward four-step synthesis of **3** and **4** (Scheme 1) roughly analogous to that set forward by Stoddart et al.,<sup>11</sup> whereby monoprotection of **6** would allow the convenient assembly of the ‘half crown’ bridged through the southern polyether moiety. Removal of the protecting groups, followed by completion of the northern polyether moiety, would yield a mixture of **3** and **4**. The isolation of the C and D

isomers was expected to be considerably easier than that described by Stoddart,<sup>12</sup> however, since **7** would not be present in the product mixture.

Diol **6** was first protected as its monobenzyloxy ether **11**.<sup>21</sup> The construction of the lower polyether chain was then attempted by condensing two equivalents of cyclohexanol **11** with either (2-bromoethyl)ether (**8**) or di(ethylene glycol) di-*p*-toluene sulfonate (**9**). Significant differences in the outcome of the reaction were observed depending on the electrophile, base and reaction conditions used (Table 1).<sup>22</sup> As shown, attempts to alkylate **8** with **11** in refluxing THF were unsuccessful. Only **11** was returned from the reaction and none of the dibromide was recovered. Presumably, the elimination of dibromide **8** was faster than its alkylation with **11**. The alkylation of **9** with **11**, also in refluxing THF, did lead to a small amount (~30% yield) of **12**, along with a number of impurities. Analysis of the product mixture showed that a significant amount (43% yield) of vinyl ether **10** was present<sup>23</sup> in addition to **12** and unreacted **11**. More detailed characterization of the mixture was hampered by the difficulty in isolating compounds of suitable purity for further analysis. The addition of DMF led to an increase in the isolated yield of **12**, although **10** was again a significant impurity. Using DMSO as the reaction solvent and NaH as the base further improved the isolated yield of the desired product. Interestingly, using a NaH dispersion in mineral oil consistently led to a significant (21%) improvement in the yield of **12** over that obtained with dry NaH.

Hydrogenolysis of **12** cleanly gave diol **13**.<sup>24</sup> Condensation of the resulting diol with one equivalent of the ditosylate gave a mixture of the C and D diastereomers. The combined yield of both diastereomers from this step was 64% (36% C and 28% D).<sup>25</sup> Thus, the overall yield for all four synthetic steps was 40% for isomer C and 31% for isomer D, a nearly four- and threefold increase, respectively, over the best previously reported yields for these compounds.



**Table 1.** Condensation of **11** with di(ethylene glycol)-derived electrophiles

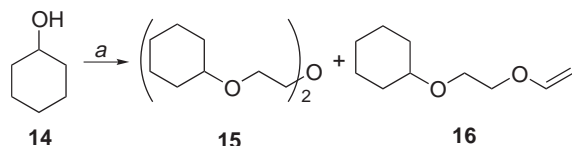
Entry	Base	<b>8/9</b>	Solvent	Temp.	Time (h)	Yield (%)
1	KH	<b>8</b>	THF	Reflux	14	0 <sup>a</sup>
2	KH	<b>9</b>	THF	Reflux	14	30 <sup>b</sup>
3	KH	<b>9</b>	33% THF/DMF	Reflux	14	42
4	NaH <sup>c</sup>	<b>9</b>	DMSO	Rt	24	64
5	NaH <sup>d</sup>	<b>9</b>	DMSO	Rt	24	85

<sup>a</sup> Only **6** was recovered from the reaction mixture.

<sup>b</sup> Major product was the vinyl ether.

<sup>c</sup> Dry NaH was used.

<sup>d</sup> Unwashed 60% NaH was used.



**Scheme 2.** (a) **14** (2.5 mmol), base (5.0 mmol), **9** (1.25 mmol), solvent (5 mL).

Repeating the reaction sequence starting with enantiomerically pure (1*S*,2*S*)-*trans*-1,2-cyclohexanediol gave **4** directly. The only adjustments from the procedure described above were to further decrease the ratio of the diol to benzyl bromide to 1:1. The yield of (+)-**11** was 37%; however, the isolated yield of its dibenzyl ether gave a convenient means of recovering and recycling the chiral diol not converted to **11**. The modest yield of (+)-**11** notwithstanding, the yields of the chiral intermediates and products are consistent with those in the racemic synthesis. The overall yield of (+)-**4** was 19%.<sup>26</sup>

In an attempt to determine the origin of the improvement in the yield of **12** observed when a mineral oil dispersion of NaH was employed in the alkylation of **9**, the product distributions obtained in the reaction of cyclohexanol **14** with **9** (Scheme 2) were determined for various combinations of NaH (dry or as a 60% suspension) and solvents.<sup>27</sup> The results of these experiments are summarized in Table 2. As shown, increasing the solvent polarity leads to an improvement in the yields of the desired product, triether **15**, although a considerable percentage of cyclohexanol and vinyl ether **16** are also present in the product mixture. Also, using a 60% suspension of NaH with DMSO leads to a modest increase (13%) in the yield of **15** versus dry NaH under identical conditions. Although this increase is smaller than that observed in the synthesis of the DCH18C6 stereoisomers, it was reproducible over several experiments. Conducting the alkylation using dry NaH in either THF or DMSO yields essentially identical product distributions. Interestingly, however, the combination of 60% NaH and DMF leads to a significant decline in the yield of **15**. Taken together, these results suggest that the poor solubility of mineral oil in DMSO may account for the improved yields observed with the

**Table 2.** The alkylation of **9** with **14** in the presence of NaH

Entry	Base	Solvent	Temp.	Yield <b>14</b> , <b>16</b> , <b>15</b> (%)
1	NaH <sup>a</sup>	THF	Rt	<sup>c</sup>
2	NaH <sup>a</sup>	THF	Reflux	55, 15, 30
3	NaH <sup>a</sup>	DMSO	Rt	29, 16, 55
4	NaH <sup>a</sup>	DMF	Rt	28, 17, 55
5	NaH <sup>b</sup>	DMSO	Rt	15, 17, 68
6	NaH <sup>b</sup>	DMF	Rt	51, 13, 36

<sup>a</sup> Dry NaH was used.

<sup>b</sup> 60% NaH was used.

<sup>c</sup> The reaction was not complete at 48 h. A number of unidentified peaks were also present.

NaH suspension. That is, displacement of the tosylate from **9** can occur via either elimination or substitution. The immiscibility of mineral oil with DMSO, by minimizing the concentration of NaH and Na–DMSO present in solution at any given time, apparently leads to a low background concentration of the alkoxide, which favors substitution over elimination. There is, as yet, no ready explanation for the considerable difference between the results obtained with DMSO and DMF when the mineral oil suspension of NaH is employed. Further studies are needed to precisely define the role of the solvent and other factors (e.g. temperature and cation) in this reaction. Work addressing these opportunities is now in progress.

In summary, we have demonstrated that the efficiency of alkylation of ditosylates with alkoxides can be significantly enhanced by employing unwashed 60% NaH/DMSO. The result is an improved method for the preparation of polyethers in general and of the *trans* isomers of DCH18C6 in particular.

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22. A solution of cyclohexanol **11** (3.00 g, 2 equiv.) in the reaction solvent (10 mL) was added to a solution of base (4 equiv.) in the reaction solvent (15 mL) followed by **8** (1 equiv.) or a solution of **9** (1 equiv.). The resulting mixture was stirred until TLC indicated no further reaction. Water was added and the mixture was partitioned between additional water and ether. The ether phase was separated and washed with brine, then dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by column chromatography (silica gel; 10% EtOAc/hex). The structural assignment of **12** was consistent with its TLC behavior and its <sup>1</sup>H and <sup>13</sup>C NMR spectra. Complete separation of **12** from residual **11** was not achieved however, and ca. 2–7% of **11** (based on <sup>1</sup>H NMR) remains in the product mixture after column chromatography. Yields of **12** have been adjusted to reflect the amount of **11** present. Key <sup>1</sup>H NMR signals (300 MHz): δ (ppm) 1.20–1.39 (m, 10H), 1.60–1.79 (m, 4H), 1.95–2.10 (m, 4H), 3.18–3.35 (m, 4H), 3.60–3.70 (m, 2H), 3.72–3.80 (m, 2H), 4.67 (d, 4H, *J*=9 Hz), 7.20–7.41 (m, 10H).
23. Compound **10** was obtained as a colorless oil from the purification of crude **12**. Key <sup>1</sup>H NMR signals (300 MHz): δ (ppm) 1.20–1.39 (m, 5H), 1.60–1.75 (m, 2H), 1.99–2.04 (m, 2H), 3.22–3.37 (m, 2H), 3.72–3.86 (m, 5H), 4.01 (dd, 1 H, *J*<sub>1</sub>=2 Hz, *J*<sub>2</sub>=7 Hz), 4.18 (dd, 1 H, *J*<sub>1</sub>=2 Hz, *J*<sub>2</sub>=14 Hz), 4.68 (d, 2 H, *J*=4 Hz), 6.51 (dd, 1 H, *J*<sub>1</sub>=2 Hz, *J*<sub>2</sub>=14 Hz), 7.28–7.38 (m, 5H).
24. 10% Pd/C (0.50 g) was added to a solution of **12** (2.82 g) in CH<sub>3</sub>OH (50 mL) followed by HOAc (1 mL). The reaction vessel was evacuated, then back-filled with H<sub>2</sub>, and the resulting mixture stirred for 72 h. The mixture was then filtered through a pad of Celite and the filtrate evaporated in vacuo to give a waxy semi-solid. The residue was suspended in DCM (35 mL) and the resulting mixture was washed with water (2×25 mL). The clear organic solution was then dried over MgSO<sub>4</sub> and evaporated in vacuo, giving a colorless oil. <sup>1</sup>H NMR was consistent with that of the expected product. The crude product was used without further purification.
25. DMSO (25 mL) was added to 60% NaH (1.28 g; 32.1 mmol) followed by a solution of **13** (1.94 g; 6.42 mmol) in DMSO (10 mL). The resulting solution was stirred for 16 h at room temperature. Water (100 mL) was then added, followed by brine (50 mL), and the resulting mixture was extracted with ether (3×50 mL). The combined ether extracts were washed with brine (25 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo to yield a yellowish semi-solid. The crude residue was crystallized from ether, giving 0.86 g of **3**. The supernate was evaporated and the residue chromatographed (silica gel; 10% EtOAc/hex), then recrystallized from 25% hexanes/ether, yielding 0.68 g of **4**. The physical and spectroscopic properties of **3** and **4** agree with literature values (e.g. mp<sub>3</sub>=116°C, lit.<sup>11</sup>=120–121°C; mp<sub>4</sub>=76–77°C, lit.<sup>11</sup>=77–80°C).
26. (+)-**4** was obtained as a white solid; mp=76–77°C (lit.<sup>13</sup>=71–74°C); [α]<sub>D</sub><sup>25</sup>=+35.4 (*c*=0.65, CHL) (lit.<sup>13</sup>[α]<sub>D</sub><sup>20</sup>=+39.2 (*c*=1, EtOH)).
27. General procedure: cyclohexanol **14** (2.5 mmol) was added to a mixture of NaH (5.0 mmol) in the solvent (5 mL), followed by addition of **9** (1.25 mmol). The resulting mixture was stirred at room temperature until the reaction was complete as indicated by GC. An aliquot (250 μL) of the reaction mixture was partitioned between ether (2 mL) and water (2 mL) and the composition of the ether phase evaluated by GC. Retention times of the key products: **14** (3.2 min), **15** (20.2 min), **16** (11.4 min). Compounds **15** and **16** were isolated and their structures confirmed by <sup>1</sup>H and <sup>13</sup>C NMR.<sup>28</sup>
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