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An Efficient Synthesis of Lithium-Selective Extractants: Tertiary-Alkyl-14-Crown-4 Ethers

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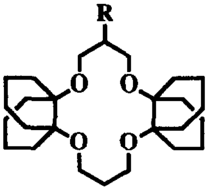
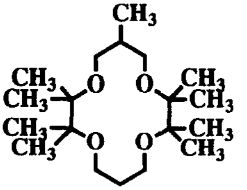
Abstract: Highly-substituted crown ethers can be synthesized efficiently from tertiary and neopentyl diols. Nonamethyl-14-crown-4 and methyl-didecalino-14-crown-4 ethers are lipophilic and highly soluble in organic solvents and function as efficient, lithium-selective extractants.

Small-ring crown ethers have been shown to be selective for the extraction and transport of small, hard cations such as lithium.[1-6] Based on the available literature, substituent effects play an important role in this regard. One particularily interesting report[7] described the synthesis of a novel crown ether, didecalino-14-crown-4 (**1**) that extracted lithium picrate much more strongly than sodium picrate. This selectivity was attributed to the cylindrical cavity formed by the two decalin moities. To investigate in greater detail the role of decalino and related substituents, it was desirable to find an improved synthetic method, since the reported synthesis generated **1** in very low yield (0.2% for 6 synthetic steps) from the expensive precursor 9,10-decalindiol[8] (**2A**).

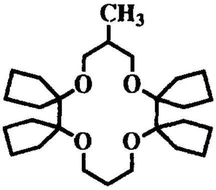
In an effort to prepare gram quantities of didecalino-14-crown-4, we have in fact developed an efficient, general synthesis of small-ring crown ethers from vicinal tertiary diols (Scheme 1). We have synthesized 6-methyl, didecalino-14-crown-4 (**6A**) in four steps (74% yield), a 350-fold improvement in yield over the synthesis of **1**,[7] making gram quantities of **6A** available for study. Using this procedure, we have also prepared multigram quantities of three additional crown ethers, **6B-D**. All of these crowns are highly lipophilic and highly soluble in organic solvents, properties which make them well suited for solvent extraction. Two of these crowns, **6A** and **6B**, extract lithium efficiently and selectively from a mixture of alkali metal chlorides.



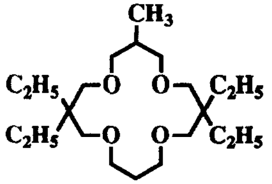
1: R = H
6A: R = CH_3



6B

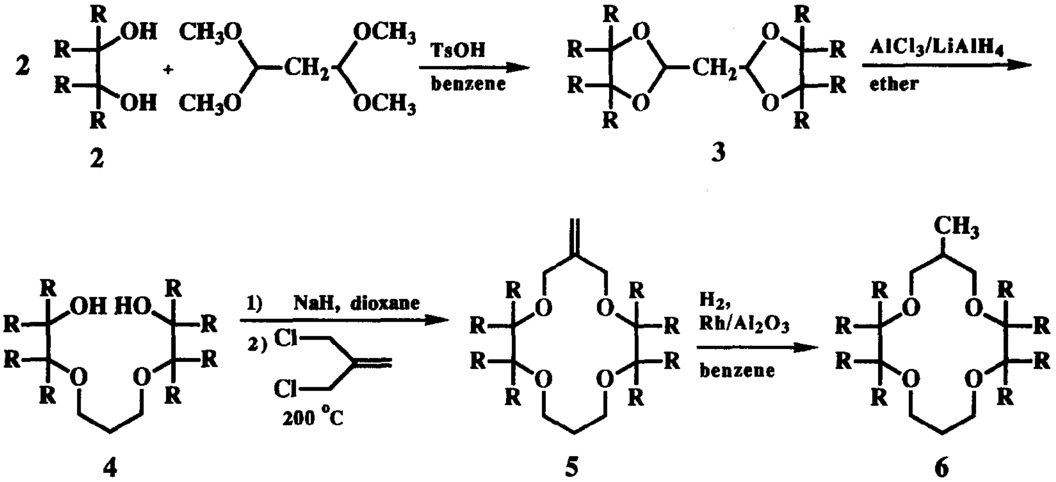


6C



6D

We attributed the poor yield of the literature synthesis to the high basicity and low nucleophilicity typical of tertiary alkoxides. Reductive ring-opening of bisacetals avoided use of the Williamson ether synthesis with hindered alkoxides and provided the intermediate diol-diethers in good-to-excellent yield (Table 1). This reaction is sensitive to the steric properties of the diol; the highest yield was obtained for the conformationally restrained decalin bisacetal, **3A**, while no diol-diether product was obtained from the reduction of the tetraethyl-substituted bisacetal, **3E**. This method is also useful for the preparation of diol-ethers from neopentyl diols, as shown by example **D**.



Scheme 1. Synthesis of Lipophilic Crown Ethers from Hindered Diols

The cyclization using methallyl dichloride provided higher yields than when dibromopropane was used, while incorporation of the methyleno substituent will allow further functionalization of these crowns. Optimum yields were obtained when the cyclization was completed as rapidly as possible. Methallyl dichloride decomposes and/or polymerizes above 100 °C, whereas the cyclization proceeds slowly below 100 °C. Therefore, we carried out the cyclization in dioxane at 200-250 °C in a stainless-steel bomb. The conditions reported by Tomoi, et al.[9] were ineffective for the cyclization of these hindered diols. Use of higher boiling solvents, such as diglyme, triglyme or DMSO gave much poorer results, in contrast to the report by Okahara and coworkers.[10] This procedure is easily scaled up when the starting diol and a pressure vessel of adequate capacity are available. We have prepared **5B** from pinacol in 5-50 g quantities.

Table 1. Yields of Diol-Diethers and Methyleno-Crowns from Diols.

	Diol (**2**)	Yield of **4**[11]	Yield of **5**[11]
A	9,10-Decalindiol	93%	63% (74% corrected)
B	Pinacol	85%	46%
C	1,1'-Bicyclopentane-1,1'-diol	66%	29% (43% corrected)
D	2,2-Diethyl-1,3-propanediol	76%	44%
E	3,4-Diethyl-3,4-hexanediol	0%	N/A

In a typical procedure, a solution of 9,10-decalindiol (**2A**) (1.0 g, 5.9 mmol), 1,1,3,3-tetramethoxy propane (0.48 mL, 2.9 mmol), and p-toluenesulfonic acid (100 mg) in benzene (100 mL) was refluxed through a Soxhlet extractor containing 4 Å molecular sieves (10 g) for two hours, and evaporated *in vacuo*. The solid product[12] (**3A**) was added to a stirred suspension of anhydrous $AlCl_3$ (2.5 g, 18 mmol) and $LiAlH_4$ (0.20 g, 5.2 mmol) in anhydrous ether (25 mL).[13] After 3 hours, the excess hydride was destroyed by careful addition of water. The resulting suspension was treated with 10% H_2SO_4 (10 mL). The organic phase was washed with brine, followed by $NaHCO_3$/brine, dried with $MgSO_4$, and evaporated *in vacuo* to obtain **4A** (1.1 g, 93%).

Solid **4A** (2.14 g, 5.72 mmol) was added to a stirred suspension of NaH (0.40 g, 16 mmol) and dioxane (250 mL, distilled from Na) in a 300 mL stainless-steel pressure vessel[14] and heated to 90 °C for one hour. The vessel was cooled to room temperature, and the excess pressure was vented. Methallyl dichloride (1 mL, 9 mmol) was added, and the vessel was placed in an oil bath preheated to 220 °C.[14] After 4 hours, the vessel was cooled, excess pressure was vented, and water (10 mL) was added to destroy excess hydride. The solvent was removed *in vacuo*, and the residue was partitioned between hexanes and brine. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. Crystallization from acetonitrile gave **5A** (1.5 g, 61%). Chromatography of the mother liquor (ether/hexanes on silica gel) gave 0.28 g of **4A** and 65 mg of **5A** (net corrected yield of **5A**, 74%). A solution of **5A** (1.5 g, 3.5 mmol) in benzene (100 mL) was stirred overnight with 5% Rh/Al_2O_3 (100 mg) under H_2 (1 atm), filtered through Celite, and evaporated *in vacuo* to obtain **6A** (1.5 g, quant).

The extraction of alkali metals by **6A-C** was compared to that by bis-*tert*-octylbenzo-14-crown-4 (**7**).[15] Solutions of crown ether (24 mmol/kg of solution in n-octanol) were contacted with equal volumes of aqueous mixtures of alkali metal chlorides (400 mmol/kg of solution in each metal: Li, Na, K, Rb, and Cs). The organic phase was separated and stripped with water. The metal ion concentrations were determined by ion chromatography of the stripping solution. The loading and selectivity data are shown in Table 2. **6A** and **6B** are both efficient extractants as evidenced by the high loading factors (86.9% and 44.6%, respectively) and are both highly selective for lithium ($[Li^+]/[Na^+] > 65$). The extraction efficiency of **6A** is consistent with the results reported for **1** by Kobiro.[7] Remarkably, high loading was achieved without picrate, necessitating the coextraction of the hard, hydrophilic chloride anion. Somewhat surprisingly, **6C**, an isomer of **6A**, proved both much less efficient and less selective than **6A** and **6B** and thus was more similar in extraction behavior to **7**. The underlying cause for these differences is not understood at this time and is the subject of ongoing research.

Table 2. Competitive Extraction of Alkali Metal Chlorides with **6A-C** and **7**.

Crown	Loading[16]	[Li]/[Na]	[Li][17]	[Na][17]	[K][17]	[Rb][17]	[Cs][17]
BOB14C4 (**7**)	0.023	6.2	0.412	0.065	0.053	0.039	0.026
MDD14C4 (**6A**)	0.869	65.9	21.21	0.322	0.012	0.018	0.024
NM14C4 (**6B**)	0.446	75.8	10.68	0.141	0.028	0.038	0.040
MTcP14C4 (**6C**)	0.009	5.1	0.254	0.050	-0.006	-0.008	-0.004

Highly efficient and selective lithium extraction has been demonstrated in alkyl-substituted 14-crown-4 ethers. An earlier report[7] to this effect for **1** has been confirmed for **6A**. A significantly improved synthesis makes the preparation of gram quantities of decalino-substituted crowns feasible, allowing more in-depth study of the cation-binding properties of these compounds. The availability of pinacol as a starting material and the excellent extraction properties of **6B** indicate that this crown is a potentially valuable lithium ionophore. The unanticipated poor extraction performance of **6C**, isomeric to **6A**, raises significant questions of a more general nature as to the effect of structural factors on the recognition of ions by this class of crown ethers. We anticipate that further investigations will provide insight into this matter. Calorimetric studies and NMR studies to obtain thermodynamic parameters for cation binding by these crowns are in progress, as are structural studies (X-ray crystallography, solution and solid-state NMR) of the free ligands and their alkali metal complexes.

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11) Analytical data (IR, NMR, MS) were consistant with the assigned structures.

12) For **3B-E**, the acetals were dissolved in ether and added in solution.

13) Eliel, E. E.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.*, **1962**, *84*, 2371-2377.

14) Parr Instruments Model 4561, equipped with a 2500 psi rupture disk. Appropriate precautions, as outlined by the manufacturer, should be taken when heating a sealed system.

15) A lipophilic derivative of the known lithium ionophore dibenzo-14-crown-4, ref 1.

16) Loading is expressed as the sum of the final organic phase metal ion concentrations divided by the initial crown ether concentration.

17) Concentrations are expressed as millimoles of solute per kg of solution.

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