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2,2,3,3,11,11,12,12-Octamethyl-1,4,7,10,13-pentaoxacyclohexadecane: improved synthesis and crystal structure with NaSCN

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ABSTRACT

An efficient synthesis of 2,2,3,3,11,11,12,12-octamethyl-1,4,7,10,13-pentaoxacyclohexadecane (**1**, OM16C5) is described, which affords over an order of magnitude improvement in yield over the previously reported method. The first X-ray crystal structure of **1**, as a complex with NaSCN, is also reported.

There is much interest in sodium-selective ionophores[1,2] for their use in electrodes[1,3] and optodes.[4] One such ionophore is 2,2,3,3,11,11,12,12-octamethyl-1,4,7,10,13-pentaoxacyclohexadecane (**1**, octamethyl-16-crown-5 or OM16C5), which was first prepared in 1996 by Suzuki and co-workers.[1] The synthetic procedure as reported and shown in Scheme 1 involved three steps starting from pinacol. The first two steps proceeded in excellent (95%) and good (ca. 81%) yields, respectively. However, the cyclization step, involving the addition of diethylene glycol dimesylate to 2,3,3,9,9,10-hexamethyl-4,8-dioxa-2,10-undecanediol (**2**) using NaH in THF, proceeded poorly with a low (3.7%) isolated yield, making the overall yield approximately 2.8% for the three steps starting from pinacol. We were interested in this crown ether for alkali-metal extraction studies, and sought to improve the yield so that larger (potentially gram) quantities of material could be readily prepared. We report here a modified procedure that boosts the conversion of **2** to **1** over 15-fold in an overall yield of 59% in three steps. We also report for the first time a crystal structure of **1**, as the NaSCN complex.

The low yield for the conversion of **2** to **1** can be attributed to the inherent difficulty in alkylation of the tertiary alkoxide **2**. Elimination is favored over substitution due to its high basicity and low nucleophilicity.[5] However, allylation or benzylation of tertiary alkoxides can be effected in higher yield because allyl and benzyl halides do not undergo β-elimination. Accordingly, to improve the synthetic yield of **1**, we decided to employ a strategy similar to that utilized for the preparation of octamethyl-18-crown-6,[6] based upon allylation of the tertiary alkoxide and subsequent conversion of the allyl ether groups to glycol ether groups by ozonolysis. Ring closure of the resultant diol could then be accomplished using methodologies as described by Okahara et al.[7]

The procedure utilized to convert **2** into **1** is shown in Scheme 2. Reaction of **2** in dry THF with excess NaH for 1 h at room temperature, followed by addition of excess allyl bromide, and by refluxing, can yield the bis-allyl ether 5,5,6,6,12,12,13,13-octamethyl-4,7,11,14-tetraoxa-1,16-heptadecanediene (**3**) in nearly quantitative conversion. To achieve high conversion, the reaction was monitored by TLC or GC, and additional NaH and allyl bromide were added as necessary to drive the reaction to completion. In a typical reaction,[8,9] **3** was obtained from **2** in 98% yield as a low melting solid in sufficient purity (⩾95% by GC) to be used in the subsequent step without further purification.

Conversion of the diallyl ether **3** to 4,4,5,5,11,11,12,12-octamethyl-3,6,10,13-tetraoxa-1,15-pentadecanediol (**4**) was accomplished by ozonolysis. In a typical reaction,[10] ozone was bubbled into a solution of **3** in 1:3 dichloromethane–methanol at −78 °C until the blue color persisted for ca. 15 min. Displacement of the excess ozone with argon, followed by warming to 0 °C and treatment with $NaBH_4$ overnight resulted in pure **4** in 88% yield (after workup and purification on a short silica column).

Finally, ring closure was accomplished by treating a solution of diol **4** in dry dioxane with dry powdered NaOH at 70 °C for 3 h, followed by the slow addition of 1 equiv of tosyl chloride, and

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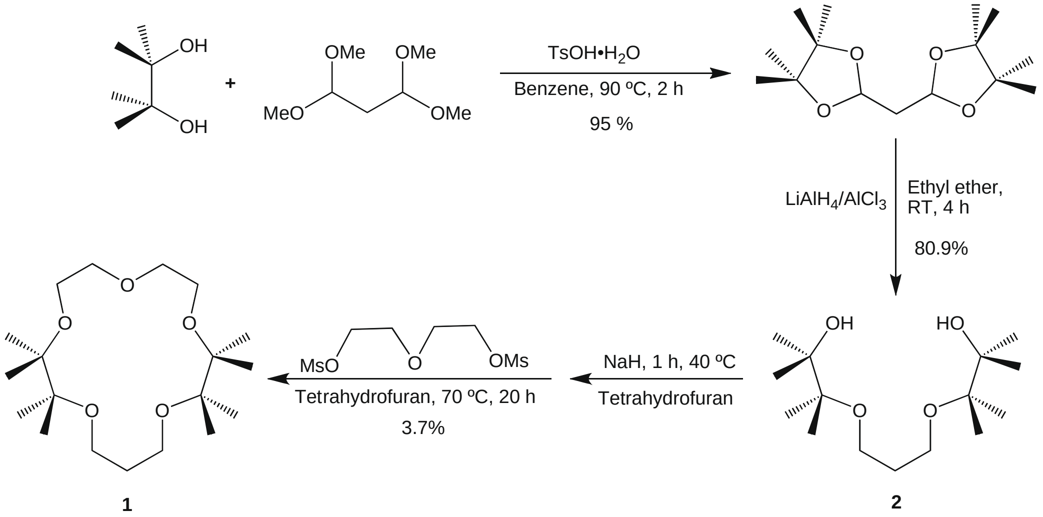
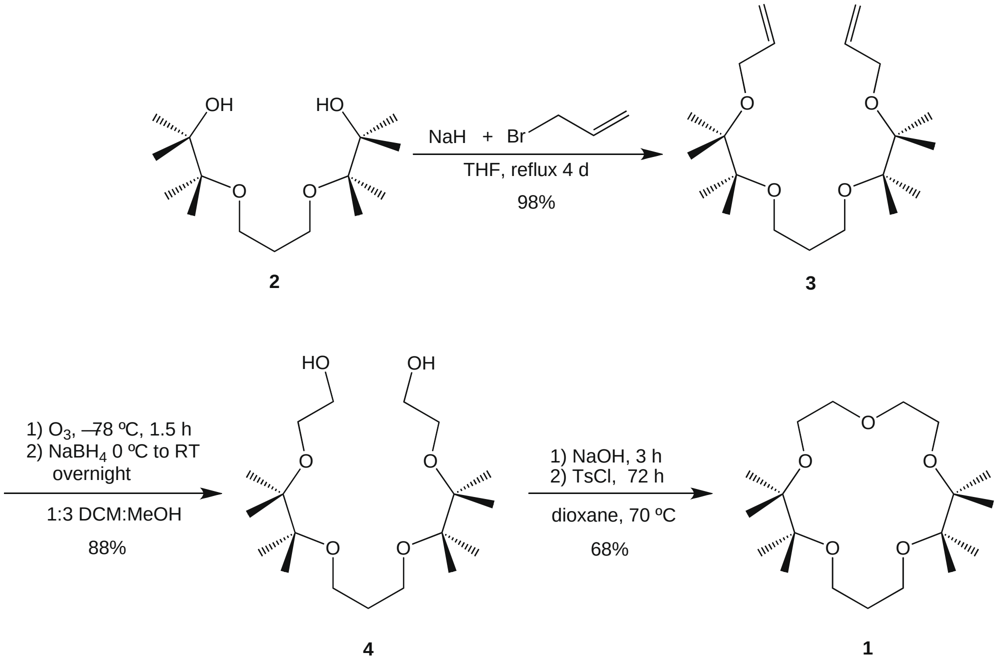


Scheme 1. Procedure used to prepare **1** as reported by Suzuki et al.



Scheme 2. Three-step procedure used to convert diol **2** into OM16C5 (**1**).

heating the mixture at 70 °C for an additional 3 days. Following workup and two chromatographic purifications, 0.78 g of crown **1** was obtained in 68% isolated yield as a pale yellow oil.[11]

A single crystal of the sodium thiocyanate complex of **1** was obtained from acetone–ethyl acetate, and the structure was determined by X-ray crystallography.[12] Figure 1 depicts the first reported crystal structure of OM16C5. The Na^+ is complexed by the crown ether, and it sits at a distance of 0.576 Å from the mean plane defined by the five oxygen atoms. The O···Na distances range between 2.382 and 2.458 Å. The SCN anion also coordinates the Na^+ through its N atom, with an observed N···Na distance of 2.343 Å.

In conclusion, we have demonstrated that OM16C5 can be prepared from diol **2** in three steps with a combined yield of 59%, which represents a substantial improvement over the previously reported method. Accordingly crown **1** can now be prepared in five steps from pinacol, in combined yields potentially approaching 45%, which permits gram quantities of this highly sodium-selective[1] crown to be prepared for investigation.

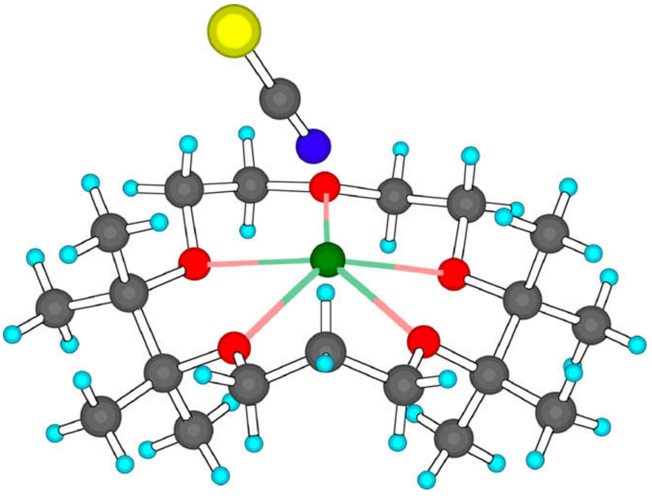


Figure 1. X-ray crystal structure of the NaSCN complex of OM16C5.

Acknowledgments

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8. *General*: All solvents and chemical reagents were used as received without further purification, with the exception of *p*-tosyl chloride, which was purified by the method described by Peletier.[14] Ozonolysis was performed using an OZONOLOGY Ozone Generator. A Hewlett Packard 6850 gas chromatograph was used for all GC analyses. All proton and carbon NMR spectra were obtained in $CDCl_3$ on either Bruker Avance DRX 400 MHz or Varian VNMRS 500 MHz spectrometers. Proton chemical shifts were referenced to internal tetramethylsilane, and carbon chemical shifts to the $CDCl_3$ resonance centered at 77.0 ppm. Melting points were determined using a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Elemental analyses were obtained from Columbia Analytical Services, Tucson, AZ.
9. *5,5,6,6,12,12,13,13-Octamethyl-4,7,11,14-tetraoxa-1,16-heptadecanediene* (***3***): To a solution of **2** (10.0 g, 36.2 mmol) in 100 mL of dry THF at room temperature under argon was added solid NaH (2.60 g, 108 mmol) using a 'Merlic' style solid-addition adapter. The slurry is stirred for 1 h, whereupon a solution of allyl bromide (13.0 g, 107 mmol) in 100 mL dry THF was added dropwise over 30 min. The reaction was refluxed overnight. TLC (ethyl acetate–hexanes 1:1) indicated a mixture of mono- and di-allylated product; accordingly additional NaH (1.0 g, 42 mmol) and allyl bromide (5.0 g, 41 mmol) were added and the reaction mixture was refluxed for three additional days. TLC analysis of an aliquot indicated that a small amount of mono-substituted material remained, so 18 mmol each of NaH and allyl bromide were added, and the reaction mixture was refluxed for an additional 6 h. TLC analysis showed only di-allylated product. After cooling to room temperature, a small amount of methanol (10 mL) was added, and the solvents were evaporated in vacuo. The residue was extracted with dichloromethane, filtered, and the solvent was evaporated to yield 12.67 g (98%) of **3** as a yellow oil that solidifies upon standing, with a purity of $\geqslant$95% as determined by GC. Mp 37.5–38.0 °C; ^{1}H NMR (500 MHz): δ 1.16 (s, 12H, $-\mathrm{C}H_3$), 1.17 (s, 12H, $-\mathrm{C}H_3$), 1.68 (p, 2H, $J = 6.0$ Hz, $-\mathrm{CH_2C}H_2\mathrm{CH_2}-$), 3.44 (t, 4H, $J = 6.0$ Hz, $-\mathrm{C}H_2\mathrm{CH_2C}H_2-$), 4.00 (d of t, 4H, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz $-\mathrm{C}H_2\mathrm{CH}_{gem}{=}\mathrm{CH}_{cis}\mathrm{H}_{trans}$), 5.06 (d of m, 2H, $J_{trans\text{-}gem} = 10.5$ Hz, $-\mathrm{CH_2CH}_{gem}{=}\mathrm{CH}_{cis}H_{trans}$), 5.25 (d of m, 2H, $J_{cis\text{-}gem} = 17.2$ Hz, $-\mathrm{CH_2CH}_{gem}{=}\mathrm{C}H_{cis}\mathrm{H}_{trans}$), 5.91 (m, 2H, $-\mathrm{CH_2C}H_{gem}{=}\mathrm{CH}_{cis}\mathrm{H}_{trans}$); ^{13}C{^{1}H} NMR: δ 20.1, 20.5, 32.0, 58.0, 63.0, 79.0, 79.6, 114.2, 136.9. Anal. Calcd. For $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 71.11; H, 11.64.
10. *4,4,5,5,11,11,12,12-Octamethyl-3,6,10,13-tetraoxa-1,15-pentadecanediol* (***4***): A solution of **3** (2.0 g, 5.6 mmol) in 200 mL of 1:3 dichloromethane–methanol was placed under argon flow in a three-neck round-bottomed flask (300 mL) equipped with a dry ice cold finger condenser with a $CaCl_2$ drying tube. An argon/ozone bubbler inlet was attached to one of the side arms of the flask. The reaction mixture was cooled to −78 °C under argon flow with stirring, then the argon inlet was replaced with an inlet from the ozone generator, and ozone (~5% O_3 in O_2) was bubbled through the solution with stirring until a blue color (signifying the presence of excess ozone) persisted for 15 min. *Caution note: Ozone can degrade rubber hoses rapidly, thus all tubing connections should be made with Tygon or Teflon tubing.* The ozone inlet was then replaced with an argon inlet, and argon was bubbled through the solution for 10 min during which time the solution became clear. The cold bath was removed and replaced with an ice water bath, and $NaBH_4$ (1.20 g, 30.3 mmol) was slowly added to the reaction. After the $NaBH_4$ was added, the water ice bath was removed, and the reaction mixture was allowed to stir at ambient temperature overnight. The solvents were removed in vacuo, and the residue dissolved in dichloromethane (100 mL) and washed with water (100 mL). The aqueous phase was back extracted with 3 × 100 mL dichloromethane and the combined dichloromethane layers dried over anhydrous Na_2SO_4. The solvent was evaporated to afford crude **4**, which was purified on a short silica column, eluting with 5:1 hexanes–ethyl acetate, to afford pure **4** (1.80 g, 88%) as a light yellow oil which solidifies upon standing. Mp 44.5–45.0 °C; ^{1}H NMR (400 MHz): δ 1.15 (s, 12H, $-\mathrm{C}H_3$), 1.17 (s, 12H, $-\mathrm{C}H_3$), 1.68 (p, 2H, $J = 6.0$ Hz, $-\mathrm{CH_2C}H_2\mathrm{CH_2}-$), 2.34 (br t, 2H, $-\mathrm{O}H$), 3.44 (t, 4H, $J = 6.0$ Hz, $-\mathrm{C}H_2\mathrm{CH_2C}H_2-$), 3.54 (m, 4H, $-\mathrm{OC}H_2\mathrm{CH_2OH}$), 3.65 (m, 4H, $-\mathrm{OCH_2C}H_2\mathrm{OH}$); ^{13}C{^{1}H} NMR: δ 20.0, 20.5, 31.8, 58.0, 62.5, 62.9, 79.0, 79.6. Anal. Calcd for $C_{19}H_{40}O_6$: C, 62.61; H, 11.06. Found: C, 62.69; H, 10.93.
11. *2,2,3,3,11,11,12,12-Octamethyl-1,4,7,10,13-pentaoxacyclohexadecane* (***1***): Powdered dried sodium hydroxide (0.53 g, 13.2 mmol) and diol **4** (1.20 g, 3.29 mmol) were dissolved in 200 mL of dry dioxane and were stirred for 3 h at 70 °C. A solution of tosyl chloride (0.63 g, 3.3 mmol) in dioxane (100 mL) was added dropwise over the course of 1 h, and stirring continued at 70 °C for 72 h. The solvent was evaporated in vacuo, and the residue was extracted with 150 mL dichloromethane, and was washed successively with 150 mL portions of water, 0.5 M acetic acid, saturated $NaHCO_3$, and brine. After drying ($MgSO_4$), the dichloromethane was evaporated, and the residual oil was chromatographed (70/230 mesh SiO_2, ethyl acetate–hexanes 1:3) to afford slightly impure product, which upon chromatography for a second time using 40 μm SiO_2 afforded 0.78 g (68%) of pure **1** as a pale yellow oil. The proton NMR is consistent with that reported in the literature.[1] ^{1}H NMR (400 MHz): δ 1.16 (s, 12H, $-\mathrm{C}H_3$), 1.17 (s, 12H, $-\mathrm{C}H_3$), 1.69 (m, 2H, $-\mathrm{CH_2C}H_2\mathrm{CH_2}-$), 3.57–3.66 (overlapping multiplets, 12H, $-\mathrm{C}H_2\mathrm{CH_2C}H_2-$ and $-\mathrm{OC}H_2\mathrm{C}H_2\mathrm{O}-$). ^{13}C NMR: δ 21.1, 21.7, 32.4, 61.0, 61.9, 70.8, 79.9, 80.4.
12. Single-crystal X-ray data were collected on a Bruker SMART APEX CCD diffractometer with fine-focus Mo Kα radiation ($\lambda = 0.71073$ Å), operated at 50 kV and 30 mA. The structure was solved by direct methods and refined on F^2 using the SHELXTL software package.[13] Absorption corrections were applied using SADABS, part of the SHELXTL package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed on idealized positions and refined isotropically with a riding model. *Crystal data:* $C_{20}H_{38}N_1O_5Na_1S_1$, $M = 427.6$, colorless block, 0.38 × 0.34 × 0.34 mm^3, orthorhombic, space group $Pna2_1$ (No. 33), $a = 14.3958(9)$, $b = 11.6797(8)$, $c = 13.8794(9)$ Å, $V = 2333.7(3)$ Å^3, $Z = 4$, $D_c = 1.217$ g/cm^3, $T = 173(2)$ K, $2\theta_{max} = 56.6°$, 15,423 reflections collected, 4663 unique ($R_{int} = 0.0173$). Final $GooF = 1.160$, $R_1 = 0.0333$, $wR_2 = 0.0850$, R indices based on 4600 reflections with $I > 2\sigma(I)$, Lp and absorption corrections applied, $\mu = 0.186$ mm^{-1}. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 701968. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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