# Synthesis of 9-Hydroxynonyl[2.2.2]cryptand: A Useful Intermediate for the Preparation of Polymer-Bonded Cryptands

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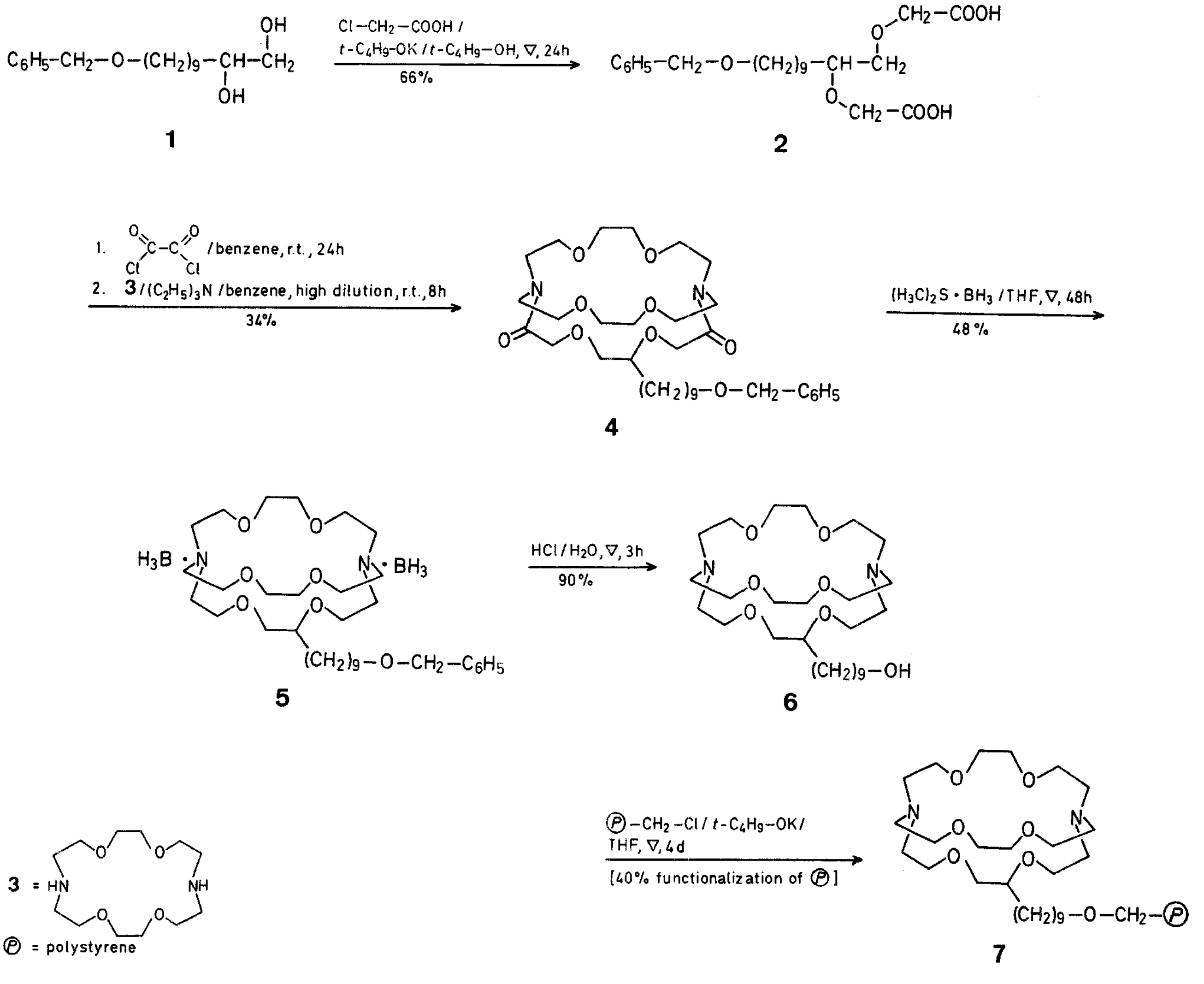
9-Hydroxynonyl[2.2.2]cryptand is prepared from 11-benzyloxyundecane-1,2-diol by an easy five-step sequence. It represents a suitable cryptand unit for the preparation of polymer-bonded cryptands.

The wide application of insoluble polymer-bonded complexing agents[1], mostly as highly efficient and recyclable phase-transfer catalysts[2], has strongly increased the interest in the synthesis of functionalized macropolycyclic ligands.

The efficiency of polymer-bonded phase-transfer catalysts reaches the optimum values when the catalytic site is bonded to the matrix through a linear spacer chain of about 10 atoms[3,4]. This can be accomplished in two ways: (A) by attaching an $\omega$-functionalized alkyl chain onto the polymer followed by attachment of the catalyst; (B) by direct reaction of chloromethylated polystyrene with the catalyst which possesses an $\omega$-functionalized alkyl chain. The latter procedure is more advantageous in the case of macrocyclic and macropolycyclic ligands[4] since it involves a single reaction on the polymeric matrix and leads to a more homogeneous catalyst as compared to those which are obtained by method A. Approach B was first realized by reacting chloromethylpolystyrene with 9-aminononyl[2.2.2]cryptand[5].

We here report the synthesis of the 9-hydroxynonyl[2.2.2]-cryptand **6** which by Williamson reaction with chloromethylpolystyrene can be transformed into a cryptand (**7**) immobilized by an inert ether bond.



Condensation of 11-benzyloxyundecane-1,2-diol[4] (**1**) with chloroacetic acid in boiling *t*-butanol with potassium *t*-butoxide as base afforded the diacid **2** which was purified as the potassium salt (66% yield). Diacid **2** was first transformed into its dichloride with oxalyl chloride in benzene at room temperature and the dichloride then condensed with [2.2] diazacoronand **3** under high-dilution conditions[6] to give the macrobicyclic diamide **4** in 34% yield. Reduction of **4** with borane-dimethyl sulfide in boiling tetrahydrofuran and hydrolysis of the resultant intermediate **5** with aqueous 6 normal hydrochloric acid gave 9-hydroxynonyl[2.2.2]cryptand **6**. It is worthy of note that hydrolysis of the bis-borane adduct and cleavage of the benzyl protective group proceed in one step. The reaction of **6** with chloromethylpolystyrene in tetrahydrofuran in the presence of potassium *t*-butoxide afforded the polymer-bonded cryptand **7** containing 0.25 mequiv of cryptand/g.

**4-(9-Benzyloxynonyl)-3,6-dioxaoctanedioic Acid (2):**

Potassium (2.6 g, 68 mmol) is added to a stirred solution of 11-benzyloxy-1,2-undecanediol (**1**; 4.0 g, 13.6 mmol) in *t*-butanol (150 ml) under an argon atmosphere. Stirring is continued until all metal has disappeared. The mixture is then heated to reflux and a solution of chloroacetic acid (3.2 g, 34 mmol) in *t*-butanol (30 ml) is added over 30 min. Stirring and boiling is continued overnight, and the solvent then evaporated under reduced pressure. The residue is acidified with 6 normal sulfuric acid and extracted with dichloromethane (3 × 50 ml). The extract is dried with sodium sulfate and evaporated to dryness. The residue (5.8 g of crude **2**) is dissolved in absolute ethanol (20 ml) and a solution of 85% potassium hydroxide (2.24 g, 34 mmol) in absolute ethanol (30 ml) is added over 20 min. The resultant white precipitate is isolated by suction under an argon atmosphere and washed with absolute ethanol (2 × 10 ml). The precipitate is dissolved in water (30 ml), acidified to pH 1 with aqueous sulfuric acid, and extracted with ether (3 × 50 ml). The organic extract is dried with anhydrous sodium sulfate and evaporated to afford product **2** as a highly viscous oil; yield: 3.7 g (66%).

$C_{22}H_{34}O_7$ calc. C 64.36 H 8.36
(410.5) found 64.10 8.21

I.R. (film): $\nu = 1740\ cm^{-1}$ (CO).

$^1$H-N.M.R. ($CDCl_3$/$TMS_{int}$): $\delta = 1.0-1.6$ (m, 16H); 3.3–3.7 (m, 5H); 3.9–4.2 (m, 4H); 4.4 (s, 2H); 7.25 (m, 5H); 8.6 ppm (br. s. 2H).

**5-(9-Benzyloxynonyl)-2,9-dioxo-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (4):**

A solution of diacid **2** (3.0 g, 7.31 mmol) and oxalyl chloride (2.8 g, 22.0 mmol) in benzene (30 ml) is stirred overnight at room temperature. After evaporation of the solvent, the remaining oxalyl chloride is removed by addition and evaporation of benzene (3 × 10 ml). The resultant oily diacid dichloride (quantitative yield) [I.R. (film): $\nu = 1800\ cm^{-1}$ (C=O); absence of the CO band of the acid] is used without further purification. A solution of the diacid dichloride (3.27 g, 7.31 mmol) in anhydrous benzene (200 ml) and a solution of [2.2]diazacoronand **3** (1.9 g, 7.31 mmol) and triethylamine (3.0 g, 29.2 mmol) in anhydrous benzene (200 ml) are simultaneously added, dropwise over an 8 h period, to vigorously stirred anhydrous benzene (1500 ml) (high-dilution conditions). Triethylamine hydrochloride is then filtered off, the solvent is removed from the filtrate, and the remaining crude mixture is column-chromatographed on neutral alumina using ethyl acetate as eluent to give product **4** as a viscous oil; yield: 1.6 g (34%).

| | | | | |
|---|---|---|---|---|
| $C_{34}H_{56}N_2O_9$ | calc. | C 64.11 | H 8.88 | N 4.40 |
| (636.9) | found | 64.40 | 8.91 | 4.14 |

I.R. (film): $\nu = 1640\,cm^{-1}$ (C=O).

$^1$H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.0-1.7$ (m, 16H); 3.3–4.5 (m, 35H); 7.25 ppm (m, 5H).

**5-(9-Benzyloxynonyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane Bis-borane Adduct (5):**
A 10 molar solution of borane dimethyl sulfide in hexane (1.0 ml, 10 mmol) is dissolved in anhydrous tetrahydrofuran (10 ml) and this solution is added to a stirred solution of compound **4** (1.27 g, 2 mmol) in tetrahydrofuran (30 ml). The mixture is stirred and refluxed for 48 h. Excess borane is then destroyed with methanol and the mixture is evaporated to dryness in vacuum. The residue is taken up in dichloromethane (50 ml) and the resultant mixture is filtered. The solvent is removed from the filtrate and the residue is column-chromatographed on neutral alumina eluting with ethyl acetate to give **5** as a waxy solid; yield: 0.61 g (48%).

| | | | | |
|---|---|---|---|---|
| $C_{34}H_{66}B_2N_2O_7$ | calc. | C 64.13 | H 10.47 | N 4.40 |
| (636.6) | found | 64.00 | 10.35 | 4.58 |

I.R. (nujol): $\nu = 2380\,cm^{-1}$ (BH).

$^1$H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.0-1.6$ (m, 16H); 2.8–4.0 (m, 43H); 4.4 (s, 2H); 7.25 ppm (m, 5H).

**5-(9-Hydroxynonyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (6):**
A mixture of compound **5** (1.27 g, 2.0 mmol) and aqueous 6 normal hydrochloric acid (10 ml) is refluxed for 3 h, and then evaporated in vacuo. The residue is taken up in water (10 ml) and the pH is adjusted to 12 with lithium hydroxide.This mixture is extracted with chloroform (2 × 50 ml). The extract is dried with molecular sieves (4 Å) and evaporated to afford product **6** as a viscous oil; yield: 0.93 g (90%).

| | | | | |
|---|---|---|---|---|
| $C_{27}H_{54}N_2O_7$ | calc. | C 62.50 | H 10.51 | N 5.40 |
| (518.7) | found | 62.71 | 10.40 | 5.31 |

$^1$H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.0-1.6$ (m, 16H); 1.85 (br. s, 1H $D_2O$ exchange); 2.5–2.9 (m, 12H); 3.35–3.75 ppm (m, 25H).

**Polymer-Bonded Cryptand 7:**
Potassium *t*-butoxide (0.112 g, 1 mmol) is added to a solution of cryptand **6** (0.256 g, 0.5 mmol) in anhydrous tetrahydrofuran (25 ml) and this mixture is stirred at room temperature for 2 h; then, chloromethyl polystyrene (Fluka AG, 2% cross-linked with divinylbenzene containing 0.7 mmol Cl/g; 0.6 g, 0.42 mmol) is added and the mixture is stirred and refluxed for 4 days. After cooling, the polymer is filtered off and washed with water, methanol, ether, dichloromethane, ether, methanol, dichloromethane, and ether and is then dried for 3 h (65°C/2 torr). Element analysis of the resultant polymer (0.78% N and 2.50% O) shows a content of 0.25 mequiv of cryptand/g, corresponding to 40% functionalization.

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