Pergamon

Tetrahedron Letters 42 (2001) 2735–2737

TETRAHEDRON LETTERS

# Synthesis of 2,6,10,14,18,22-hexaazaspiro[11.11]tricosane, the first example of a spiro aza crown derived from 2,2-bis(aminomethyl)propane-1,3-diamine

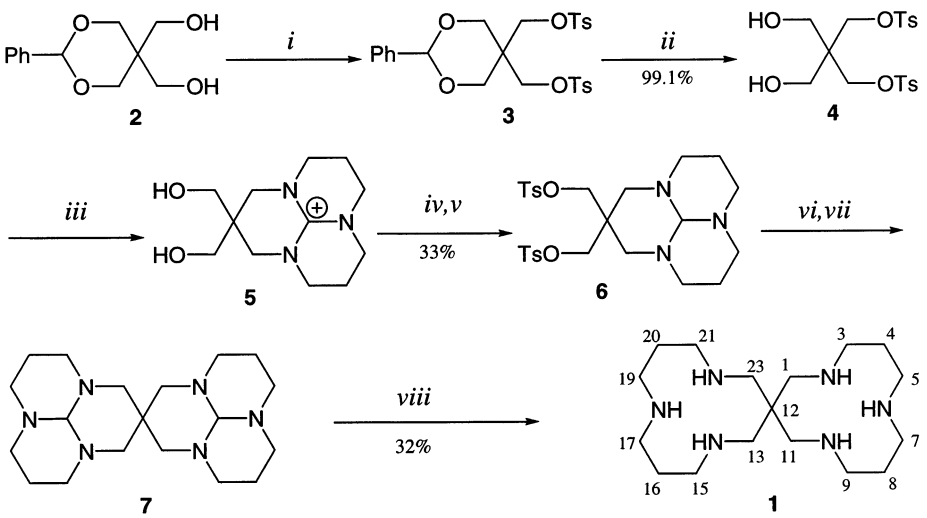
Qi Wang, Satu Mikkola and Harri Lönnberg*

*Department of Chemistry, University of Turku, FIN-20014 Turku, Finland*

Received 13 December 2000; revised 26 January 2001; accepted 7 February 2001

**Abstract**—2,6,10,14,18,22-Hexaazaspiro[11.11]tricosane **1** has been prepared in seven steps from pentaerythritol. The key steps include two successive cyclizations by displacement of two tosyloxy groups from the appropriate pentaerythritol derivatives (**4**; **6**) with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), each reaction being followed by sodium borohydride reduction. Hydrolysis of the spiro bis(hexahydro-1*H*,4*H*,7*H*-3a,6a,9a-triazaphenalene) formed **1**. © 2001 Elsevier Science Ltd. All rights reserved.

While the first syntheses of spiro crown ethers, having the two crown ether moieties linked via a pentaerythritol unit, were reported in early 1980s,[1,2] no respective spiro compounds derived from aza crowns have been prepared. The latter compounds might, however, prove useful in construction of artificial ribonucleases,[3] i.e. catalysts that sequence selectively cleave RNA. This assumption receives support from two lines of evidence. Firstly, metal ion chelates of monocyclic aza crowns are known to promote rather effectively the cleavage of ribonucleoside phosphodiesters.[4–7] Secondly, dinuclear metal complexes have been shown to be more effective catalysts than the mononuclear ones.[8,9] Accordingly, spiro aza crowns that in principle may bind two metal ions relatively close to each other, but in such a manner that the ions are not bridged by common aquo ligands,




**Scheme 1.** (i) TsCl, Py, rt; (ii) $H_2$ (5 atm), 10% Pd/C, EtOH, 15 h, rt; (iii) TBD, DME, 24 h, 40°C; (iv) TsCl, DMAP, Py/DCM (1:1), 24 h, 0°C; (v) $NaBH_4$, THF, 48 h, rt; (vi) TBD, DME, 24 h, 40°C; (vii) $NaBH_4$, DME, 48 h, rt; (viii) aq. HCl (6 mol $L^{-1}$), 1 week at reflux.

*Keywords*: spiro compounds; aza crowns; cyclization; polyamines; polyazacycloalkanes.

* Corresponding author. E-mail: harlon@utu.fi



PII: S0040-4039(01)00238-6

appear attractive as catalysts. Among various possible spiro aza crowns, the one consisting of two 1,5,9-triazacyclododecane rings is of particular interest since it has previously been shown to exhibit catalytic activity superior to that of other monocyclic aza crowns.[10] We now report the synthesis of this compound, 2,6,10,14,18,22-hexaazaspiro[11.11]tricosane, as the first example of the preparation of spiro aza crowns.

The synthetic route is outlined in Scheme 1. 2-Phenyl-5,5-bis(hydroxymethyl)-1,3-dioxane **2**, prepared from pentaerythritol as described previously,[11] was converted into 2-phenyl-5,5-bis(toluene-4-sulfonyloxymethyl)-1,3-dioxane **3** with toluene-4-sulfonyl chloride in pyridine. The product was purified by column chromatography, and the benzylidene protection was removed by catalytic hydrogenation on Pd/C in ethanol, giving 2,2-bis-(toluene-4-sulfonyloxymethyl)propane-1,3-diol[12] **4** as a solid foam in virtually quantitative yield. The reason for the removal of the benzylidene protection was that **4** proved to be more soluble than **3** in 1,2-dimethoxyethane (DME), which was used as a solvent in the subsequent nucleophilic displacement of the tosyloxy groups.

The well established[13–16] displacement of tosyloxy groups with amine nucleophiles was applied in a stepwise manner to form the two triaza macrocycle moieties. Accordingly, the two tosyloxy groups of **4** were first displaced with a 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in DME.[17–19] The reaction took place almost quantitatively in 24 h at 40°C when TBD was used in a twofold excess. The progress of the reaction was followed by appearance of a LC/ESI-MS signal at $m/z$ 240 $[M]^+$, referring to formation of the 2,2-bis(hydroxymethyl)-1*H*,4*H*,7*H*-pentahydro-3a,6a,9a-triazaphenalenium cationic salt **5**. Crude **5** was then tosylated at low temperature with toluene–4-sulfonyl chloride in a mixture of pyridine and dichloromethane using 4-dimethylaminopyridine (DMAP) as a catalyst. Reduction with sodium borohydride in THF and purification by column chromatography (silica gel, 5–10% MeOH in DCM) then gave 2,2-bis(toluene-4-sulfonyloxymethyl)-1*H*,4*H*,7*H*-hexahydro-3a,6a,9a-triazaphenalene[20] **6** in 33% overall yield (from **2**).

The second 1*H*,4*H*,7*H*-hexahydro-3a,6a,9a-triazaphenalene ring was introduced similarly by displacement of the tosyloxy groups with TBD and subsequent hydride reduction. The formation of spiro bis(1*H*,4*H*,7*H*-hexahydro-3a,6a,9a-triazaphenalene) **7** was followed by the appearance of a LC/ESI-MS signal at $m/z$ 347 $[M+H]^+$. Crude **7** was then hydrolyzed in aqueous hydrogen chloride (6 mol $L^{-1}$) to the desired 2,6,10,14,18,22-hexaazaspiro[11.11]tricosane **1**, which took one week at refluxing temperature. However, the progress of the hydrolysis was followed by the appearance of a LC/ESI-MS signal at $m/z$ 327 $[M+H]^+$. The purification of **1** proved difficult. The pure product was obtained by protecting the amino functions with *tert*-butoxycarbonyl (Boc) groups and purifying the Boc protected compound on a silica gel column. The protection was carried out by treating crude **1** with *tert*-butoxyformic anhydride ($(Boc)_2O$) in a mixture of THF and aqueous sodium hydroxide. The protected compound, which according to LC/ESI-MS contained four Boc groups, was purified on a silica gel column using a 1:1 mixture (v/v) of dichloromethane and ethyl acetate ($R_f = 0.58$) as eluent. The Boc protecting groups were finally removed with aqueous hydrogen chloride (1 mol $L^{-1}$, 2 h, 40°C), giving pure **1** as the hexahydrochloride in 32% yield (from **6**).[21] The free base form was obtained by passing the hydrochloride through an ion exchange column (Dowex lx2, $OH^-$ form). The oily product was characterized by $^1H$ and $^{13}C$ NMR spectroscopy, LC/ESI-MS and high resolution mass spectrometry.[22]

The spiro carbon of **1** resonates at $\delta$ 41.45 in NaOD/$D_2O$ (at $\delta$ 38.41 for the hydrochloride in $D_2O$). It is worth noting that the four methylene carbons bonded to the spiro carbon (C1, C11, C13, C23) exhibit only one resonance signal ($\delta$ 52.38 in NaOD/$D_2O$ and $\delta$ 52.74 for the hydrochloride in $D_2O$), while the methylene groups of the fragments $–HN(CH_2)_3NH–$ clearly show two distinct set of signals in the $^{13}C$ NMR spectrum. In NaOD/$D_2O$, one set of the carbon resonances appears at $\delta$ 32.52, 39.61 and 47.16, each of the signals being coupled with a single methylene group, the corresponding proton resonances occur at $\delta$ 1.52, 2.55 and 2.50, respectively. The other set is found at $\delta$ 25.58, 48.50 and 49.50, the respective methylene proton resonance being at $\delta$ 1.61, 2.77 and 2.69. The protons are coupled to each other within each set, the coupling constants being 5.8 and 4.2 Hz, respectively. Similar double signals for these three methylene carbons are observed on recording the spectrum of the hydrochloride of **1** in pure $D_2O$. However, in this case, the proton resonance signals of the methylene groups overlap extensively. The reason for the observed multiplicity of the signals of the $–HN(CH_2)_3NH–$ fragments remains obscure.

## Acknowledgements

The authors wish to thank Dr. Kari Neuvonen for his skilful technical help and fruitful discussions concerning the NMR spectroscopy of the compounds prepared. Financial aid from the Academy of Finland is gratefully acknowledged.

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12. Compound **4**: LC/ESI-MS *m/z* 445 (100%) $[M+H]^+$, 467 (32%) $[M+Na]^+$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (4H, d, $J=8.3$ Hz), 7.32 (4H, d, $J=8.3$ Hz), 3.93 (4H, s), 3.53 (4H, d, $J=5.1$ Hz), 2.66 (2H, t, $J=5.1$ Hz), 2.41 (6H, s). $^{13}C$ NMR (100.4 MHz, $CDCl_3$) $\delta$ 145.29, 131.81, 129.98, 127.82, 67.67, 60.94, 45.05, 21.59.
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20. Compound **6**: LC/ESI-MS *m/z* 550 (100%) $[M+H]^+$, 572 (34%) $[M+Na]^+$, $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (2H, d, $J=8.1$ Hz), 7.64 (2H, d, $J=8.1$ Hz), 7.27 (2H, d, $J=8.1$ Hz), 7.23 (2H, d, $J=8.1$ Hz), 4.28 (2H, s), 3.68 (2H, s), 2.68 (2H, m), 2.51 (4H, m), 2.37 (3H, s), 2.35 (3H, s), 2.11 (1H, s), 1.88 (8H, m), 1.30 (2H, m). $^{13}C$ NMR (100.40 MHz, $CDCl_3$) $\delta$ 144.95, 144.48, 132.68, 131.94, 129.80, 129.65, 127.75, 127.71, 99.44, 70.42, 70.32, 55.60, 53.41, 53.31, 37.70, 23.47, 21.50, 21.44.
21. For the hydrochloride of **1**: $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 3.26 (4H, t, $J=6.1$ Hz), 3.13 (8H, s), 3.11 (4H, t, $J=9.75$), 3.04 (8H, m), 2.03 (8H, m). $^{13}C$ NMR (125.65 MHz, $D_2O$) 52.74 (C1, C11, C13, C23 coupled to $^1H$ at $\delta$ 3.13), 46.15 (C3, C9 coupled to $^1H$ at $\delta$ 3.04), 45.55 (C15, C21 coupled to $^1H$ at $\delta$ 3.11), 44.44 (C5, C7 coupled to $^1H$ at $\delta$ 3.26), 38.41 (C12), 37.41 (C17, C19 coupled to $^1H$ at $\delta$ 3.04), 24.57 (C4, C8 coupled to $^1H$ at $\delta$ 2.03), 22.90 (C16, C20 coupled to $^1H$ at $\delta$ 2.03). The assingment of the carbon signals is tentative, except those of C12 and C1, C11, C13 and C23.
22. Compound **1**: LC/ESI MS *m/z* 327.4 (100%) $[M+H]^+$, 132.4 (8%), 115.3 (8%). $^1H$ NMR (500 MHz, NaOD/$D_2O$) $\delta$ 2.77 (4H, t, $J=4.3$ Hz), 2.69 (4H, t, $J=4.2$ Hz), 2.55 (4H, t, $J=5.8$ Hz), 2.50 (4H, t, $J=5.8$ Hz), 2.46 (8H, s), 1.61 (4H, quin. $J=4.2$ Hz), 1.52 (4H, quin. $J=5.8$ Hz). $^{13}C$ NMR (125.65 MHz, NaOD/$D_2O$) 52.38 (C1, C11, C13, C23 coupled to $^1H$ at $\delta$ 2.46), 49.50 (C3, C9 coupled to $^1H$ at $\delta$ 2.69), 48.50 (C15, C21 coupled to $^1H$ at $\delta$ 2.77), 47.16 (C5, C7 coupled to $^1H$ at $\delta$ 2.50), 41.45 (C12), 39.61 (C17, C19 coupled to $^1H$ at $\delta$ 2.55), 32.52 (C4, C8 coupled to $^1H$ at $\delta$ 1.52), 25.58 (C16, C20 coupled to $^1H$ at $\delta$ 1.61). The assingment of carbon signals is tentative, except that of C12 and C1, C11, C13 and C23. HR-MS for $C_{17}H_{39}N_6^+$: requires 327.3236, found 327.3245.