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# Synthesis of Cyclic Hydropyran Oligolides with Convergent Amine, Amide, Phosphonate and Furan Appendages

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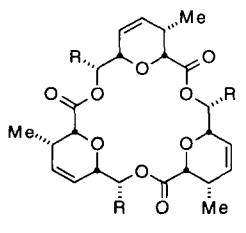
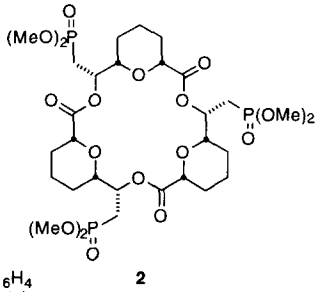
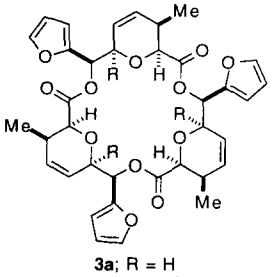
**Abstract**: The syntheses of $C_3$-symmetric macrocycles with pendant amino, phosphono, and furan groups are described. These functional groups, amenable to further elaboration, were installed early in the syntheses and carried through the iterative sequence of module coupling and macrolactonization.


We have recently reported the synthesis and study of 18- to 72-membered cyclic hydropyran oligolides bearing methyl and phenyl appendages.[1] Further studies have led to the elucidation of structural elements important for control of the shape and cation binding efficacy of these unnatural ionophores.[2] Optimal preorganization of the 18-membered ligand arrays was observed when the methyl (**1a**) or phenyl (**1b**) groups ("R" in generalized structure **1**) were oriented perpendicular to the mean plane of the macrocycle. The availability of these conformationally homogeneous ionophores with convergent appendages suggests their employment as templates for ion channel mimics. Application as such requires more functionalized pendant groups "R". Described herein are synthetic routes leading to tris(aminomethyl) derivatives **1c-1i**, tris[(dimethylphosphono)methyl] analogue **2**, and the tri-and hexafurans, **3a** and **3b**, wherein the furan residues are masked carboxyl groups.[3]







**1a**; R = $CH_3$
**1b**; R = $C_6H_5$
**1c**; R = $CH_2NHBoc$
**1d**; R = $CH_2NH_2$•HCl
**1e**; R = $CH_2NHTs$
**1f**; R = $CH_2NHC(O)$-*p*-$NO_2C_6H_4$
**1g**; R = $CH_2NHC(O)$-1-adamantyl
**1h**; R = $CH_2NHC(O)$-*n*-$C_9H_{19}$
**1i**; R = $CH_2NHC(O)CH_2Br$

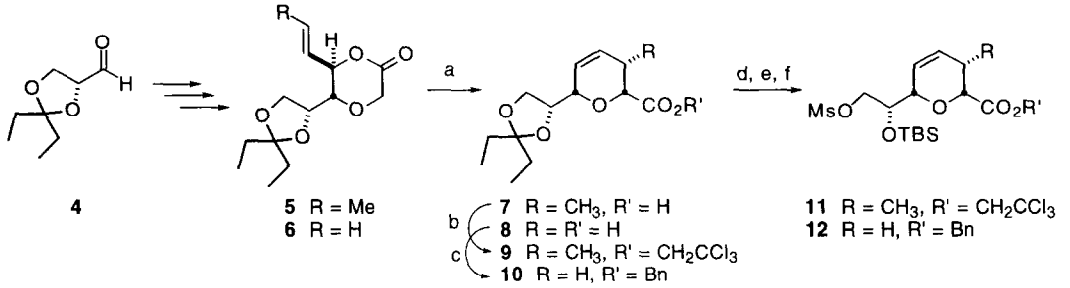
**2**

**3a**; R = H
**3b**; R = 2-furyl

These "second generation" macrocycles are all derived from (*R*)-glyceraldehyde pentylidene acetal (**4**). Analogous to methods described previously,[4] the optically pure aldehyde **4**[5] was converted to dioxanones **5** and **6** (Scheme 1), which served as substrates for an Ireland-Claisen rearrangement[6] to the dihydropyran carboxylic acids **7** and **8**. Protection of **7** as its trichloroethyl ester **9**, or **8** as its benzyl ester **10**, was followed

by a three step procedure (pentylidene ketal removal, selective mesylation, then protection of the secondary alcohol as its *tert*-butyldimethylsilyl ether) yielding mesylates **11** and **12**.

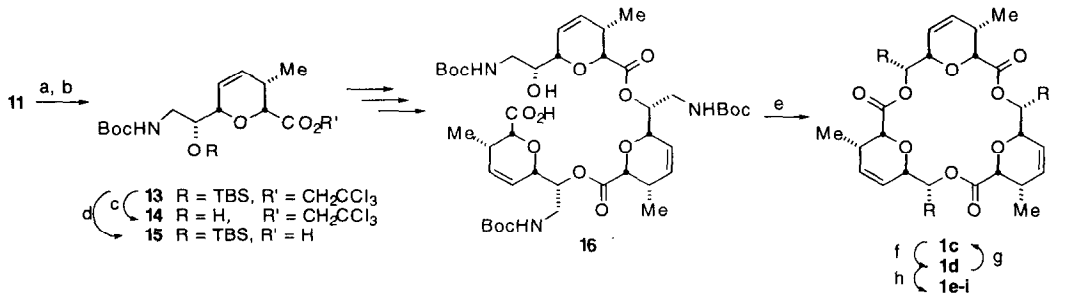
**Scheme 1**[7]




**Conditions and Reagents**: a) LiHMDS, TMSCl, $Et_3N$, THF, -78 °C; ↑↓: **5**→**7**, 90%; **6**→**8**, 76%. b) $HOCH_2CCl_3$, DIC, DMAP, DMAP•TFA, $CH_2Cl_2$, 32 °C, 99%. c) DBU, BnBr, $CH_3CN$, rt, 80%. d) 4:1 AcOH:$H_2O$, rt, 93%. e) MsCl, collidine, $CH_2Cl_2$, 0 °C, 86%. f) TBSCl, imidazole, DMF, rt, 98% for **11**; 87% for **12**.

Mesylate **11** was elaborated to the triamine derivatives **1c-i** as detailed in Scheme 2. Azide displacement of the mesylate followed by Staudinger reduction[8] and protection of the resulting amine as its *tert*-butylcarbamate produced amine derivative **13**. Unmasking of the alcohol or the acid produced coupling modules **14** and **15**, respectively. Iterative coupling esterifications via the Keck protocol,[9] followed by alcohol unmasking and cleavage of the trichloroethyl ester (Zn, THF, NH4OAc buffer) gave seco acid **16**. Macrocyclization to yield **1c** was performed using Yamaguchi high dilution conditions;[10] cleavage of the Boc groups gave **1d**. Concerns over possible *O*-to-*N* acyl transfer were obviated by reprotection of **1d** to the tris(Boc)-protected triamine **1c**. Furthermore, the tris(amine hydrochloride) **1d** was readily acylated to give derivatives **1e**, **1f**, **1g**, **1h**, and **1i**.[11]

**Scheme 2**[7]

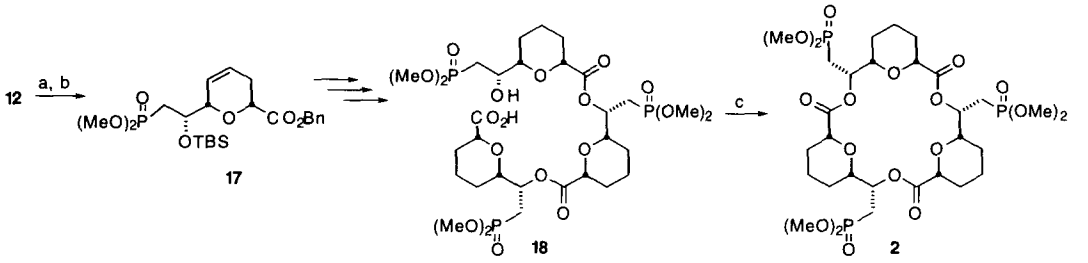



**Conditions and Reagents**: a) $NaN_3$, DMSO, 90 °C, 85%. b) $PPh_3$, THF, $H_2O$, rt; $(Boc)_2O$, 87%. c) HF(aq), $CH_3CN$, 0 °C, 94%. d) LiOH, $^tBuOH$, $H_2O$, 45 °C, 100%. e) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF; -THF, $PhCH_3$, DMAP, ↑↓, 65%. f) HCl/dioxane, 100% . g) $(Boc)_2O$, $K_2CO_3$, THF/$H_2O$, 0 °C to rt, 100%. h) **1e**; TsCl, $Et_3N$, $CH_2Cl_2$, rt, 97%. **1f**; *p*-$NO_2$-$C_6H_4C(O)Cl$, $Et_3N$, $CH_2Cl_2$, 0 °C, 57%. **1g**; 1-adamantanecarboxylic acid, DIC, HOBT, $Et_3N$, $CD_3CN$, rt, 66%. **1h**; decanoic acid, EDCI, HOBT, $Et_3N$, $CH_2Cl_2$, 35 °C, 79%. **1i**; $BrCH_2C(O)Br$, $Et_3N$, DMAP, $CH_2Cl_2$, -78 °C to rt, 75%.

The tris(phosphonate) **2** was prepared in a similar manner from mesylate **12** (Scheme 3). Displacement of the mesylate with bromide followed by Arbuzov reaction[12] with P(OMe)3 gave the protected coupling

module **17**. Appropriate unmasking of the alcohol or acid of **17** followed by iterative coupling esterifications, followed by cleavage of the TBS ether and benzyl ester gave seco acid **18**.[13] Macrolactonization was performed under modified Keck-Steglich conditions,[9] utilizing slow addition of **18**, to give tris(phosphonate) **2**.[11]

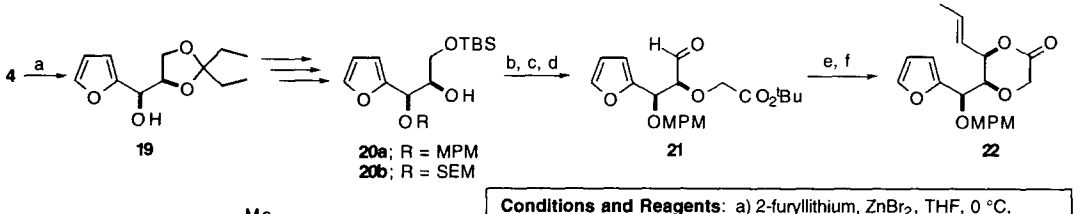
**Scheme 3**[7]



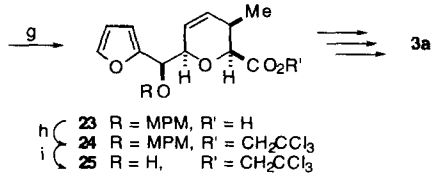
**Conditions and Reagents**: a) $Bu_4NBr$, PhH, ↑↓, 96%. b) $P(OMe)_3$, ↑↓, 95%. c) DIC, DMAP, DMAP•TFA, $CHCl_3$, ↑↓, 62%.

Synthesis of the trifuran derivative **3a** began with the addition of 2-furyllithium to **4** in the presence of $ZnBr_2$, proceeding through β-chelation control, giving alcohol **19** (Scheme 4).[14] Straightforward protecting group manipulations produced alcohols **20a** and **20b**. Alcohol **20a** was converted in three steps (*O*-alkylation, removal of the silyl protecting group and oxidation) to aldehyde **21**. Treatment of **21** with the cuprate derived from *trans*-propenyllithium followed by lactonization gave dioxanone **22**. Ireland-Claisen rearrangement[6] of **22** produced dihydropyran acid **23**. Protection of the acid as its trichloroethyl ester followed by liberation of the secondary alcohol gave coupling module **25**. Iterative esterification of **23** and **25** followed by macrolactonization as described previously resulted in the trifuran macrocycle derivative **3a**.

**Scheme 4**[7]



**20a**; R = MPM
**20b**; R = SEM



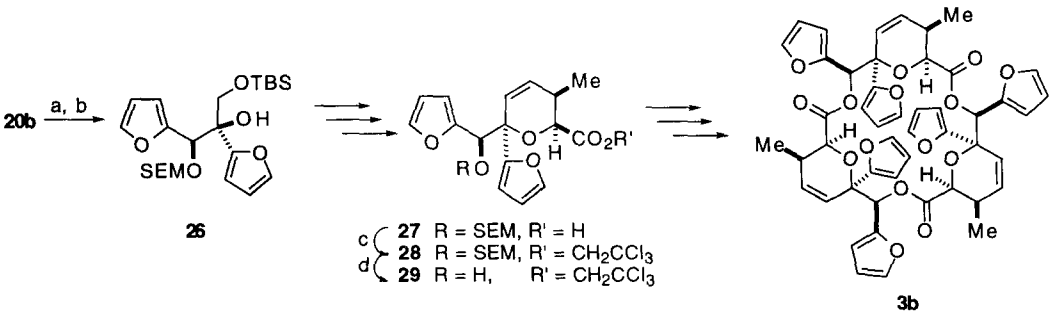
**23** R = MPM, R' = H
**24** R = MPM, R' = $CH_2CCl_3$
**25** R = H, R' = $CH_2CCl_3$

**Conditions and Reagents**: a) 2-furyllithium, $ZnBr_2$, THF, 0 °C, 94%; **19**→**20a**, 72% for 3 steps; **19**→**20b**, 67% for 3 steps. b) NaH, $BrCH_2CO_2{}^tBu$, THF, ↑↓, 95%. c) HF, $CH_3CN$, -40 °C, 98%. d) Dess-Martin periodinane, pyridine, $CH_2Cl_2$, rt. e) *trans*-propenyllithium, CuI•$PBu_3$, THF, -55 °C, 76% for 2 steps. f) TFA, PhH, ↑↓. g) LHMDS, TMSCl, $Et_3N$, THF, -78 °C to ↑↓, 76% for 2 steps. h) $Cl_3CCH_2OH$, DIC, DMAP, 98%. i) DDQ, $CH_2Cl_2$, rt, 79%.

The hexafuran **3b** was fashioned in a similar manner. Alcohol **20b** was oxidized to the ketone under Swern conditions,[15] followed by addition of the Grignard reagent derived from 2-furyllithium producing tertiary alcohol **26** (Scheme 5). Dihydropyran coupling module **27** was generated analogous to the sequence described for **20a** in Scheme 4. Protection of the acid as its trichloroethyl ester followed by removal of the 2-

trimethylsilylethyl ether gave alcohol **29**. Once again, **27** and **29** were carried though the iterative esterification/macrolactonization protocol described previously to give hexafuran derivative **3b**.[11]

**Scheme 5**[7]




**Conditions and Reagents**: a) $COCl_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78→0 °C, 94%. b) 2-furyllithium, $MgBr_2$, $Et_2O$, -78 °C, 93%. c) $Cl_3CCH_2OH$, DIC, DMAP, DMAP•TFA, $CH_2Cl_2$, rt, 100%. d) $LiBF_4$, wet $CH_3CN$, 80 °C, 82%.

Further studies of these ligand structures are currently being pursued, including their solution and solid state behavior, cation binding efficacy, conversion of the 2-furyl appendages to carboxyl groups, and elaboration of these triolides into transmembrane ion channel mimics.[16] These studies will be reported in due course.

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