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CHIRAL SYNTHETIC MACRODIOLIDE AND MACROTRIOLIDE IONOPHORES WITH C_2- AND C_3-SYMMETRY

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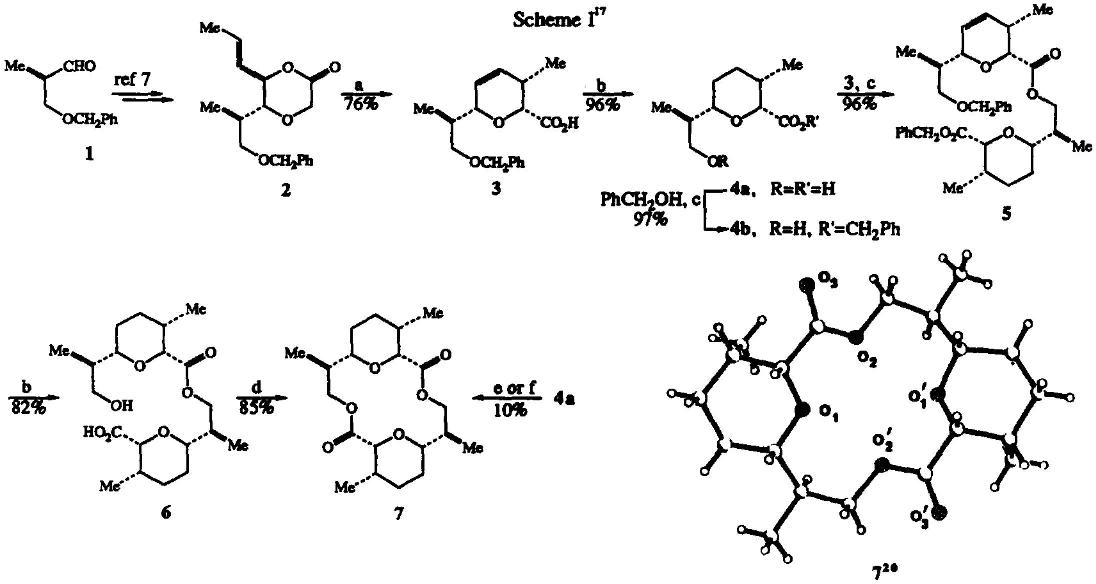
Summary: Macrodiolide and macrotriolide synthetic ionophores 7 and 12 have been prepared from hydropyran subunits. Ion binding data and crystallographic analyses for this new class of optically pure macrocyclic hosts are reported. Macrodiolide 7 shows moderate selectivity for Li^+, with an association constant (K_a) of 1.5×10^5 M^{-1}.

We have extended our interests[2] in natural polyether and macrolide antibiotics to include the synthesis and study of unnatural macrooxacyclic ligand arrays that are chiral and non-racemic. The importance of preorganization, convergence of binding sites and rigidity is widely acknowledged in the design of effective and selective host molecules.[3] We sought to satisfy these requirements by constructing macrocycles from hydropyran subunits connected by ester linkages.[4] The combined constraints of the *cis*-2,6-disubstituted oxacycle and *Z*-ester conformations[5] were expected to define the shape of the macrocycle. Moreover, three different types of oxygens as potential ligating sites would line the cavity of the host. Described below are syntheses of the C_2-symmetric macrodiolide 7 and the C_3-symmetric macrotriolide 12,[6] along with ion binding and crystallographic data for each.

As detailed previously,[7] the optically pure aldehyde 1 was converted to the dioxanone 2 (Scheme I), which served as a substrate for an Ireland-Claisen rearrangement[8] to the dihydropyran carboxylic acid 3. Catalytic hydrogenation of the

Scheme I[17]

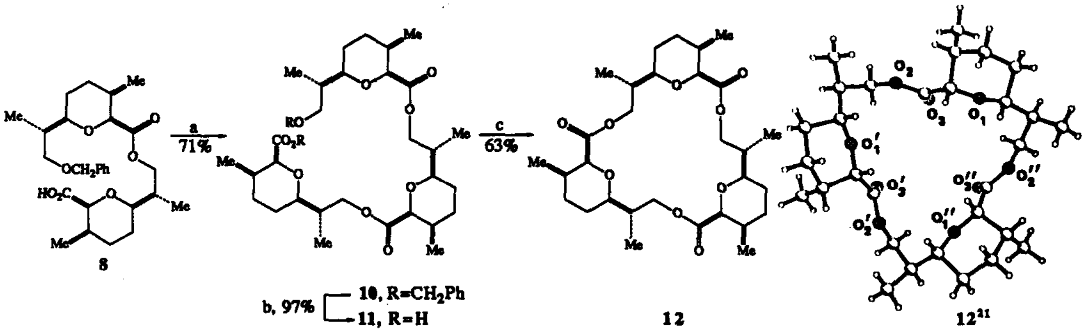


7^{20}

a) 1 eq LiHMDS, 5 eq 1:1 TMSCl/Et_3N, THF, -78°C, then reflux 4.5h; 5% aq HCl. b) H_2 (1 atm), Pd/C, EtOH, r.t., 10 h. c) DCC, DMAP, DMAP·TFA, CH_2Cl_2, 25°C. d) DCC, DMAP, DMAP·TFA, $CHCl_3$, reflux; 6 added over 11h, then reflux additional 3h. e) 2,2'-dipyridyldisulfide, Ph_3P, xylene; reflux, xylene. f) Ph_3P, DEAD, PhH, 25°C, 4d.

olefin and concomitant hydrogenolysis of the benzyl ether, yielding **4a**, was followed by conversion to the hydroxy ester **4b** via the Keck procedure.[9] Coupling of **4b** and **3**, again using the DCC, DMAP, DMAP·TFA procedure[9] proceeded in 96% yield to give **5**. Exposure of this substance to H_2 and 5% Pd/C in ethanol effected saturation of the olefin and hydrogenolyses of the benzyl ether and ester moieties. A third application of the Keck-Steglich coupling gave the C_2-symmetric macrodiolide **7** as colorless crystals [mp 126-127°C, $[\alpha]_D^{23}$ +42.5 (c 0.93, $CHCl_3$), M^+=368.2194, calcd 368.2199] in 85% yield. As expected, the symmetry of this substance was reflected in the ^{13}C NMR spectrum, which exhibited only ten resonances ($CDCl_3$, δ 172.2, 83.9, 80.0, 70.2, 36.7, 30.2, 29.9, 23.8, 13.2, 12.9). The enantiomer [mp 126-127°C, $[\alpha]_D^{23}$ -42.2 (c 1.32, $CHCl_3$)] of **7** was also constructed, starting from the epimer of aldehyde **1**. Direct dimerization of hydroxy acid **4a** by either the Corey procedure [e) in Scheme I][10] or the Mitsunobu coupling [f) in Scheme I][11] provided a two-step, albeit low-yielding (10%), route to **7** from **3**.

Scheme II[17]



a) 9 (ent-4b), DCC, DMAP, DMAP·TFA, CH_2Cl_2, r.t., 10h. b) H_2 (1 atm), 10% Pd/C, EtOH. c) DCC, DMAP, DMAP·TFA, $CHCl_3$, reflux; 11 added over 12h, then reflux additional 4h.

The extension of this route to a hydropyran trimer with C_3-symmetry is shown in Scheme II. The bis(tetrahydropyran) **8**[12] was coupled with the hydroxy ester **9** (the antipode of **4b** in Scheme I) to give in 71% yield the pseudotrimer **10**. Hydrogenolysis of the benzyl groups proceeded in high yield to give the hydroxy acid **11**. Closure of the 21-membered macrotriolide gave **12** [dec 226-227°C, $[\alpha]_D^{23}$ -17.7 (c 0.85, $CHCl_3$)] in 63% yield. Mass spectrometric (M^+=552.3299, calcd 552.3298) and ^{13}C NMR data ($CDCl_3$, δ 170.6, 79.5, 79.1, 66.2, 37.1, 30.3, 29.8, 22.5, 13.3, 12.8) are diagnostic for this substance. Shown in Schemes I and II are X-ray crystal structures of macrodiolide **7** and macrotriolide **12**. The cavity size in **7** is indicated by the distances from O_1 to O_1' and O_2 to O_2' which are 3.73 and 3.76Å, respectively. Interestingly, the ester carbonyl oxygens in **12** determine the shortest intracavity distance O_3 to O_3' of 4.47Å. The distances for O_1 to O_1' and O_2 to O_2' are 5.74Å and 5.93Å, respectively.

Molecular modeling of macrolides **7** and **12** from the X-ray coordinates produced a minimized energy conformation for each macrocycle which differed only slightly from that present in the crystal.[13] Macrodiolide **7** thus has a 14-membered core whose conformation reflects the restrictions imposed by the *cis*-2,6-diequatorial attachments to the hydropyran rings and the preferred syn (or Z) ester conformations.[5] The 21-membered macrotriolide **12** has similar local geometrical constraints, but the larger ring is more flexible. An interesting distinction between **7** and **12** is that the carbonyls in the latter are more nearly perpendicular to the mean plane of the macrocycle.

The association constants (K_a) and binding free energies (-ΔG°) of the macrocyclic hosts **7** and **12** in $CDCl_3$ saturated with H_2O at 23-25°C were determined by measurements from the $CDCl_3$ layer using Cram's picrate extraction method (Table I).[14] The absorption maxima ($348 \le \lambda_{max} \le 362$nm) of the picrate salts are indicative of 1:1 complexes between metal picrate and macrocyclic host.[15] The macrocyclic hosts **7** and **12** do not diffuse from the $CDCl_3$ layer to the

Table I. Comparative association constants (K_a) and binding free energies ($-\Delta G°$) of macrocyclic hosts for picrate salt guests in $CDCl_3$ saturated with H_2O at 23-25°C.

	K_a (M^{-1}); $-\Delta G°$ (kcal/mol) for guests M^+			
Macrocyclic host	Li^+	Na^+	K^+	Rb^+
12-[Crown]-4	1.6×10^4; 5.7	7.3×10^3; 5.2	$<5.0 \times 10^3$; <5.0	-------
Diolide **7**	1.5×10^5; 7.0	4.6×10^4; 6.3	4.2×10^3; 4.9	-------
15-[Crown]-5[18]	1.0×10^5; 6.8	4.1×10^6; 9.0	7.7×10^5; 8.0	-------
18-[Crown]-6-(dicyclohexano)[19]	1.9×10^5; 7.2	2.3×10^6; 8.7	2.0×10^8; 11	5.1×10^6; 9.1
Triolide **12**	3.1×10^3; 4.7	6.1×10^3; 5.1	5.3×10^3; 5.1	3.4×10^3; 4.8

H_2O layer. Macrodiolide 7 exhibits significant selectivity in its complexation of the guest cations, with the preference for Li^+>Na^+>K^+ in line with expectations based upon cavity size. The association constant for the interaction of 7 with Li^+ exceeds that of 12-[Crown]-4 by one order of magnitude. The thirty-fold selectivity of 7 for Li^+ over K^+ exceeds that of 12-[Crown]-4 by a similar factor. The macrotriolide 12, with its larger and less rigid cavity, exhibits little selectivity between Li^+, Na^+, K^+, and Rb^+.

Further related studies on the solution and solid state conformations of these and similar ligands and complexes are under way, including the recognition and transport of chiral guests.[18]

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20. The diolide **7** crystallizes in the monoclinic space group P2$_1$ with cell dimensions a=9.864(3)Å, b=12.120(3)Å, c=16.858(4)Å, β=100.88(2)°, Volume=1979.2(21)Å^3. With an empirical formula $C_{20}H_{32}O_6$ and formula weight 368.5, this compound has 4 formula units per unit cell with a density of 1.237 g/mL. A single crystal with dimensions 0.3x0.3x0.3 mm was mounted on a Nicolet P3$_F$ diffractometer equipped with graphite monochromated Mo K$_\alpha$ radiation (λ=0.71073Å). Of the 6161 data measured, 2706 were unique (R_{int}=3.32%) and 2507 were observed reflections (F>5.0σ(F)) yielding R=3.25% and R_w=4.25%. Only one of the two unique molecules in the asymmetric unit is presented in Scheme I; the two molecules differ slightly in conformation.
21. The triolide **12** crystallizes in the trigonal space group P$_3$ with cell dimensions a=22.405(6)Å, c=5.498(3)Å, Volume=2390.1(16)Å^3. With an empirical formula $C_{30}H_{48}O_9$ and formula weight 552.7, this compound has 3 formula units per unit cell with a density of 1.152 g/mL. An apparently single crystal with dimensions 0.2x0.4x0.4 mm was mounted on a Syntex P1 equipped with graphite monochromated Cu K$_\alpha$ radiation (λ=1.54184Å). A total of 12335 data were measured in a complete hemisphere. Only one of the 3993 unique data (R_{int}=8.7%) was considered unobserved (F>4.0σ(F)). The molecular 3-fold axis was found to be coincident with a crystallographic 3-fold axis. The two molecules around the 3-fold axes at (1/3, 2/3, z) and (2/3, 1/3, z) appeared to be related by a 2-fold axis normal to the *c* axis. Also, the molecule around the 3-fold axis at the origin appeared to be disordered. It is presumed that the crystal investigated was twinned. Current refinements in P$_3$ gave R=19.7% and R_w=26.9%. Refinement in the space group P$_{321}$ yielded no better results. Refinement of anisotropic thermal parameters consistently yielded several non-positive definite carbons. The results reported here are for isotropic refinement in P$_3$. Attempts to locate single crystals have been unsuccessful. By symmetry, the O to O′ distance also defines the O′ to O" and O" to O distances.

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