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Cyclic Hydropyran Oligolides as Preorganized Ligand Arrays: Modular Assembly of 18-, 24-, 36-, 48-, 54- and 72-Membered Rings via Iteration and Cyclooligomerization

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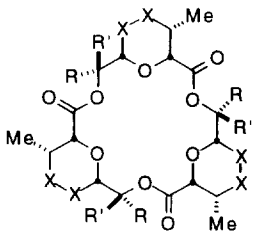
Abstract: Modular assembly routes to cyclic hydropyran oligolides of diverse structures are described. Macrolactonization of the appropriate tris(hydropyran) hydroxy acid provided compounds **1-8,** whereas macrocycles **9-13** resulted from the cyclodimerization, cyclotrimerization, and cyclotetramerization of the bis- or tris(hydropyran) seco acids, utilizing the "normal" or "modified" Yamaguchi lactonization conditions.

The design, synthesis, and study of ligand arrays for ionic and molecular recognition, transport, and sequestration are of continuing importance.[1] These efforts serve as excellent tests of current computational, preparative, structural, and analytical methods and are of broad chemical and biological relevance.[2] They are especially pertinent to the study of non-covalent interactions as structural determinants in hosts and host-guest complexes.[3] In this context, we have been investigating cyclic oligolides of hydropyran subunits as versatile ligand arrays.[4] Described in this paper are: 1) synthetic routes to cyclic hydropyran oligolides with 18-, 24-, 36-, 48-, 54-, and 72-membered rings; and 2) a striking temperature dependence in ring size selectivity.

Figure 1

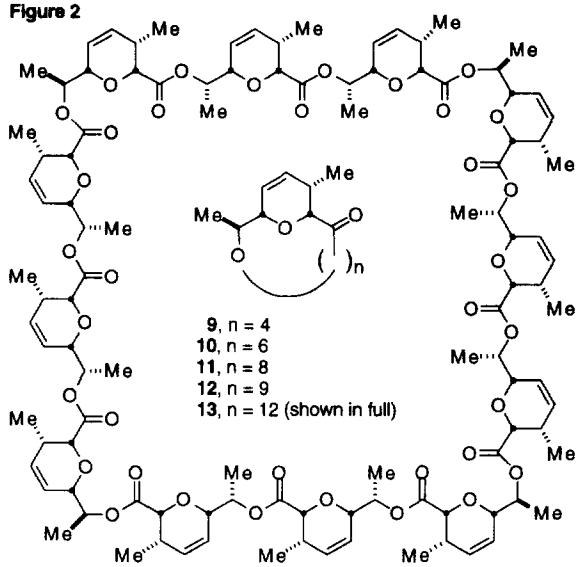


1, R = Me, R' = H, X-X = CH=CH
2, R = H, R' = Me, X-X = CH=CH
3, R = Me, R' = H, X-X = CH_2CH_2
4, R = H, R' = Me, X-X = CH_2CH_2
5, R = Ph, R' = H, X-X = CH=CH
6, R = H, R' = Ph, X-X = CH=CH
7, R = Ph, R' = H, X-X = CH_2CH_2
8, R = H, R' = Ph, X-X = CH_2CH_2

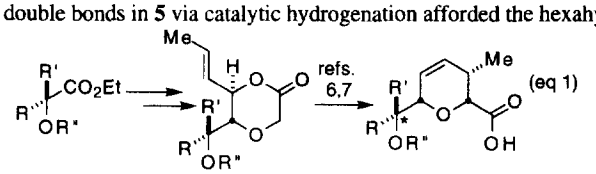
Specific hydropyran cyclic oligolides made and studied are the 18-membered ring triolides **1-8** (Fig. 1), prepared enantiomerically pure from lactic or mandelic acid esters, and the larger oligolides **9-13** (Fig. 2), all based upon a lactate-derived hydropyran module. Each representative of the first group was synthesized by an iterative sequence in which hydropyran hydroxy acid derivatives were linked via esterification reactions. The second group (Fig. 2) resulted from cyclooligomerizations of bis- and tris(hydropyran) hydroxy acids.

Conversion of protected lactate (**14**) or mandelate (**15**) esters[5] to dihydropyran modules **16-19** was accomplished via methods described previously,[6,7] as outlined in eq 1. All of these modules are depicted in the same enantiomeric series for comparison,[8] because the consequential difference[9] rests in the *relative* stereochemistry at the off-ring stereogenic center marked (*).

Figure 2



An illustration of the iterative, stepwise linking of hydropyran modules for construction of macrotriolides **1-8** (Fig. 1) is presented in Scheme I. Dihydropyran carboxylic acid module **18** is utilized three times in this sequence, beginning with the first of four Keck-Steglich (K-S) esterifications[10] to give the trichloroethyl ester **20**. Cleavage of the (β-trimethylsilyl)ethoxymethyl (SEM) ether[11] afforded hydroxy ester **21**, which was coupled with acid **18** to give pseudodimer **22**. SEM-ether cleavage unmasked alcohol **23**, which gave the pseudotrimer **24** upon K-S coupling with module **18**. Cleavage of both alcohol and acid[12] protecting groups (**24**→**25**→**26**) and intramolecular K-S coupling gave the crystalline macrotriolide **5**, with the ring closure proceeding in a noteworthy 95% yield. Saturation of the double bonds in **5** via catalytic hydrogenation afforded the hexahydro analogue **7**.[13]

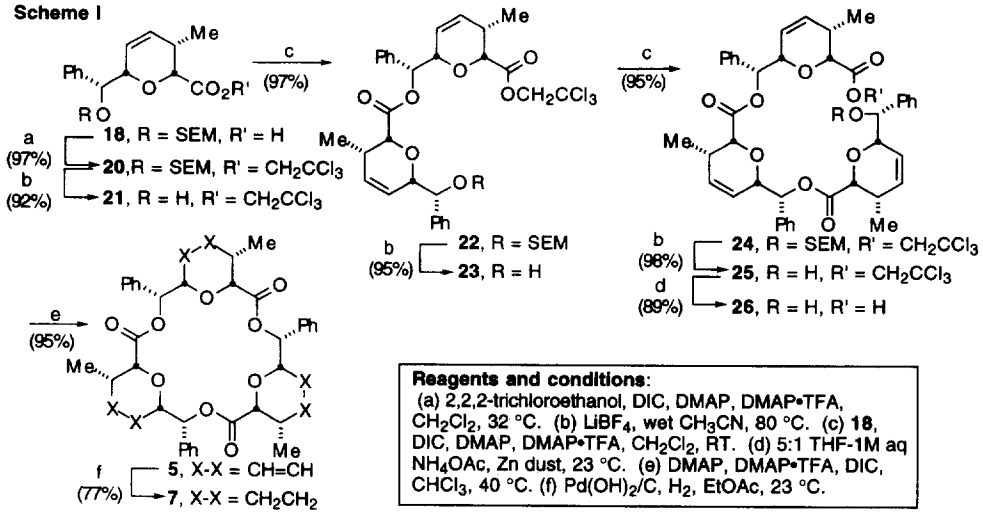


14, R = H, R' = Me, R" = BOM
15, R = Ph, R' = H, R" = SEM

16, R = H, R' = Me, R" = BOM
17, R = Me, R' = H, R" = BOM
18, R = Ph, R' = H, R" = SEM
19, R = H, R' = Ph, R" = SEM

Pseudotrimeric seco acid **27** (eq 2) exhibited intriguing reactivity upon subjection to the Yamaguchi lactonization protocol.[14] Subjection of the derived mixed anhydride **28** to "normal" Yamaguchi conditions (entry 1, Table) yielded a 3.5:1 separable mixture of the expected 18-membered triolide **2** and the 36-membered hexalide **10**.[15] Because such larger cyclic oligolides are not readily available via the iterative sequence discussed earlier, it was hoped that the fortuitous tendency of **28** to dimerize could be enhanced and exploited.[16] Based upon the assumption that dimerization to the larger ring is the entropically less-favored pathway, it was reasoned that the yield of **10** might increase if lactonization was attempted at lower temperature.[17] In the event (entry 2), a gratifying reversal of product ratio was observed upon cyclization at room temperature, with the cyclodimerization product **10** (52%) favored by 4:1 over triolide **2**. Furthermore, conditions were developed (entries 3 and 4) by which

Scheme I



cyclotrimerization and cyclotetramerization products **12** and **13** (Fig. 2) were formed directly. Entry 4 is especially intriguing, in that the 36-, 54- and 72-membered[18] oligomerization products are each formed in significantly greater quantities than the triolide **2**. Similarly, cyclodimerization, -trimerization, and -tetramerization of the bis(hydropyran) hydroxy acid **29** afforded, respectively, the 24-, 36-, and 48-membered oligolides **9**, **10**, and **11**.[15]

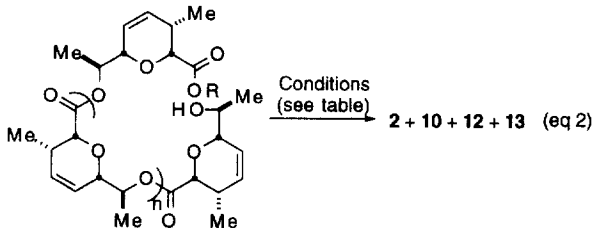


Table: Macrolactonization of **27** under "normal"[14] and "modified"[17a] Yamaguchi conditions.

	Reaction Conditions			Product Distributions(%)				
Entry	Initial [**28**]mM	Catalyst Solvent	Temp (°C)	**2**	**10**	**12**	**13**	Mass balance
1	0.98	DMAP[a] toluene	111	61	17	—	—	78
2	1.00	DMAP toluene	22	13	52	—	—	65
3	10	DMAP xylenes	22	8	38	16	—	62
4	10	4-PPY[b] o-xylene	22 → 70	3	31	19	20	73

[a]DMAP = 4-(dimethylamino)pyridine [b]PPY = 4-pyrrolodinopyridine

Conformational effects significantly influence the facility and mode of cyclization in these poly(hydropyran) seco acids. Ring closures yielding **1** and **5** proceeded in higher yields (93%, 95%) than those in the diastereomeric series leading to **2** and **6** (78%, 61%). Moreover, the seco acid precursor to **1** did not share the pronounced tendency to cyclooligomerize exhibited by diastereomeric seco acid **27** under modified Yamaguchi lactonization conditions (eq 2, Table). Observations and interpretations that clarify the relationships between structure, reactivity, and function in these synthetic macrocycles and their precursors will be presented elsewhere.[4b]

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5. BOM = benzyloxymethyl, $PhCH_2OCH_2$-; SEM = β-(trimethylsilyl)ethyoxymethyl, $Me_3SiCH_2CH_2OCH_2$-.
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8. Modules **17** and **19** and the derived macrocycles **1**, **3**, **6**, and **8** were actually prepared in the other enantiomeric series, consistent with starting esters **14** and **15**.
9. The structural and functional distinctions that result between diastereomers **1** and **2**, **3** and **4**, **5** and **6**, and **7** and **8** are discussed in ref. 4b.
10. (a) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394-2395. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522-524. (c) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069-2076.
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13. Properties of the hexahydro analogues **3**, **4**, **7**, and **8** mirrored those of their respective parents **1**, **2**, **5**, and **6**. Alternative transformations of the alkene moieties will be reported elsewhere.
14. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.
15. Because of constitutional symmetry and conformational flexibility in solution, the NMR spectra of **2**, **9**, **10**, **11**, **12**, and **13** are not mutually distinctive. Structural assignments of these macrocycles, readily separable by silica gel chromatography, are based upon crystallographic and/or FAB (liquid SIMS) mass spectrometric analyses.
16. For observations regarding cyclooligomerization of (*R*)-3-hydroxybutanoic acid via the Yamaguchi protocol, see: Seebach, D.; Brändli, U.; Schnurrenberger, P.; Przybylski, M. *Helv. Chim. Acta* **1988**, *71*, 155-167.
17. (a) For "modified" Yamaguchi lactonization conditions, see: Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9. (b) For a related temperature dependence in monomer versus dimer formation, see: Hammond, P. J.; Beer, P. D.; Hall, C. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1161-1163.
18. These large cyclic oligomers do not interconvert under the reaction conditions, suggesting that their formation is a kinetically-controlled process.

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