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The *cis*-2-alkyl-3-oxy-tetrahydropyran unit as a building block for new ionophores with C_2-symmetry ☆

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Dedicated to Professor Julius Rebek, Jr. on the occasion of his 60th birthday

Abstract—The use of *cis*-2-alkyl-3-oxy-tetrahydropyran unit is reported as a novel structure for the design and synthesis of a new type of ionophore with C_2-symmetry. The synthesis of five macrolides and their complexation properties were investigated. The template effect as an effective tool to improve the selectivity and yield in the macrolactonization process is described.

In living systems, molecular recognition is at the origin of highly selective chemical reactions and transport phenomena. The study of synthetic model systems contributes to the understanding of these processes and, at the same time, offers new perspectives for controlling specificity and reactivity in chemistry. Over the last 30 years, a great number of functional groups have been incorporated into the design of new cation receptors. Tetrahydropyrans are widely found in known natural ionophores[1–3] and have been frequently used as elements in cation recognition[4,5] since they confer more rigidity and new properties to the systems. Thus, mention can be made of the molecules designed and synthesized by Okada and co-workers[6] and Burke and co-workers,[7] which are chorand-type cyclooligolides that incorporate tetrahydropyran units in their structures. On the other hand, Still and co-workers designed and synthesized a podand-type system of linked tetrahydropyran rings whose conformation is controlled by the presence of methyl groups at C-3.[8] However, all these receptors use the tetrahydropyran rings linked through positions C-2 and C-6.

Considering the well-established relationship between ladder toxins and metallic cations,[9] we have directed our attention to the search for simple models of fused tetrahydropyrans that allows us to establish a relationship between structure–activity and binding capacity of polyether toxins. Thus, we focused our attention on the 2-alkyl-3-oxy-tetrahydropyran unit as a masterpiece for the design of new ionophores. This structural unit is widely displayed in polyether toxins of marine origin, and is generally in *trans* disposition (Fig. 1).

This configuration has the oxygens directed towards the opposed faces, generating a practically flat system,[10] that may not be well adapted for the cation recognition. Alternatively, the *cis* configuration can preferably be found in two conformations, one with the 3-oxy group

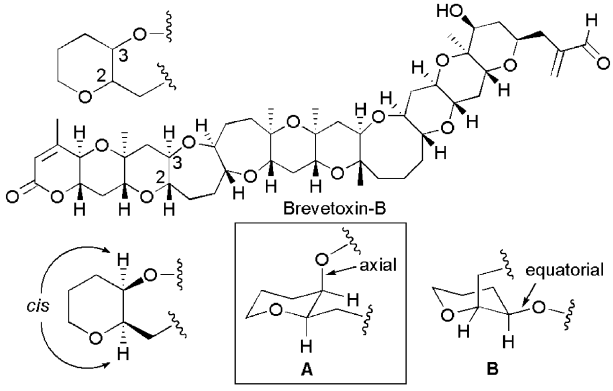

Figure 1.

Keywords: Ionophores; Lariat ethers; Template effect.

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axial (**A**), such that both oxygens go to the same face, and the other one with this group equatorial (**B**), forcing both oxygens to be located on opposite faces, the first of these being the one that may generate the suitable curvature, so that both oxygens can participate in the recognition.

On the other hand, it is well known that the best and easiest way to maintain the chirality of a unit is by transforming this into a molecule with C_2-symmetry. How can molecules that display C_2-symmetry be generated from this unit of recognition? To accomplish this, we linked the oxy group of a unit with the alkyl group of the other, using identical spacers (Fig. 2a). Thus, we designed the tricyclic diolide **1**, structurally characterized by the presence of two *cis*-tetrahydropyran units, linked by two 2-oxy-acetyl groups as spacers, forming a 14-membered macrodiolide (Fig. 2).

Using the same design, and in order to check the importance of the configuration of the 2-alkyl-3-oxy-tetrahydropyran moieties, we decided to synthesize compound **2**, which displays the *trans* fusion. In principle this structure can be considered to be a formal ether lariat, where the central macroring is a formal 14-crown-4 and the tetrahydropyran rings are the sidearms that confer greater conformational rigidity and whose oxygens can participate in the complexation. From modelling,[11] it can be predicted that the *cis* fusion could create a hydrophilic concave face where the oxygen atoms could act as ligands wrapping the cation guest and a hydrophobic convex face where the carbon skeleton is on the outer surface (Fig. 2b). However, the *trans* fusion shows a practically flat structure (Fig. 2c). Additionally, we synthesized the central 14-membered macrodiolide **3** to verify that metal complexation does not take place in the macrocyclic plane.

Retrosynthetic analyses for macrodiolides **1** and **2** are shown in Figure 3. Macrodiolides **1** and **2** were envisioned as being synthesized from two suitable hydroxy-acids **4** or **6** ($R_1 = R_2 = H$), by an intermolecular esterification followed by macrolactonization. Tetrahydropyrans **4** or **6** could be obtained from the commercially available tri-*O*-acetyl-D-galactal and tri-*O*-acetyl-D-glucal, respectively.

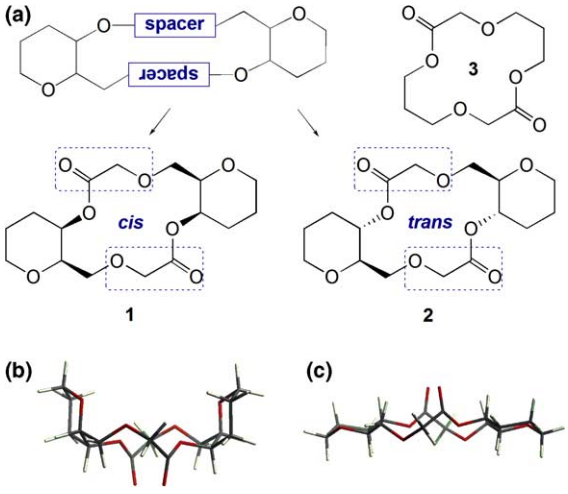


Figure 2. (a) General design of molecules with C_2-symmetry. (b) Molecule **1** in the suitable conformation such that cation recognition may take place (U-shaped). (c) Low-energy conformation of molecule **2**.

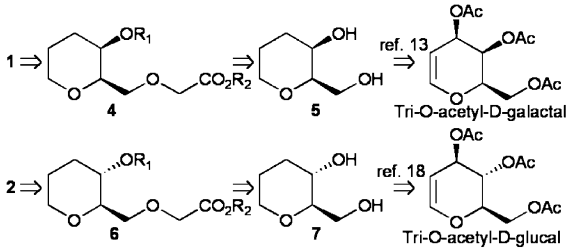
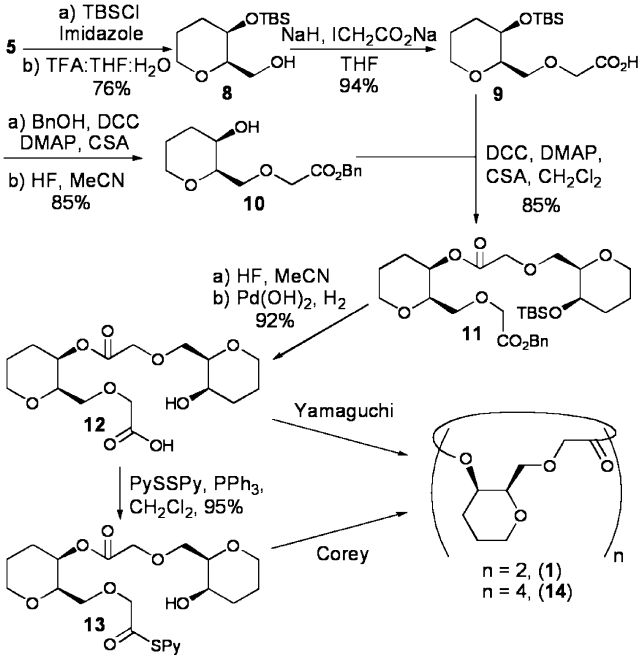


Figure 3. Retrosynthetic analysis for macrodiolides **1** and **2**.

The direct dimerization approach of **4** or **6** ($R_1 = R_2 = H$), however, is entropically unfavourable, affording the lactonization product, even using 2-chloro-1,3-dimethylimidazolinium chloride in presence of DMAP or NaH or KH in CH_2Cl_2.[12] To overcome this difficulty, a convergent strategy was applied: iterative esterification couplings of two suitably functionalized tetrahydropyran units **4** or **6** (R_1 or $R_2 = H$), followed by macrolactonization of the resulting hydroxy-acid. Thus, to carry out the synthesis of compound **1** (Scheme 1), the diol **5**[13] was protected, as the bis-silyl ethers, followed by selective deprotection of the silyl ether of the primary alcohol to afford the *cis*-alcohol **8**, which was alkylated with sodium iodoacetate to provide the carboxylic acid **9**. Esterification of **9** with benzyl alcohol and further deprotection of the *tert*-butyl-dimethylsilyl (TBS) ether afforded the hydroxy ester **10**. Coupling of acid **9** with hydroxy ester **10** gave pseudodimer **11**.



Scheme 1.

Cleavage of both alcohol and acid protecting groups afforded the hydroxy acid **12**, which was transformed into the thioester **13**. Unfortunately, **13** under Corey and Nicolaou macrolactonization conditions,[14] afforded exclusively the macrotetraolide **14**.

However, when compound **12** was treated under Yamaguchi and co-workers conditions,[15] the macrodiolide **1** was obtained in 20% yield along with **14** in 40% yield.[16] The template effect improved selectivity and yield in the macrolactonization (vide infra). Using the diol **6**[17] and applying the same sequence of reactions described above, we obtained the receptor **2** and the macrotetraolide **15** (*trans* isomer of **14**), using Yamaguchi conditions in the cyclization step, with 55% and 35% yields, respectively. The same strategy was applied to obtain compound **3**, using as starting material 3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol. The structures of the macrolides were unambiguously determined by NMR spectroscopy (^{1}H and ^{13}C) and FAB mass spectrometry.[18]

The association constants (K_a) of the macrodiolides **1**, **2** and **3**, and the macrotetraolides **14** and **15** in $CHCl_3$ saturated with water at 23–25 °C were determined by measurements from the $CHCl_3$ layer using Cram's picrate extraction method (Table 1).[19] The absorption maxima in $CHCl_3$ ($352 < \lambda_{max} < 359$ nm) of the picrate salts are indicative of 1:1 complexes between metal picrate and the host macrolides.[20] The results of Table 1 show that the only substrate that displays moderate association constants is **1**, and that in addition it is slightly specific for Na^+ and K^+ ($Na^+/Li^+ = 5.4$, $K^+/Li^+ = 3.5$).

It should be emphasized that the configuration of the tetrahydropyrans is of extreme importance, since when this is *trans*, no extraction was observed. This implies that the *cis*-tetrahydropyran oxygen participates in the recognition process and this along with the null complexation observed by macrodiolide **3** allows us to conclude that the complexation in **1** takes place out of the macrodiolide plane, like a clamp-type rather than a chorand-type ionophore, despite the fact that **1** is a macrocycle. This is in agreement with the association constant values and with the minimized structures shown in Figure 2b and c. Host **1** wraps the metal cation and can change the cavity size according to the metal cation size, so that it shows comparable binding ability to all alkali metal cations. Interestingly, in macrotetraolides the result is reversed, *trans* being better than *cis*, perhaps as a result of folding of compound **15** over ion K^+.

In addition, we observed that the conformation of the tetrahydropyrans of compound **1** is the same before and after the complexation. In the free receptor, the NOE effects ($CDCl_3$) indicate that a large number of molecules have the tetrahydropyran rings in the **A** conformation (Fig. 1), that implies a partially preorganized system. Thus, when one deals with potassium thiocyanate and ultrasound, to form the complex $\mathbf{1}\cdot K^+$ ($CDCl_3$),[21] the NOE effects continue as before, although changes take place in the chemical shift of the signals in the proton (Fig. 4) and carbon NMR spectra. This, along with the value of the association constant, allows us to conclude that almost all the molecules adopt the U-shaped conformation in the complex (Fig. 2b) and that the change in the chemical shift must be mainly due to the change in conformation of the flexible part of the molecule, that is to say, the 14-membered macrodiolide.

Finally, in view of the low yields obtained in the macrolactonization process, and considering the association constants observed for **1** and **14**, we decided to explore the possible template effect that could be exerted by metallic cations in the cyclization step. In our first attempt we used the standard Yamaguchi conditions, method A (Table 2). The addition of an alkali metal cation did not improve yield and selectivity, thus the solvent was changed to a more polar one, dichloromethane (method B). In this case the use of K_2CO_3

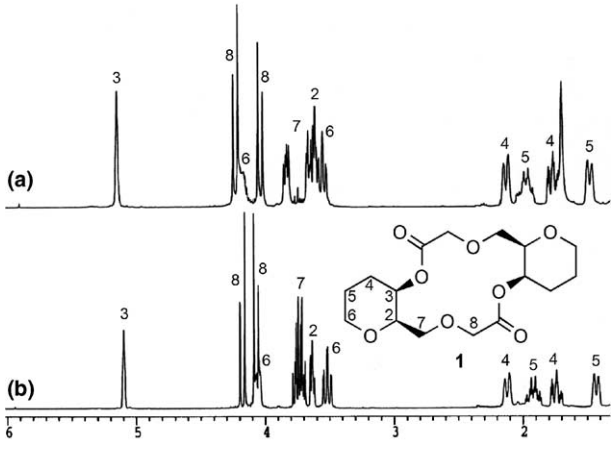


Figure 4. ^{1}H NMR induced shifts of host **1** by binding KSCN at 298 K in $CDCl_3$. (a) Host **1**. (b) Complex $\mathbf{1}\cdot K^+$.

Table 1. Association constants K_a (M^{-1}) of macrolides[a,b]

Host	Li^+	Na^+	K^+	NH_4^+	Cs^+
1	4.6×10^3	2.5×10^4	1.6×10^4	2.0×10^3	2.0×10^3
2	—	—	—	—	—
3	—	—	—	—	—
14	—	—	—	—	—
15	—	—	2.3×10^3	—	—

[a] These values are the average of three independent measurements.
[b] '—' Means that no extraction was observed.

Table 2. Template effect

Substrate	Method[a]	Solvent (M)	Additive (equiv)	Time	Yield[b] (%)	**1**:**14**
12	A	Toluene (0.001)	—	6 h	60	33:67
12	B	CH_2Cl_2 (0.002)	K_2CO_3 (20)	22 h	65	87:13
13	C	Toluene (0.001)	—	1 d	50	0:100
13	C	CH_2Cl_2 (0.002)	—	7 d	—	—
13	C	CH_2Cl_2 (0.002)	Na_2CO_3 (20)	9 d	55	65:35
13	C	CH_2Cl_2 (0.002)	K_2CO_3 (20)	7 d	95	87:13

[a] *Method A:* Et_3N (2 equiv), 2,4,6-trichlorobenzoyl chloride (1.3 equiv) in THF (0.01 M), then was diluted with toluene (0.001 M) and poured over DMAP (10 equiv) in boiling toluene. *Method B:* Et_3N (2 equiv), 2,4,6-trichlorobenzoyl chloride (1.3 equiv) in CH_2Cl_2 (0.01 M), then was diluted with CH_2Cl_2 (0.002 M) and K_2CO_3 (20 equiv) was added and the mixture was warmed up to reflux. *Method C:* reflux.
[b] Yields corresponding to compounds **1** + **14**.

enhanced selectivity, but this reaction was difficult to reproduce and follow by TLC. Then we decided to explore the macrolactonization using thioester **13** (method C). It is noteworthy that without any cation, no cyclization product was detected. After several trials, we found that better selectivity and yields of compound **1** versus **14** were achieved in boiling dichloromethane with potassium carbonate, where the K^+ acts as a template, preorganizing the cyclization precursor for macrolactonization, favouring the formation of **1** (95% yield, **1**:**14** = 6.7) (Table 2). To the best of our knowledge, this is the first time that the Corey macrolactonization reaction is used under alkali metal cation template. It should be emphasized that the best guest (Na^+) for host **1** is not the best template for its formation. This can be because the cavity size of the transition state conducive to compound **1** is slightly greater than the cavity of the final product.

In summary, we have used a new structural unit for the design of ionophores. Host **1** behaves like a clamp-type ionophore, where the recognition takes place out of the macrocyclic plane, with assistance of *cis*-tetrahydrofuran oxygen. The template effect has been proved to be a useful tool to improve the yield and selectivity in the synthesis of macrodiolide **1**. Chiral discrimination and biological activities of these compounds are being evaluated. In addition, this design can be used to obtain new receptors, by simply changing the nature and length of the spacers.

Supplementary materials

^1H, ^{13}C NMR and FAB spectra for compounds **1**, **1**·K^+, **2**, **3**, **14** and **15**; COSY, HSQC, NOEs spectra for compounds **1** and **1**·K^+ are available.

Acknowledgements

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18. Compound **1**: $[\alpha]_D^{25}$ −31.2 (*c* 0.33, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 1.41 (d, $J = 12.6$ Hz, 2H), 1.68–1.77 (m, 2H), 1.85–1.97 (m, 2H), 2.10 (d, $J = 14.2$ Hz, 2H), 3.50 (ddd, $J = 1.8$, 1.8, 11.8 Hz, 2H), 3.62 (dd, $J = 5.4$, 5.4 Hz, 2H), 3.67–3.77 (m, 4H), 4.05 (d, $J = 14.2$ Hz, 4H), 4.16 (d, $J = 14.3$ Hz, 2H), 5.08 (s, 2H); ^{13}C NMR (δ, $CDCl_3$): 20.6 (t), 27.2 (t), 68.1 (t), 68.2 (d), 70.4 (t), 70.8 (t), 76.2 (d), 169.4 (s); IR (film) (cm^{-1}): 2928, 2854, 1736, 1217, 1095; MS (FAB) *m*/*z* (relative intensity): 367 $[M+Na]^+$ (19), 147 (6), 135 (8), 109 (12), 81 (51), 69 (100); HRMS (FAB): calcd for $C_{16}H_{24}O_8Na$ $[M+Na]^+$: 367.1369, found: 367.1387. Compound **2**: mp 108–111 °C; $[\alpha]_D^{25}$ +44.1 (*c* 1.4, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 1.18–1.23 (m, 1H), 1.45–1.75 (m, 6H), 2.26–2.31 (m, 1H), 3.41 (ddd, $J = 3.1$, 11.4, 11.4 Hz, 1H), 3.48–3.68 (m, 3H), 3.93–3.98 (m, 2H), 4.29 (d, $J = 16.9$ Hz, 1H), 4.50 (ddd, $J = 4.9$, 10.3, 10.3 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$): 24.6 (t), 29.1 (t), 67.6 (t), 68.8 (t), 69.3 (d), 71.9 (t), 78.7 (d), 169.6 (s); IR (film) (cm^{-1}): 2949, 2863, 1734, 1261; MS (FAB) *m*/*z* (relative intensity): 367 $[M+Na]^+$ (7), 345 $[M+H]^+$ (30), 307 (14), 173 (31), 97 (93); HRMS (FAB): calcd for $C_{16}H_{25}O_8$ $[M+H]^+$: 345.1549, found: 345.1558. Compound **3**: mp 134–136 °C; ^1H NMR (δ, $CDCl_3$): 1.97 (dddd, $J = 5.6$, 5.6, 5.6, 5.6 Hz, 2H), 3.66 (dd, $J = 5.9$, 5.9 Hz, 2H), 4.11 (s, 2H), 4.38 (dd, $J = 5.5$, 5.5 Hz, 2H); ^{13}C NMR (δ, $CDCl_3$): 28.5 (t), 60.8 (t), 66.8 (t), 69.1 (t), 170.7 (s); MS (FAB) *m*/*z* (relative intensity): 255 $[M+Na]^+$ (4), 233 $[M+H]^+$ (24), 154 (100), 137 (73); HRMS (FAB): calcd for $C_{10}H_{17}O_6$ $[M+H]^+$: 233.1025, found: 233.1035. Compound **14**: mp 135–139 °C; $[\alpha]_D^{25}$ −42.7 (*c* 1.4, $CHCl_3$); ^1H NMR (δ, $CDCl_3$): 1.40 (d, $J = 13.0$ Hz, 4H), 1.57–1.92 (m, 8H), 2.06 (d, $J = 13.4$ Hz, 4H), 3.32–3.68 (m, 12H), 3.99 (m, 4H), 4.05 (d, $J = 16.8$ Hz, 4H), 4.21 (d, $J = 16.8$ Hz, 4H), 5.01 (s, 4H); ^{13}C NMR (δ, $CDCl_3$): 20.5 (t), 27.6 (t), 68.0 (d), 68.2 (t), 71.4 (t), 77.2 (d), 169.8 (s); IR (film) (cm^{-1}): 2954, 2855, 2362, 1751, 1437, 1202, 1132, 1094; MS (FAB) *m*/*z* (relative intensity): 711 $[M+Na]^+$ (8), 367 (5), 173 (16), 97 (100), 69 (17); HRMS (FAB): calcd for $C_{32}H_{48}O_{16}Na$ $[M+Na]^+$: 711.2840, found: 711.2793. Compound **15**: mp 152–155 °C; $[\alpha]_D^{25}$ +28.2 (*c* 1.3, $CHCl_3$); ^{1} H NMR (δ, $CDCl_3$): 1.48 (dddd, $J = 4.6$, 12.0, 12.0, 12.0 Hz 4H), 1.68–1.80 (m, 8H), 2.16–2.20 (m, 4H), 3.34–3.46 (m, 8H), 3.54 (dd, $J = 6.0$, 10.0 Hz, 4H), 3.73 (d, $J = 10.0$ Hz, 4H), 3.95 (d, $J = 10.6$ Hz, 4H), 4.11 (dd, $J = 17.0$, 17.0 Hz, 8H), 4.76 (ddd, $J = 4.7$, 10.4, 10.4 Hz, 4H); ^{13}C NMR (δ, $CDCl_3$): 24.8 (t), 29.1 (t), 67.7 (t), 68.6 (t), 68.7 (d), 71.5 (t), 78.7 (t), 169.5 (s), 20.5 (t), 27.6 (t), 68.0 (d), 68.2 (t), 71.4 (t), 77.2 (d), 169.8 (s); IR (film) (cm^{-1}): 2949, 2857, 1753, 1456; MS (FAB) *m*/*z* (relative intensity): 711 $[M+Na]^+$ (66), 689 $[M+H]^+$ (11), 173 (14), 136 (39), 97 (100), 73 (28); HRMS (FAB): calcd for $C_{32}H_{49}O_{16}$ $[M+H]^+$: 689.3021, found: 689.2986.
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21. Complex **1**·K^+: ^1H NMR (δ, $CDCl_3$): 1.47 (d, $J = 13.7$ Hz, 2H), 1.76 (m, 2H), 1.96 (m, 2H), 2.12 (d, $J = 14.4$ Hz, 2H), 3.54 (ddd, $J = 2.1$, 11.9, 11.9 Hz, 2H), 3.60 (m, 2H), 3.64 (dd, $J = 3.9$, 9.7 Hz, 2H), 3.82 (dd, $J = 5.8$, 9.7 Hz, 2H), 4.02 (d, $J = 14.3$ Hz, 2H), 4.16 (m, 2H), 4.21 (d, $J = 14.3$ Hz, 2H), 5.13 (s, 2H); ^{13}C NMR (δ, $CDCl_3$): 20.6 (t), 27.5 (t), 68.6 (t), 69.1 (d), 70.5 (t), 71.4 (t), 76.3 (d), 169.0 (s); MS (FAB) *m*/*z* (relative intensity): 383 $[M+K]^+$ (100), 367 $[M+Na]^+$ (10), 154 (14), 136 (15), 95 (14), 69 (36); HRMS (FAB): calcd for $C_{16}H_{24}O_8K$ $[M+K]^+$: 383.11083, found: 383.11134.