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# MACROCYCLISATION: THE TIN DIRECTED REACTION OF A CARBOHYDRATE DERIVATIVE WITH SUCCINYL CHLORIDE

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**Abstract:** Condensation of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-*D*-glucopyranoside with succinyl chloride furnished two macrocyclic tetralactones, a hexalactone and an octalactone.

The synthesis of chiral crown ethers incorporating sugar units have received considerable attention in the past decade.[1] As part of our continued interest in the regioselective activation of carbohydrate hydroxyl groups using organotin reagents,[2] we have started an investigation on the synthesis of carbohydrate-derived macrocycles based on the use of tin derivatives as covalent templates.[3] More specifically, results described by Shanzer[4] suggested the possibility that the condensation of dicarboxylic acid chlorides with carbohydrate 1,2-diols *via* the use of tin covalent templates may furnish potential siderophores, i.e. macrocycles (including ionophores) with chelating side chains. We now describe the condensation products of methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-*D*-glucopyranoside (**1**)[5] with succinyl chloride.

A solution of **1** in toluene was prepared by the reaction of methyl 4,6-*O*-benzylidene-α-*D*-glucopyranoside with dibutyltin oxide. The addition of 1 mol equiv. of succinyl chloride at ambient temperature yielded a mixture of four macrocyclic lactones in 69% overall yield together with oligomers which have carboxylic acid residues. The macrocyclic lactones were separated by chromatography over silica.[6] E.I.- and F.A.B.-mass spectra revealed the products, obtained in a m/m proportion of 78:14:5:3, to be two tetra-, a hexa- and an octalactone. We were able to determine the structure of each of these products with the use of $^1$H- and $^{13}$C-nmr together with symmetry considerations.

There are two possible constitutionally isomeric tetralactones, both with $C_2$-symmetry. The determination of the constitutional structure of such compounds has at times been formidable.[1] Stoddart and co-workers[7] made use of the fact that the parallel isomer of their macrocyclic ether analogue has homotopic faces and the antiparallel isomer, heterotopic faces. Shanzer and co-workers[8,9] showed that analogous parallel tetralactones, at least in certain instances, can be distinguished on the basis of differences in the $^{13}$C-signals of their unsymmetrical diacid moieties. On the other hand, we have observed that the unsymmetrical succinyl moieties in structure **2**, the major tetralactone, can be readily identified by $^1$H-nmr spectroscopy. The 500 MHz $^1$H-nmr spectrum of **2** displays two superimposed AA'BB'-spinsystems which belong to two discrete succinyl moieties, respectively bisected by an axis of symmetry. In contrast, the same region in the $^1$H-nmr spectrum of the minor tetralactone indicated a dissymmetrical ABCD-spinsystem, confirming it to be **3**.

Only two hexalactones can be formulated as schematically represented in Fig. 1 (in which the arrows represent the dissymmetric glucosidic moieties). One with $C_3$-, and the other with no symmetry. Both $^1$H- and $^{13}$C-nmr revealed three sets of resonances for the glucosidic and succinate moieties in the respective spectra,

thus proving the hexalactone to be without symmetry, i.e. **4**.

Finally, four possible octalactones can be formulated as schematically represented in Fig. 2 together with the relevant symmetry elements. The $^1$H-nmr spectrum of the octalactone displayed a single and well defined set of signals belonging to the identical glucosidic moieties. A thorough investigation of the succinate signals once again revealed two superimposed discrete AA'BB'-spinsystems. These data when taken together with symmetry considerations are consistent only with structure c (Fig. 2), i.e. **5**.

The results described above were unexpected since the condensation of diacid chlorides or acid anhydrides with stannylene derivatives of vicinal diols have thus far yielded single macrocyclic tetralactones only.[3,4] Optically pure chiral diols furnished parallel tetralactones only.[8] Conversely, racemic mixtures of chiral diols furnished mesomeric antiparallel tetralactones exclusively, i.e. with $C_i$-symmetry.[8,9] Compound **3** is thus the first antiparallel tetralactone with a single $C_2$ axis of symmetry to be synthesised using the covalent tin template, and **4** and **5** are the first macrocycles with more than four lactone groups to be synthesised by this method.

A study of the effects of reaction conditions on the product distribution showed that lowering the reaction temperature to -30°C favoured formation of **4** and **5**. Under these conditions **4** is the major product. Formation of **5** was also considerably increased by the slow addition of the acid chloride or by the use of **1** in excess. In contrast, formation of **4** was enhanced by the use of an excess of the acid chloride. The kinetics and reaction mechanism of these condensation reactions are presently under investigation with the view to further improvements in hexa- and octalactone formation.

**ACKNOWLEDGEMENT**: We thank the South African Foundation for Research Development for financial support.

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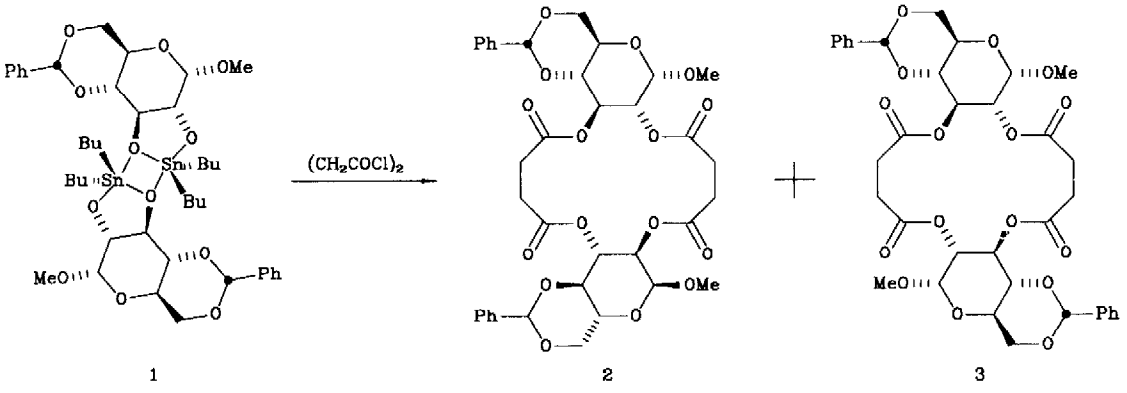
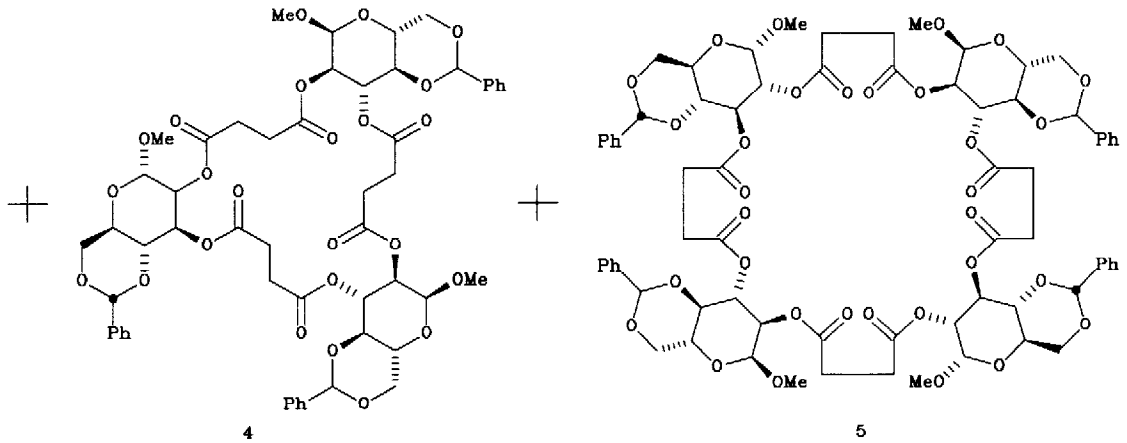
6. The four products have the following physical properties ($^{13}$C-nmr signals were assigned using HETCORR): compound **2** mp 198-200°C, $\alpha_D^{27}$ +57,6° (*c* 0,93; $CHCl_3$), $\delta_H$ ($CDCl_3$) 2,429-2,842 (m, 8H, 2x$CH_2CH_2$), 3,387 (s, 6H, MeO), 3,691 (t, 2H, J=9,7 Hz, H-4), 3,751 (t, 2H, J=10,3 Hz, H-6ax), 3,891 (td, 2H, J=9,9 and 4,8 Hz, H-5), 4,280 (dd, 2H, J=10,3 and 4,8 Hz, H-6eq), 4,785 (dd, 2H, J=9,8 and 3,6 Hz, H-2), 4,984 (d, 2H, J=3,8 Hz, H-1), 5,480 (t, 2H, J=9,7 Hz, H-3), 5,490 (s, 2H, CHPh), and 7,303-7,436 (m, 10H, H-arom.), $\delta_C$ ($CDCl_3$) 28,88 and 29,34 (2xt, 2x$CH_2CH_2$), 55,41 (q, MeO),




1 2 3




4 5

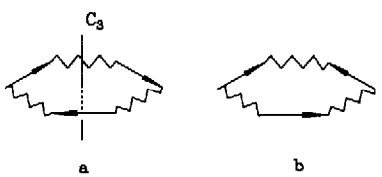



Fig 1

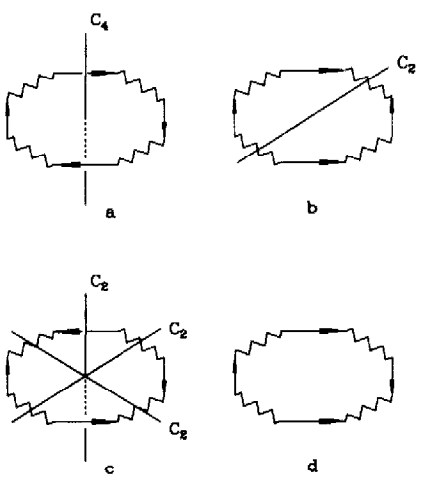



Fig 2

62,17 (d, C-5), 68,81 (t, C-6), 69,90 (d, C-3), 72,74 (d, C-2), 78,55 (d, C-4), 97,45 (d, C-1), 101,71 (d, CHPh), 126,21 and 128,20 (2xd, C-*o*- and *m*-arom.), 129,13 (d, C-*p*-arom.), 136,88 (s, C-*ipso*-arom.) and 170,68 and 171,44 (2xs, 4xCOO); compound **3** mp 227-229°C, $\alpha_D^{24}$ +8,4° (*c* 1,50; $CHCl_3$), $\delta_H$ ($CDCl_3$) 2,465-2,869 (m, 8H, $2xCH_2CH_2$), 3,376 (s, 6H, MeO), 3,736 (t, 2H, J=9,6 Hz, H-4), 3,786 (t, 2H, J=9,9 Hz, H-6ax), 3,861 (td, 2H, J=10,0 and 3,4 Hz, H-5), 4,286 (dd, 2H, J=9,4 and 4,0 Hz, H-6eq), 4,644 (dd, 2H, J=9,9 and 3,7 Hz, H-2), 5,073 (d, 2H, J=3,7 Hz, H-1), 5,515 (t, 2H, J=9,7 Hz, H-3), 5,529 (s, 2H, CHPh) and 7,318-7,444 (m, 10H, H-arom.), $\delta_C$ ($CDCl_3$) 29,70 and 30,21 (2xt, $2xCH_2CH_2$), 55,38 (q, MeO), 62,23 (d, C-5), 68,76 (t, C-6), 69,66 (d, C-3), 72,77 (d, C-2), 78,62 (d, C-4), 97,22 (d, C-1), 101,67 (d, CHPh), 126,15 and 128,25 (2xd, C-*o*- and *m*-arom.), 129,15 (d, C-*p*-arom.), 136,86 (s, C-*ipso*-arom.) and 170,10 and 171,28 (2xs, 4xCOO); compound **4** mp 180-182°C (amorph.), $\alpha_D^{24}$ +91,6° (*c* 1,05; $CHCl_3$), $\delta_H$ ($CDCl_3$) 2,415-3,025 (m, 12H, $3xCH_2CH_2$), 3,379, 3,450 and 3,464 (3xs, 3x3H, 3xMeO), 3,584, 3,590 and 3,597 (3xt, 3H, 3xH-4), 3,758, 3,764, and 3,774 (3xt, 3H, 3xH-6ax), 3,895, 3,919 and 3,924 (3xtd, 3H, 3xH-5), 4,280, 4,287 and 4,289 (3xdd, 3H, 3xH-6eq), 4,880 (dd, 1H, H-2), 4,889, 4,898 and 4,906 (3xd, 3H, 3xH-1), 4,926 and 4,982 (2xdd, 2x1H, 2xH-2), 5,457, 5,466 and 5,488 (3xs, 3x1H, 3xCHPh), 5,547 and 5,605 (2xt, 2H and 1H resp., 3xH-3) and 7,310-7,450 (m, 15H, H-arom.), $\delta_C$ ($CDCl_3$) 26,82, 27,82, 28,86, 29,05, 29,69 and 30,21 (6xt, $3xCH_2CH_2$), 55,42, 55,66 and 55,78 (3xq, 3xMeO), 62,18, 62,75 and 62,86 (3xd, 3xC-5), 68,19, 68,37 and 68,77 (3xd, 3xC-3), 2x68,83 and 68,96 (2xt, 3xC-6), 70,80, 71,19 and 71,46 (3xd, 3xC-2), 78,93, 79,09 and 79,26 (3xd, 3xC-4), 97,81, 97,86 and 98,00 (3xd, 3xC-1), 101,57 (d, 3xCHPh), 126,15, 126,21 126,27 and 3x128,23 (4xd, 3xC-*o*- and 3x*m*-arom.), 3x129,08 (d, 3xC-*p*-arom.), 136,76, 136,88 and 136,99 (3xs, C-*ipso*-arom.) and 171,38, 171,46, 171,53, 2x171,70 and 172,31 (5xs, 6xCOO); and compound **5** mp > 250°C, $\alpha_D^{24}$ +51,2° ($CHCl_3$), $\delta_H$ ($CDCl_3$) 2,569-2,772 (m, 16H, $4xCH_2CH_2$), 3,351 (s, 12H, 4xMeO), 3,612 (t, 4H, J=9,6 Hz, H-4), 3,757 (t, 4H, J=10,3 Hz, H-6ax), 3,908 (td, 4H, J=9,9 and 4,8 Hz, H-5), 4,282 (dd, 4H, J=10,2 and 4,8 Hz, H-6eq), 4,825 (d, 4H, J=3,6 Hz, H-1), 4,932 (dd, 4H, J=10,2 and 3,6 Hz, H-2), 5,484 (s, 4H, CHPh), 5,518 (t, 4H, J=10,0 Hz, H-3), and 7,318-7,490 (m, 20H, H-arom.), $\delta_C$ ($CDCl_3$) 29,01 and 29,09 (2xt, $4xCH_2CH_2$), 55,41 (q, MeO), 62,62 (d, C-5), 68,90 (t, C-6), 69,06 (d, C-3), 71,15 (d, C-2), 79,35 (d, C-4), 97,87 (d, C-1), 101,73 (d, CHPh), 126,28 and 128,29 (2xd, C-*o*- and *m*-arom.), 129,03 (d, C-*p*-arom.), 136,98 (s, C-*ipso*-arom.) and 170,93 and 171,65 (2xs, 8xCOO).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