Observations on Dibutylstannylene as Template for the Assembly of Macrocyclic Oligolactones[1]

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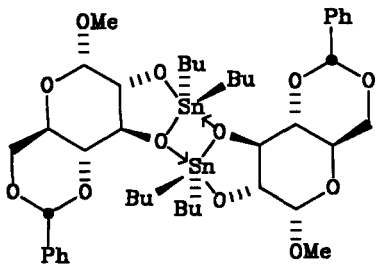
Dibutylstannylene-mediated macrolactonization of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**2**) with glutaryl and phthaloyl dichloride yields the respective dilactones **6e** and **6f** and parallel tetralactones **5e** and **5f** as well as the antiparallel tetralactone **4e** in the case of glutarylation. The reaction with malonyl dichloride yields a negligible amount of the parallel tetralactone **5d** and that of fumaryl and isophthaloyl dichloride yields polyesters only, a byproduct in all these reactions. The mechanism of stannylene-mediated macrolactonization is discussed incorporating data pertaining to known hexa- and octalactone formation when succinyl dichloride is used. A correlation between stannylene dimer symmetry and tetralactone constitutional isomer selectivity is introduced.

Tin oxides, dibutyltin oxide in particular, have evoked much interest due to their remarkable ability to selectively activate specific hydroxy groups of mono-[2–4] and disaccharide[4,5] derivatives. Recently it has been shown that the protecting groups of terminally protected open-chain arabinose derivatives determine the position of acylation following dibutylstannylene activation[6]. Furthermore, the solvent plays a discrete role in directing the acylation of certain pyranoside derivatives[3]. The reaction of structurally non-symmetric and/or chiral 1,3,2-dioxastannolane derivatives (see **1** for example) with dicarboxylic acid dichlorides yields macrocyclic tetralactones[7] and shows discrete constitutional and/or enantiomer selectivity. Enantiomeric dioxastannolane derivatives, for example, yield the parallel enantiomeric tetralactones, while the racemates of the same dioxastannolane derivatives yield the antiparallel *meso*-tetralactones[8,9]. This selectivity was rationalized in terms of a stannylene template model based on the aptitude of dioxastannolanes to aggregate in order to expand the coordination number of the tin atom. The template model for tetralactone formation has, however, been challenged by Roelens and co-workers who studied oligolactone formation using other stannylene derivatives[10]. These conclusions were based on evidence that all four possible constitutional and stereoisomers were obtained when treating racemic dioxastannolanes with diacid dichlorides. Roelens was, how-



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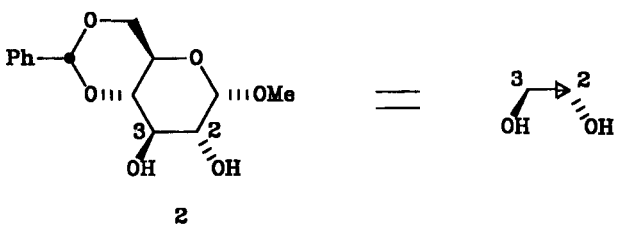

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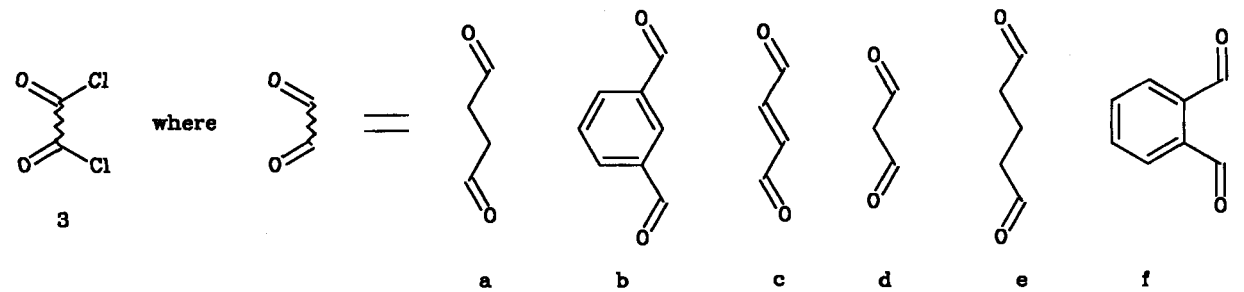

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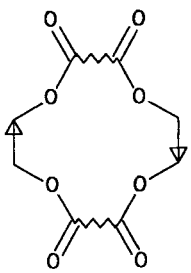
ever, unable to rationalize the preponderance of certain of the constitutional isomers. We have recently reported that the reaction of the dioxastannolane **1**, derived from dibutyltin oxide and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**), with succinyl dichloride (**3a**) furnished, in addition to both the possible tetralactones, small to moderate amounts of a single specific constitutional isomer from each of the possible macrocyclic hexa- and octalactone products[11].

On the basis of related studies[8,12], the heterotopic antiparallel tetralactones **4** derived from **2** show (with the annulated side chains poised to be orientated over the same face of the tetralactone) considerable potential for elaboration into ionophores. However, **4a** was obtained as the minor isomer in the reported[11] macrocyclization reacton using succinyl dichloride (**3a**). We therefore investigated the dependence of the yield (relative and absolute) of the heterotopic antiparallel tetralactones **4** on the structure and reactivity of the diacid dichlorides **3**. We herein report and discuss the reaction of several diacid dichlorides with **1**.

The acid chlorides were selected to ascertain the influence of i) reactivity of the acid chloride, ii) the rigidity of the backbone connecting the acid chloride groups, and iii) the interfunctional-group distances of these components in stannylene-activated oligolactone formation. Of the six acid chlorides chosen, isophthaloyl dichloride (**3b**) and fumaryl dichloride (**3c**) did not yield detectable amounts of macrocyclic lactones and malonyl dichloride (**3d**) yielded insignificant amounts of the parallel tetralactone **5d**. All six acid chlorides **3** did, however, react with the dioxastannolane **1** to form polar heterogeneous compounds which are likely to be acyclic polyesters.



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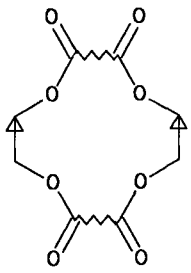

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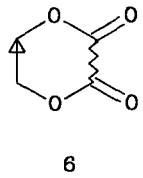

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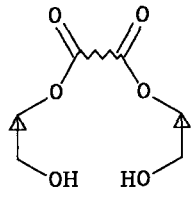

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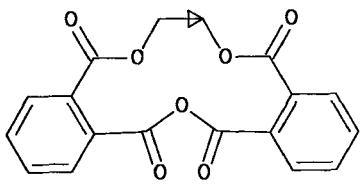

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Glutaryl dichloride (**3e**) reacted with **1** to yield both constitutionally isomeric tetralactones **4e** and **5e**, and the dilactone **6e**, the first of its kind to be prepared in this manner. Under certain conditions the C_2 symmetrical 2,2′-bisglucopyranosyl glutarate derivative **7e** was also obtained. The tetralactones **4e** and **5e** were characterized on the basis of their ^{1}H- and ^{13}C-NMR as well as mass spectra. The latter required pure samples in order to ascertain the correct molecular masses of the compounds. Due to the C_2 symmetry which both isomers possess, ^{1}H and ^{13}C NMR display only one set of sugar moiety signals in their respective spectra. The M^+ peaks (m/z = 756) in the mass spectra of **4e** and **5e**, especially pronounced for the parallel isomer **5e**, proves the tetralactonic structure. Their respective constitutional isomeric identities were deduced on the basis of symmetry principles[8,9]: In any C_2 symmetric molecule, each atom which is removed from the axis of symmetry is identical to the atom which replaces it in its location by the C_2 symmetry operation. Each atom which is on the axis of C_2 symmetry is unique. The glutarate moieties of the parallel tetralactone **5e** are bisected by the C_2 axis of symmetry through the β-methylene carbons. The respective glutarate β-carbon atoms are thus unique while the α-carbon atoms are paired, giving a total of four different glutarate methylene carbon atoms. By contrast, the antiparallel tetralactone **4e**, which has no atoms on the C_2 axis of symmetry, has three pairs of respectively identical methylene carbon atoms. The ^{13}C-NMR spectra of **5e** and **4e** both have three glutaryl methylene carbon signals. The three signals of **4e** are of similar intensity, two of which are assigned to α-methylene carbon atoms (δ = 32.82 and 32.93). The remaining signal is assigned to the β-methylene carbon atom (δ = 19.88). Two of the signals of **5e**, however, are half the intensity of that of the average signal in the spectrum, and are assigned to the non-equivalent β-methylene carbon atoms (δ = 19.57 and 20.53). The remaining signal has a greater intensity than that of the average signal in the spectrum and is assigned to the two pairs of α-methylene carbon atoms which coincidently have the same chemical shift (δ = 32.95). The dilactone **6e** was characterized by EI- and FAB-MS (m/z = 378). The integrals of the ^{1}H-NMR signals of **7e** indicate a ratio of one glutarate to two sugar moieties. The single set of sugar signals, 3-H of which is shifted downfield (from δ = 4.113, typical of a free OH, to 5.536) on addition of trichloroacetyl isocyanate to the sample in the NMR tube, identified **7e** as the C_2 symmetrical 2-*O*-glutary-bridged bissugar derivative.

Reaction conditions for glutarylation were varied in an effort to ascertain the role of different conditions in product distribution and enhancement[11], with special interest in favouring the formation of the antiparallel tetralactone **4e** which may be elaborated to a *cis*-appended macrocycle. As reflected in Table 1, fair to good yields of macrolactones were obtained. In harmony with Shanzer's isolation of the parallel constitutional isomer exclusively when enantiomerically pure diols are used[9], the parallel isomer **5e** is generally the dominant oligolactonic product. The yield of the antiparallel tetralactone **4e** is enhanced by low-temperature addition of glutaryl dichloride at the expense of the other tetralactone **5e** and a lower total lactone yield (runs 2 and 5). The dilactone **6e** is a generally significant product in glutarylation and is the main product in the high dilution experiment (run 3). Excess glutaryl dichloride (**3e**) enhances

Table 1. Effect of reaction conditions on the product distribution of the dibutyltin oxide-mediated glutarylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**)

Run	Yield (%)[a] 4e	5e	6e	7e	% Total lactone	Reaction conditions[b]
1	–	61	15	–	76	Standard
2	4	19	19	13	42	Addition at -30°C
3	–	35	63	–	98	Dilute (8.6x)
4	–	37	39	–	76	2 equiv. of glutaryl chloride
5	12	35	11	–	58	Addition at -50°C

[a] The "–" indicates a product that could not be detected by TLC or HPLC. – [b] Standard conditions: An equimolar amount of acid chloride was added to compound **1** in toluene (35 ml) at ambient temperature, reaction time 2 h.

the formation of the dilactone **6e** at the expense of the tetralactone **5e** (run 4 vs 1).

Phthaloyl dichloride (**3f**), which is less reactive than aliphatic acid chlorides, reacted with **1** to yield the parallel tetralactone **5f**, the dilactone **6f** usually contaminated by the diester diacid anhydride **8**, and the C_2-symmetrical 2,2′-bisglucopyranosyl phthalate derivative **7f** which was often the major product. The antiparallel tetralactone **4f**, however, was not isolated in any of the reactions. Once again, ^{1}H and ^{13}C NMR as well as MS were imperative for the unambiguous identification of the structures of these oligoesters and -lactones. In contrast with the glutarate macrocycle **5e**, no atoms are on the axis of symmetry when the phthalate moieties of **5f** are bisected by the axis of C_2 symmetry. Both **4f** and **5f** are therefore expected to display four aromatic methine signals in their ^{13}C-NMR spectra assignable to their respective phthalate moieties. The key to discriminating between **4f** and **5f** is found in the coupling patterns displayed by the protons of the phthalate moieties in their ^{1}H-NMR spectra[11]. The phthalate moieties of **5f** which are bisected by the C_2 axis of symmetry should display two independent sets of AA′BB′ spin systems. On the other hand the phthalate moieties of **4f** are identical by the symmetry operation, but each of the protons within one moiety are magnetically unique. The phthalate moieties should thus display a single ABCD spin system. The ^{1}H- and ^{13}C-NMR spectra of tetralactone **5f** display only one set of signals for the sugar components. The phthalate moieties are shown to be respectively bisected by the axis of C_2 symmetry by the presence of what appears to be a single set of signals in the ^{13}C spectrum and more so by the two discrete sets of AA′BB′ spin systems which the phthaloyl proton signals display in the ^{1}H-NMR spectrum. The mass spectrum of **5f** reveals a significant M^+ peak (m/z = 824). The M^+ peak (m/z = 412) in the EI- and FAB-MS indicated **6f** to be a dilactone[13]. The unusual shift to higher field (ca. 1 ppm, δ = 4.182 and 4.637, respectively) of 2-H and 3-H are due to the anisotropic shielding cone of the phthalate ring resulting from its orientation in the strained medium ring. A crystalline sample of **8** showed an M^+ peak of m/z = 560 and integrated for 13 aromatic protons in the ^{1}H-NMR spectrum and also displayed appropriate aromatic signals in the ^{13}C-NMR spectrum. Of the four carbonyl carbon signals, two (δ = 165.86 and 166.87) are typical of glucopyranosyl phthalates (see analogous chemical shifts of **5f**, **6f** and **7f**) and the remaining two (δ = 162.40 and 163.27) correlate with that of phthalic anhydride (δ = 163.4)[14]. The ^{1}H-NMR spectrum of the phthalate-bridged sugar **7f** indicates a single C_2-symmetrical phthalate moiety (AA′BB′ spin system), integrating for only one phthaloyl component relative to two identical sugar components. Furthermore, the 3-H signal of the sugar moieties is upfield (δ = 4.232) relative to the lower field equivalents of **5f** (δ = 5.879), **6f** (4.637) and **8** (5.872). Reaction of **7f** with trichloroacetyl isocyanate resulted in the down-field shift of its 3-H signals to δ = 5.677, confirming the 3-OH groups of **7f** to be underivatized.

Phthaloylation of **1** was also subjected to varying reaction conditions in order to get a better understanding of the parameters that influence the yields of the respective oligolactones and in the hope of finding conditions that will yield the antiparallel tetralactone **4f** (Table 2). There is evidence for an interaction between tin compounds and the oligolactonic products, i.e. a tin-mediated disintegration of oligolactones[15], especially with respect to the ring-strained dilactone **6f** (compare runs 4 and 6 with 3 and 1). It should thus be borne in mind that the product distributions presented in Table 2 reflect the final picture of the primary and secondary mechanistic role of tin-mediated oligolactonization, and not just the initial selectivities of macrolactone formation. Oligolactone formation as a whole is favoured by higher reaction concentrations (compare runs 3, 4, and 6 with run 1) and to a lesser extent by an excess of phthaloyl dichloride. The parallel tetralactone **5f** is generally the major oligolactone in these reactions. Its formation is furthermore favoured by longer reaction time at the expense of the dilactone **6f** (compare runs 4 and 6 with run 1) but disfavoured by reduced reaction temperatures in favour of the dilactone (runs 5 and 7). The bridged compound **7f** is enhanced by higher dilution (run 2) and reduced reaction temperatures (runs 5 and 7).

Table 2. Effect of reaction conditions on the product distribution of the dibutyltin oxide-mediated phthaloylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**)

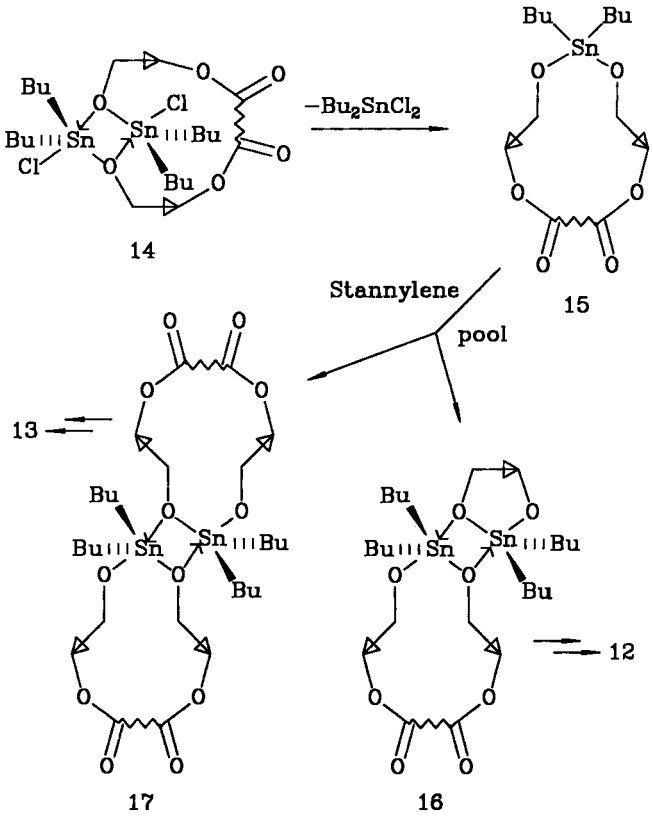
Run	Yield (%)[a] 5f	6f[b]	7f	% Total lactone	Reaction conditions[c]
1	18	9	23	27	Standard
2	9	5	71	14	30 min a./d. (8.6x)
3	35	9	25	44	c. (3.5x)
4	43	3	45	46	20 h reaction time/c. (1.8x)
5	–	13	31	12	a. at -50°C
6	60	–	12	60	2 equiv. of **3f**/20 h/c. (1.8x)
7	19	29	40	48	2 equiv. of **3f**/-50°C a./6 h

[a] Same as Table 1, footnote[a]. – [b] Often contaminated with trace amounts of **8**. – [c] Same as Table 1, footnote[b]; a.: addition, d.: dilution, c.: concentration.

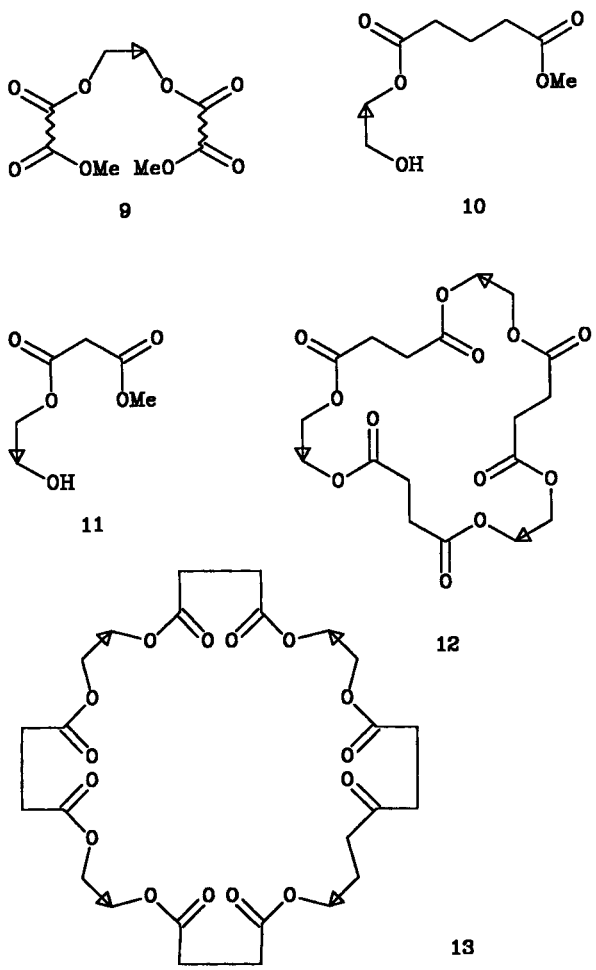
The initial steps in the formation of the parallel tetralactones **5** may be formulated as the successive reaction of the two electrophilic moieties of a diacid dichloride **3** with the more reactive 2-*O*-positions[16–19] of the respective sugar components of the stannylene complex dimer **1**[18,20] (across template[8,12,21] diacylation). The dimeric stannylene complex in general is vital to these reactions since products of specific constitutional isomer selectivity are formed in good yield with a wide variety of diacid dichlorides, diols and reaction conditions[8–11,22]. In cases where the across template secondary acylation is slow due to reactivity, ring strain, or steric factors, intermolecular secondary acylation becomes competitive. When glutarylation and malonylation reactions were worked up with imidazole and quenched with methanol, glucopyranoside esters of monomethyl glutarate **9e** and **10** and monomethyl malonate **9b** and **11** were isolated. The above considerations may suggest that the formation of the succinyl hexa- and octalactones **12** and **13** are likewise the result of the reaction of succinyl dichloride (**3a**) with greater oligomers[9,16,18] in the stannylene pool. This possibility seems unlikely on account of the following factors: the exclusivity of the phenomenon to **3a**; the constitutional specificity of the reactions in the formation of **12** and **13** which are one out of two and four possible constitutional isomers, respectively[11]; and the preponderance and relative longevity of the dimeric stannylene complex compared to all the other components (monomers, dimers, trimers etc. in dynamic equilibrium)[9,20] of the stannylene pool.

The formation of the succinyl hexa- and octalactones **12** and **13** may suggest the formation of macrocyclic stannylene intermediates such as **14** and/or **15** (Scheme 1) which on interaction with the stannylene pool may form new reactive stannylene complexes **16** and **17**. Complexes **16** and **17** may, by the repetition of the above processes, undergo the steps necessary for the formation of the hexa- and octalactones **12** and **13**. The constitutional specificities in the formation of the hexa- and octalactones **12** and **13** are dictated by the bridging of the two more reactive 2-*O* positions of the respective sugar components in the initial stannylene complex dimers. The fact that higher-order lactones could not be detected in the reaction of diacid dichlorides other than succinyl dichloride (**3a**) may be due to a delicate balance between ring closure and chain extension which is critically dependent on the nature (reactivity, rigidity and chain length) of the acylating agent.

Scheme 1. Possible mechanistic route for the formation of the hexa- and octalactones **12** and **13**

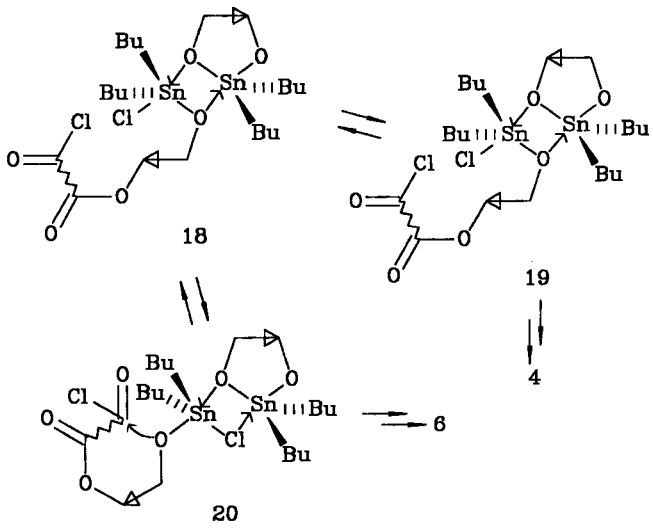


When across template secondary acylation does not rapidly follow primary acylation, the integrity of the stannylene intermediate **18** may be lost by interaction with the stannylene pool or spontaneous partial dissociation or rearrangement (cf. Scheme 2). Decomplexation and across template secondary acylation of the complementary sugar 3-*O* position of intermediate **19** are the initial steps necessary for the formation of the antiparallel tetralactone **4**. The lower



reactivity of aromatic acid chlorides and their steric bulkiness may be the reason why across template secondary phthaloylation does not occur at the 3-*O* postition, even when that O atom is only dicoordinated, thus preventing the formation of the antiparallel tetralactone **4f**. Decomplexation and, in cases (phthaloylation and glutarylation) not precluded by ring strain, secondary acylation of the 3-*O* position of the sugar component of primary acylation (intermediate **20** in Scheme 2) leads to the formation of the dilactone **6**. This latter (or related) mechanism comprises the final process in the formation of the parallel tetralactones **5** by the primary and secondary acylation of the intermediate macrocyclic stannylene complex **15** or the/a macrocyclic component of **16** or **17**. Analogous processes are probably responsible for the macrocyclization step in the formation of all the oligolactones.

Scheme 2. A mechanistic route for the formation of the antiparallel tetralactone **4** and the macrolactonization of the dilactone **6**



The results described above are considered to be supportive of Shanzer's template hypothesis on organotin-mediated macrolactonization[8,12,21]. Clearly the template effect is well disposed for tetralactone formation on condition that the reactivity and structure of the diacid dichloride accommodates across template diacylation. The available data are, however, insufficient to rationalize the peculiar stereo- and constitutional specificities displayed when the same diol is used optically pure or racemically modified in reaction with diacid dichlorides[8,9]. We suggest that symmetry properties dictate this phenomenon: Stannylene complex dimers which enjoy C_i symmetry are more reactive than those with C_2 symmetry. When primary acylation occurs, however, the dimer rapidly loses its integrity, causing the formation of the antiparallel tetralactone. The reason for this rapid loss or inversion of integrity is not clear. When dimers of C_i symmetry are unavailable, the C_2 symmetric dimer reacts, allowing across template secondary acylation without loss of integrity. We are further investigating this phenomenon with enantiomers and racemates of cyclic diols, using diacid dichlorides of varying chain length in order to get more insight into this symmetry-controlled process.

Experimental

Diacid dichlorides, dibutyltin oxide, and imidazole were unprocessed commercial (Aldrich and Fluka) reagents. Toluene was distilled from a liquid Na/K alloy (1:5) and MeOH was commercial AR grade. EtOAc for chromatography was distilled from anhydrous K_2CO_3 through a 50-cm Vigreux column. Distilled hexane and commercial AR ether, benzene, and toluene were used for chromatography. Column chromatography: Silica gel 60 (Merck, 63–200 μm). – Flash chromatography: MN-Kieselgel 60 (Macherey Nagel, 40–63 μm). – TLC: Silica gel 60 F_{254} plates (Merck, 0.15 mm). – Melting points: Koffler hot-stage apparatus, uncorrected. – ^1H and ^{13}C NMR: Varian VXR 200 spectrometer, $CDCl_3$ as solvent and internal reference [converted to tetramethylsilane as reference on the basis of $\delta_H(CHCl_3) = 7.24$ and $\delta_C(CDCl_3) = 77.00$]. – MS (EI) and accurate mass analyses: Varian Mat 8200. – MS (FAB): VG 70–70 E double focusing mass spectrometer fitted with an Ion Tech FAB gun. Xenon was used as bombarding gas and glycerol was used as matrix. – Optical rotations: Perkin-Elmer 141 and Jasco DIP-370.

The NMR data of the products are presented in Tables 3 and 4 and the remaining physical data in Table 5. Due to the stereotype methodology of this chemistry, a standard procedure is presented below followed by variations from the standard procedure with the respective product yields.

In order to determine the position of free hydroxy groups (if any) of a compound in an NMR tube, 30–50 μl of trichloroacetyl isocyanate (Aldrich) was added in situ, and the NMR spectrum rerun. Significant downfield shifts ($\Delta\delta_H > 1$ ppm) of signals of protons vicinal to an oxygen atom are indicative of the oxygen atom being a hydroxy group having been derivatized.

Methyl 4,6-O-Benzylidene-α-D-glucopyranoside (**2**): A mixture of methyl α-D-glucopyranoside (720 g, 3.71 mol), anh. $ZnCl_2$ (540 mg, 3.96 mol), and benzaldehyde (1.20 l, 11.8 mol) was stirred for 3 d at ambient temp. The product was precipitated by pouring the mixture into ice cold water/hexane (15 l, 2:1). The precipitate was filtered, washed (water and hexane) and vacuum-desiccatored (over P_2O_5) furnishing **2** (754 g, 72%), m.p. 164–165°C (ref.[23] 163–164°C). – ^1H NMR: same as ref.[24] – ^{13}C NMR: same as ref.[25]

Standard Procedure for Dibutylstannylation: A suspension of **2** (800 mg, 2.83 mmol) and dibutyltin oxide (705 mg, 2.83 mmol) in toluene (35 ml) is brought to reflux for 2.5 h using a Dean-and-Stark separator. When the solution has reached ambient temp. an equimolar amount of diacid dichloride **3** is added and allowed to stir for 2 h. The product mixture is then worked up in one of two ways:

a) The product mixture is diluted with $CHCl_3$ and washed with aq. $NaHCO_3$, dried and the solvent removed in vacuo. The residue is then column-chromatographed and if necessary rechromatographed to eliminate stannylene contaminants and obtain better product separation.

b) Two equiv. of imidazole is added to complex the dibutyltin dichloride, the mixture stirred for 30 min and then any gelatinous residue brought into solution by the addition of $CHCl_3$. The homogeneous solution is then adsorbed onto silica gel for flash chromatography by the removal of the solvent in vacuo, and the free-flowing residue brought onto a column and chromatographed.

Table 3. ^{1}H-NMR data[a] of the macrocyclic oligolactones and -esters

1	2	3	4[b]	5	6_{ax}[b]	6_{eq}	H′	MeO	Bn-Ar[c]	Acid moiety
5d										
5.004*d*[d]	4.899*dd*[d]	5.592*t*	3.608*t*[d]	3.896*td*[d]	3.742*t*[d]	4.279*dd*	5.459*s*	3.372*s*	7.28–7.45*m* 5H	3.35–3.52*m* 2H
3.6	10.1/3.5	9.8	9.5	9.6/4.6	10.0	9.9/4.3				
9d										
4.920–4.998*m*		5.613*t*	3.658*t*[d]	3.919*td*[d]	3.759*t*[d]	4.294*dd*	5.487*s*	3.407*s*	7.30–7.35*m* 3H	3.36–3.46*m* 4H
–	–/3.7	9.4	9.6	9.7/4.4	10.0	9.8/4.4			7.38–7.48*m* 2H	3.617, 3.729 Me
4e										
4.947*d*	4.820*dd*	5.606*t*	3.604*t*[d]	3.898*td*[d]	3.747*t*[d]	4.281*dd*	5.472*s*	3.375*s*	7.30–7.45*m* 5H	1.879q_n 7.0 2H β
3.7	9.9/3.7	9.8	9.5	9.6/4.5	10.0	9.8/4.4				2.24–2.45*m* 4H α
5e										
4.872–4.947*m*		5.581*t*[e]	3.613*t*[d]	3.898*td*[d]	3.747*t*[d]	4.279*dd*	5.470*s*	3.374*s*	7.28–7.35*m* 3H	1.76–1.98*m* 2H β
–	–/–	9.7	9.4	9.6/4.3	10.0	9.8/4.2			7.39–7.44*m* 2H	2.21–2.50*m* 4H α
6e										
4.908–4.981*m*		5.492*t*	3.800*t*[d]	3.921*td*[d]	3.775*t*[d]	4.290*dd*	5.507*s*	3.451*s*	7.29–7.35*m* 3H	2.00–2.30*m* 2H β
–	–/3.4	9.8	9.9	9.4/3.9	9.5	9.7/3.9			7.42–7.48*m* 2H	2.30–2.58*m* 4H α
7e										
4.896*d*[d]	4.792*dd*[d]	4.113*t*	3.504*t*	3.66–3.85*m*		4.256*d*[e]	5.500*s*	3.350*s*	7.27–7.32*m* 3H	1.978q_n 6.8 1H β
3.9	9.6/3.8	9.4	9.2	–/3.9	10.3	5.4			7.42–7.47*m* 2H	2.38–2.65*m* 2H α
7e + trichloroacetyl isocyanate										
4.866–4.950*m*		5.536*t*	3.764*t*[d]	3.919*td*[d]	3.735*t*[d]	4.294*dd*	5.501*s*	3.394*s*	7.30–7.33*m* 3H	1.896q_n 6.7 1H β
–	–/3.7	9.3	9.9	9.7/4.1	9.4	10.0/4.4			7.39–7.45*m* 2H	2.25–2.46*m* 2H α
										8.703*s* 1H (NH)
9e										
4.929*d*[d]	4.868*dd*[d]	5.575*t*	3.616*t*[d,f]	3.894*td*[d]	3.742*t*[d]	4.278*dd*	5.474*s*	3.378*s*	7.27–7.33*m* 3H	1.81–2.00*m* 4H β
3.8	9.7/3.7	9.2	–	9.7/4.4	10.0	9.9/4.3			7.38–7.43*m* 2H	2.25–2.44*m* 8H α
										3.583, 3.647 Me
5f										
5.440*d*	5.054*dd*	5.879*t*	3.871*t*[d]	4.068*td*[d]	3.840*t*[d]	4.371*dd*	5.591*s*	3.498*s*	7.29–7.37*m* 3H	7.463[g] 7.549[g]
3.4	10.2/3.4	9.9	9.5	9.7/4.5	10.0	10.0/4.6			7.40–7.49*m* 2H	7.748[g] 7.806[g]
6f										
5.235*d*	4.182*dd*	4.637*t*	4.116*t*[d]	3.809*td*[d]	3.914*t*[d]	4.353*dd*	5.618*s*	3.526*s*	7.29–7.35*m* 3H	7.56–7.64*m* 2H
2.9	10.0/3.1	9.8	9.9	8.3/3.9	9.8	9.7/4.0			7.45–7.50*m* 2H	7.690[d,h] 7.831[i]
7f										
5.045–5.102*m*		4.232*t*	3.571*t*	3.790*td*[d]	3.752*t*[d]	4.292*dd*	5.517*s*	3.390*s*	7.34–7.39*m* 3H	7.805[g]
–	–/3.7	8.8	9.2	9.5/4.3	10.3	8.7/3.9			7.50–7.55*m* 3H	
7f + trichloroacetyl isocyanate										
5.056*d*	5.321*dd*	5.677*t*	3.832*t*[d]	4.001*td*[d]	3.849*t*[d]	4.350*dd*	5.547*s*	3.442*s*	7.33–7.36*m* 3H	7.539[g] 7.711[g]
3.4	9.8/3.7	9.5	9.4	9.4/4.2	9.9	9.9/4.1			7.44–7.48*m* 2H	8.526*s* 1H (NH)
8										
5.170*d*	5.333*dd*	5.872*t*	3.843*t*[d]	3.995*td*[d]	3.809*t*[d]	4.337*dd*	5.509*s*	3.457*s*	7.31–7.40*m* 3H	7.54–7.89*m* 8H
3.7	10.0/3.7	9.8	9.6	10.2/4.3	10.1	10.1/4.5			7.40–7.48*m* 2H	

[a] For all but the last two columns the first line contains the chemical shifts and multiplicities (q_n meaning quintet) and the second line the coupling constants in Hz. In the last two columns the region of the multiplet is indicated followed by the relative proton integral. When specific chemical shifts are indicated, it is followed by multiplicity and then the coupling constant in Hz. For the glutaryl moieties the signals are also assigned as α or β with respect to the carbonyl groups. – [b] The assignments in these columns may be interchanged on the same line excepting compound **6f** where assignments have been proven by decoupling. – [c] When discrete, the lower-field signal integrating 2H represents the *o*-protons and the higher-field signal integrating for 3H represents the *m*- and *p*-protons. – [d] Calculated chemical shift. – [e] Signal with satellites due to higher order effects. – [f] Only the middle peak of triplet visible, chemical shift calculated by analogy to **5e**. – [g] AA′ or BB′ component of AA′BB′ spin system integrating for 1H. – [h] *td* 7.0/1.4 Hz. – [i] *dd* 7.9/1.0 Hz.

Glutarylation

Run 1. – Standard: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (35 ml) was treated dropwise at ambient temp. with glutaryl dichloride (**3e**) (362 µl, 2.84 mmol). After 2 h stirring, the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 160 mg (15%) of **6e** and 650 mg (61%) of **5e**.

Run 2. – Cold Reaction: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (35 ml) was treated at –30°C with glutaryl dichloride (**3e**) (362 µl, 2.84 mmol). The mixture was allowed to slowly (2 h) thaw to ambient temp., then stirred for 30 min at ambient temp. and then worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 200 mg (19%) of **6e**, 40 mg (4%) of **4e**, 200 mg (19%) of **5e**, and 120 mg (13%) of **7e**.

Run 3. – Dilute: Stannylene complex **1** (1.42 mmol), derived from **2** (400 mg) and 1 equiv. of dibutyltin oxide, in toluene (150 ml) was treated at 0°C with glutaryl dichloride (**3e**) (180 µl, 1.41 mmol). After 3 h at ambient temp., the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 340 mg (63%) of **6e** and 190 mg (35%) of **5e**.

Run 4. – Excess Acid Chloride: Stannylene complex **1** (1.42 mmol), derived from **2** (400 mg) and 1 equiv. of dibutyltin oxide, in toluene (25 ml) was treated at 5°C with glutaryl dichloride (**3e**)

Table 4. ^{13}C-NMR chemical shifts of the macrocyclic oligolactones and -esters

	1	2	3	4	5	6	C'	MeO	*o*[a]	*m*[a]	*p*	*ipso*	Acid			
5d													CO	*α*		MeO
	96.77	72.44	69.47	79.38	62.08	68.65	101.43	55.35	126.03	128.18	129.02	136.70	164.00 164.59	41.50 42.29		
9d																
	97.47	71.99	69.66	78.91	62.35	68.78	101.58	55.54	126.14	128.20	129.09	136.78	165.29 166.11 166.66	40.85 41.25		52.42 52.56
4e													CO	*α*	*β*	
	97.44	71.84	68.65[b]	79.18	62.33	68.83[b]	101.63	55.39	126.17	128.22	129.09	136.89	171.26 172.30	32.82 32.93	19.88	
5e																
	97.40	71.44	68.61[b]	79.15	62.25	68.70[b]	101.48	55.27	126.07	128.12	128.98	136.81	171.49 171.87	32.95	19.57 20.53	
6e																
	98.50	74.43	72.44	78.63	63.99	68.74	101.68	55.42	126.29	128.20	129.18	136.66	174.44 174.88	33.23 33.43	23.11	
5f													CO	*o*	*p*	*ipso*
	97.12	73.30	69.93	80.29	62.38	68.75	101.16	55.72	125.82	128.13	128.72	136.92	165.56 165.87	131.14 131.51	129.68 130.01	129.83 130.31
6f																
	97.86	77.03[b]	76.75[b]	81.03	64.47	68.55	101.35	55.86	126.10	128.20	129.15	136.54	165.12	131.92 134.89	123.06 125.04	126.01 127.34
7f																
	97.42	74.82	68.46[b]	81.09	62.04	68.73[b]	101.83	55.34	126.26	128.16	129.08	136.93	167.09	131.58	130.92	129.54
8																
	97.75	72.69	71.20	78.94	62.52	68.76	101.46	55.56	126.04	128.20	128.99[b]	136.78	162.40 163.27 165.86 166.87	131.61 131.78 132.29 132.79	129.06[b] 129.58 130.43 130.77	129.15 130.69 130.90

[a] These assignments were confirmed by HETCORR. — [b] These chemical shift assignments may be interchanged within the same compound.

(360 µl, 2.82 mmol). After 2.5 h at ambient temp. the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 210 mg (39%) of **6e** and 200 mg (37%) of **5e**.

Run 5. — Cold Reaction: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (35 ml) was treated at −50°C with glutaryl dichloride (**3e**) (360 µl, 2.82 mmol). The mixture was allowed to slowly (2 h) thaw to ambient temp., then stirred for 30 min at ambient temp. and finally worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 118 mg (11%) of **6e**, 127 mg (12%) of **4e**, and 377 mg (35%) of **5e**.

Excess Acid Chloride, Imidazole/MeOH Quench: Stannylene complex **1** (1.77 mmol), derived from **2** (500 mg) and 1.07 equiv. of dibutyltin oxide refluxed in toluene (28 ml) for 20 min, was treated at ambient temp. with glutaryl dichloride (**3e**) (452 µl, 3.54 mmol) and stirred for 4 h. The reaction mixture was then worked up (procedure b) by the addition of imidazole (240 mg, 3.53 mmol), stirring for 30 min, and quenching with MeOH (5 ml). The solvent was removed in vacuo and the residue flash-chromatographed (EtOAc/hexane, 1:2 → 2:1) yielding 70 mg (10%) of **6e**, a mixture (149 mg) and 178 mg (27%) of **5e**. The middle mixed fraction was flash-chromatographed again (EtOAc/hexane, 1:3→1:1) furnishing 2 mg of **6e**, 40 mg (4%) of **9e**, 13 mg of a mixture of **9e** and **10**, 12 mg (2%) of **10**, and 35 mg (5%) of **5e**.

Phthaloylation

Run 1. — Standard: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (35 ml) was treated at ambient temp. with phthaloyl dichloride (**3f**) (400 µl, 2.78 mmol). After 2 h, the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4). The forefraction was a mixture of **5f** and **6f** followed by 230 mg (23%) of **7f**. The forefraction was rechromatographed (Et_2O/toluene, 1:9) furnishing 100 mg (9%) of pure **6f** and 210 mg (18%) of **5f**.

Run 2. — Dilute: Stannylene complex **1** (1.42 mmol), derived from **2** (400 mg) and 1 equiv. of dibutyltin oxide, in toluene (150 ml) was treated dropwise over 30 min at 0°C with phthaloyl dichloride (**3f**) (200 µl, 1.39 mmol). After 2 h at ambient temp., the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 30 mg (5%) of **6f**, 50 mg (9%) of **5f**, and 350 mg (71%) of **7f**.

Run 3. — Concentrated: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (prepared in 20 ml, reduced to 10 ml) was treated at 5°C with phthaloyl dichloride (**3f**) (400 µl, 2.78 mmol). After 3 h at ambient temp., the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 100 mg (9%) of **6f**, 410 mg (35%) of **5f**, and 250 mg (25%) of **7f**.

Run 4. — Prolonged Time and Concentrated: Stannylene complex **1** (1.42 mmol), derived from **2** (400 mg) and 1 equiv. of dibutyltin oxide, in toluene (prepared in 20 ml, reduced to 10 ml) was treated at 0°C with phthaloyl dichloride (**3f**) (200 µl, 1.39 mmol), and after 20 h at ambient temp. the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:4) furnishing 20 mg (3%) of **6f**, 250 mg (43%) of **5f**, and 220 mg (45%) of **7f**.

Run 5. — Cold Reaction: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (35 ml) was treated at −50°C with phthaloyl dichloride (**3f**) (400 µl, 2.78 mmol). The mixture was allowed to slowly (2 h) thaw to ambient temp., then stirred for 30 min at ambient temp. and finally worked up according to procedure a) and chromatographed (Et_2O/

Table 5. Optical rotation, melting points, mass spectra and elemental analyses of the macrocyclic oligolactones and -esters

5d

$C_{34}H_{36}O_{16}$ Calcd. 700.2003 Found 700.2026 (MS). – MS (70 eV): *m/z* (%) = 700 (4.3) [M⁺], 699 (5.2), 551 (4.2), 437 (8.9), 405 (9.1), 382 (9.7), 233 (9.0), 149 (32), 115 (34), 107 (42), 105 (100), 101 (63), 91 (49).

9d

MS (70 eV): *m/z* (%) = 482 (53) [M⁺], 481 (26), 419 (13), 333 (28), 187 (14), 149 (37), 115 (71), 105 (68), 101 (100).

4e

mp 185-187 °C, $[\alpha]_D^{24}$ = +65.8 (*c* 1.60 in $CHCl_3$). – $C_{38}H_{44}O_{16}$ Calcd. 756.2629 Found 756.2651 (MS). – MS (70 eV): *m/z* (%) = 756 (1.0) [M⁺], 755 (0.71), 493 (2.9), 378 (3.3), 229 (9.3), 149 (46), 143 (43), 141 (56), 115 (81), 105 (100), 91 (69), 87 (64), 81 (75), 69 (56), 55 (93). – $C_{38}H_{44}O_{16}$ (756.8)

Calcd. C 60.31 H 5.86 Found C 60.63 H 5.93

5e

mp 217-219 °C, $[\alpha]_D^{24}$ = +58.0 (*c* 0.88 in $CHCl_3$). – $C_{38}H_{44}O_{16}$ Calcd. 756.2629 Found 756.2620 (MS). – MS (70 eV): *m/z* (%) = 756 (18) [M⁺], 755 (11), 607 (5.1), 493 (18), 387 (12), 241 (16), 187 (11), 162 (16), 149 (70), 141 (83), 115 (64), 109 (72), 105 (100), 97 (42), 91 (55), 87 (43), 81 (60), 69 (41), 55 (81). – $C_{38}H_{44}O_{16}$ (756.8)

Calcd. C 60.31 H 5.86 Found C 60.66 H 5.76

6e

mp 169-171 °C, $[\alpha]_D^{24}$ = +90.8 (*c* 0.71 in $CHCl_3$). – MS (70 eV): *m/z* (%) = 378 (40) [M⁺], 377 (18), 229 (99.8), 201 (13), 169 (23), 149 (18), 129 (18), 115 (100), 105 (36), 55 (68). – $C_{19}H_{22}O_8$ (378.4)

Calcd. C 60.31 H 5.86 Found C 60.08 H 5.80

5f

mp 179-181 °C, $[\alpha]_D^{24}$ = +102.1 (*c* 1.07 in $CHCl_3$). – $C_{44}H_{40}O_{16}$ Calcd. 824.2316 Found 824.2339 (MS). – MS (70 eV): *m/z* (%) = 824 (10) [M⁺], 823 (4.8), 275 (6.1), 263 (10), 247 (5.7), 203 (4.9), 163 (12), 149 (81), 141 (30), 105 (100), 91 (39). – $C_{44}H_{40}O_{16}$ (824.8)

Calcd. C 64.08 H 4.89 Found C 64.51 H 4.88

6f

mp 94-96 °C, $[\alpha]_D^{24}$ = +28.5 (*c* 1.90 in $CHCl_3$). – $C_{22}H_{20}O_8$ Calcd. 412.1158 Found 412.1162 (MS). – MS (70 eV): *m/z* (%) = 412 (1.7) [M⁺], 411 (1.0), 369 (3.8), 263 (34), 221 (9.9), 161 (42), 149 (49), 137 (38), 115 (73), 105 (45), 104 (46), 91 (41), 85 (33), 83 (50), 77 (35), 76 (35), 42 (100). – $C_{22}H_{20}O_8$ (412.4)

Calcd. C 64.08 H 4.89 Found C 64.22 H 4.89

7f

mp 148-150 °C, $[\alpha]_D^{24}$ = +82.3 (*c* 1.14 in $CHCl_3$). – $C_{36}H_{38}O_{14}$ Calcd. 694.2261 Found 694.2239 (MS). – MS (70 eV): *m/z* (%) = 694 (1.7) [M⁺], 693 (8.7), 429 (10), 413 (22), 282 (21), 179 (23), 159 (50), 149 (84), 107 (88), 105 (100), 91 (63), 87 (58), 69 (74), 45 (61).

8

mp 208-212 °C, $[\alpha]_D^{30}$ = +3.2 (*c* 1.03 in $CHCl_3$). – MS (70 eV): *m/z* (%) = 560 (8.1) [M⁺], 559 (9.6), 411 (9.0), 263 (8.1), 247 (7.9), 203 (10), 149 (62), 115 (22), 105 (100), 104 (75), 91 (25), 76 (42).

toluene, 1:1) furnishing 150 mg (13%) of **6f** and 300 mg (31%) of **7f**.

Run 6. – Excess Acid Chloride, Prolonged Time and Concentrated: Stannylene complex **1** (1.42 mmol), derived from **2** (400 mg) and 1 equiv. of dibutyltin oxide, in toluene (prepared in 20 ml, reduced to 10 ml) was treated at 5 °C with phthaloyl dichloride (**3f**) (400 µl, 2.78 mmol), and after 20 h at ambient temp. the mixture was worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:9 → 1:1) furnishing 350 mg (60%) of **5f** and 60 mg (12%) of **7f**.

Run 7. – Excess Acid Chloride, Medium Time and Cold Addition: Stannylene complex **1** (2.83 mmol), derived from **2** (800 mg) and 1 equiv. of dibutyltin oxide, in toluene (25 ml) was treated at –50 °C with phthaloyl dichloride (**3f**) (800 µl, 5.55 mmol). The mixture was allowed to thaw and react at ambient temp. for 6 h, worked up by using procedure a) and chromatographed (Et_2O/toluene, 1:9) furnishing 341 mg (29%) of **6f**, 226 mg (19%) of **5f**, and 390 mg (40%) of **7f**.

Malonylation

Excess Acid Chloride, Imidazole/MeOH Quench: A mixture of stannylene complex **1** (3.54 mmol), derived from **2** (1.00 g) and 1.05 equiv. of dibutyltin oxide in toluene (50 ml), was refluxed for 50 min, then treated at ambient temp. with malonyl dichloride (**3d**) (690 µl, 7.09 mmol) and stirred for 18 h. The reaction mixture was then worked up (procedure b) by the addition of imidazole (989 mg, 14.5 mmol), stirring for 30 min and quenching with MeOH (10 ml). The solvent was removed in vacuo and the residue prechromatographed (EtOAc/hexane, 1:1 → 2:1) yielding 495 mg of a mixture and 73 mg (5%) of **11**. The mixed fraction was flash-chromatographed again (EtOAc/hexane, 1:2 → 1:1) furnishing 18 mg (1%) of **9d**, 50 mg (2%) of **5f**, and several insignificant compounds not characterized.

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1: 123618-17-7 / **2**: 57701-27-6 / **3d**: 1663-67-8 / **3e**: 2873-74-7 / **3f**: 88-95-9 / **4e**: 139658-11-0 / **5d**: 139658-09-6 / **5e**: 139658-12-1 / **5f**: 139658-17-6 / **6e**: 139658-13-2 / **6f**: 139757-03-2 / **7e**: 139658-14-3 / **7e** + trichloroacetyl isocyanate: 139658-15-4 / **7f**: 139658-18-7 / **7f** + trichloroacetyl isocyanate: 139688-16-7 / **8**: 139658-19-8 / **9b**: 139658-10-9 / **9e**: 139658-16-5