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Stereoselective Synthesis and Some Properties of New Chlorodiorganotin-Substituted Macrodiolides

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Supporting Information

ABSTRACT: Radical tandem addition of dialkyltin chlorohydrides, R_2SnHCl (R = *n*-Bu, neophyl, Ph), to TADDOL's substituted diacrylates (**4**−**7**) led to the corresponding products of cyclohydrostannation. The new optically active chlorodialkyltin-substituted 11-membered macrodiolides were obtained in very good yields and with much higher stereoselectivity than that achieved with the corresponding monohydrides, R_3SnH. Thus, the cyclohydrostannation of diacrylate **4** and dimethacrylate **5** lead to just one diastereomer in the first case and to an easily separable mixture of two diastereomers in the second. Reduction of the new organotin macrocycles with $LiAlH_4$ afforded optically active organotin derivatives structurally related to glutaric acid. Oxidation of the new chlorodiorganotin-substituted macrocycles with 30% hydrogen peroxide gave the new 11-membered macrocycles **30** and **31** free of tin in an average total yield of 43.4% from TADDOL. Full ^1H, ^{13}C, and ^{119}Sn data are also reported.

INTRODUCTION

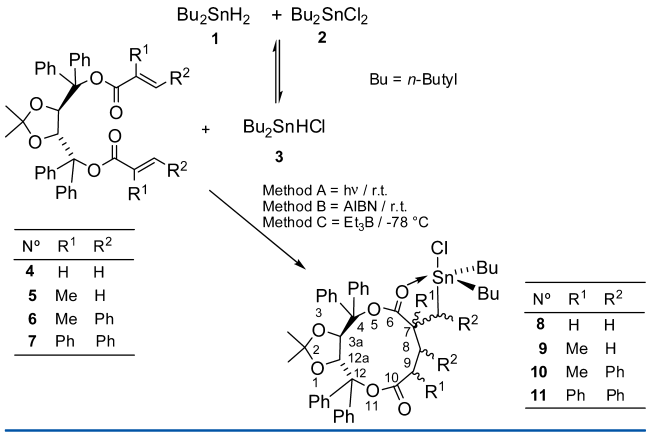
Natural products containing macrolides, i.e., macrolactones with rings that contain eight or more members, are found in plants, insects, and bacteria. Because of their biological and medicinal activity, macrolides are very important target molecules in synthetic studies. Though many of the antibiotic macrolides have highly substituted complex structures, also simple macrolides have properties that make them worth studying.[1] A number of synthetic strategies and methodologies have been developed for macrolide synthesis.[2] However, due to the fact that most of these syntheses involve many steps, the global yields are very low.[3] In the area of free radical macrocyclizations, the studies of Porter enabled defining conditions wherein intramolecular addition of carbon radicals to electron-deficient alkenes provides an effective tool for the synthesis of 11−20-membered carbocycles.[4a,b] We have recently reported a new approach based upon the fact that free radical addition of triorganotin hydrides to unsaturated diesters of TADDOL leads via a tandem cyclohydrostannation to mixtures of 11-membered organotin-substituted macrodiolides in high yields and with very good diastereoselectivity.[5] However, we could not separate these mixtures. We considered it possible to improve the utility of these reactions by carrying out the cyclohydrostannations with diorganotin halohydrides, which should lead to better stereoselectivities.[6]

In this article, we report our studies on the synthesis of 11-membered organotin-substituted macrolactones via free radical cyclohydrostannation of unsaturated diesters of TADDOL with di-*n*-butyl- (**3**), dineophyl- (**16**), and diphenyltin chlorohydride (**17**).

RESULTS AND DISCUSSION

The addition of di-*n*-butyltin chlorohydride (**3**) to the unsaturated diesters of TADDOL, **4**−**7**,[7] was carried out under argon at rt (Scheme 1). In first place, two methods were

Scheme 1. Hydrostannation of TADDOL Diesters 4−7 with *n*-Bu_2SnHCl



used: method A, where the stirred mixture of chlorohydride and unsaturated diester in dry toluene was irradiated until total reaction of the substrate or disappearance of the ν_{Sn-H} band in the IR spectrum; and method B, where the mixture of

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Table 1. Addition of *n*-Bu_2SnHCl to TADDOL Unsaturated Diesters 4−7

no.[a]	method[b] (time, h)	ratio subs/Sn−H[c]	yield (%)[d]	^{119}Sn NMR (δ, ppm)[e]	D (%)[f]	$[\alpha]^{20}_D$ (c, g/mL)[h]
8	A (1)	1:1.3	85	67.4	100	−79 (0.76)
	B (48)	1:1.5	89			
	C (12)	1:1.4	79			
9a,b	A (1)	1:1.3	80	52.5 (**9a**)	88.3	−87 (0.77)
				47.5 (**9b**)	11.7	ND[i]
9a−,b	B (48)	1:1.5	87	[g]	[g]	[g]
9a	C (12)	1:1.4	75	52.5	100	−87° (0.77)
10a−d	A (12)	1:1.3	60		25.2 (**10a**)	ND[i]
					20.6 (**10b**)	ND[i]
				32.7 (**10a**)	43.3 (**10c**)	ND[i]
				32.4 (**10b**)	10.9 (**10d**)	ND[i]
10a−d	B (72)	1:1.5	65	31.3 (**10c**)	[g]	ND[i]
10a−d	C (12)	1:1.3	65	25.3 (**10d**)	21.1 (**10a**)	ND[i]
					15.0 (**10b**)	ND[i]
					55.4 (**10c**)	ND[i]
					10.4 (**10d**)	ND[i]
11a−d	A (12)	1:1.3	62		10.5 (**11a**)	ND[i]
					14.9 (**11b**)	ND[i]
				36.7 (**11a**)	59.4 (**11c**)	ND[i]
				29.6 (**11b**)	15.2 (**11d**)	ND[i]
11a−d	B (72)	1:1.5	68	27.5 (**11c**)	[g]	ND[i]
11a−d	C (12)	1:1.3	68	26.1 (**11d**)	7.0 (**11a**)	ND[i]
					10.9 (**11b**)	ND[i]
					71.8 (**11c**)	ND[i]
					10.2 (**11d**)	ND[i]

[a]Compounds **8**−**11** in Scheme 1. [b]Method A: irradiation of the mixture of *n*-Bu_2SnHCl and substrate in toluene at rt. Method B: the mixture of *n*-Bu_2SnHCl, AIBN, and substrate in toluene left at rt. Method C: to the mixture of *n*-Bu_2SnHCl and substrate in toluene at −78 °C was added Et_3B in hexane. [c]Ratio substrate (subs) (**4**−**7**)/*n*-Bu_2SnHCl (Sn−H). [d]After chromatographic purification. [e]In $CDCl_3$; in ppm with respect to Me_4Sn. [f]D = % of diastereomer in the mixture (from ^{119}Sn NMR spectra). [g]Same proportions as using method A. [h]In $CHCl_3$. [i]Not determined (mixture of products).

chlorohydride **3**, azobis(isobutyronitrile) (AIBN) as radical initiator, and the unsaturated diester in dry toluene was stirred until total reaction of the substrate. Under these reaction conditions, using method A, the addition of chlorohydride **3** to TADDOL diacrylate **4** in toluene in a ratio **3**/**4** = 1.3 (tin hydride concentration = 0.073 M) leads to macrocycle **8** as the only reaction product (Table 1). Following method B, after 48 h and using a ratio **3**/**4** = 1.5 (tin hydride concentration = 0.085 M) the reaction leads also to **8** as the only product.

The ^{119}Sn NMR spectrum of the reaction crude product showed it to consist of only one organotin adduct. Taking into account that from the creation of one new stereogenic center at C-7 two diastereomers should be expected, this result clearly demonstrates that the reaction takes place with complete diastereoselectivity. The product was purified by column chromatography, giving **8** in 85% and 89% yield depending on the method used (Table 1). It should be noted that the ^{13}C NMR spectrum of this compound presents two C═O signals, one of them showing $^3J(^{13}C,^{119}Sn)$ coupling constants (Scheme 1, C-6).

When hydride **3** was added to TADDOL dimethacrylate **5**, the ^{119}Sn NMR spectrum of the crude product obtained using methods A and B showed that instead of the expected mixtures of four diastereomers—creation of two new stereogenic centers—the mixtures contained only two diastereomers in different proportions (Table 1, compounds **9a**,**b**), thus confirming that free radical addition of *n*-Bu_2SnHCl (**3**) is more stereoselective than that of tri-*n*-butyltin hydride.[5]

On the other hand, the ^{119}Sn NMR spectra of the crude products resulting from the cyclohydrostannation of TADDOL di(2-methyl-3-phenyl)- (**6**) and di(2,3-diphenyl)acrylates (**7**) with chlorohydride **3** using methods A and B showed them to consist in each case of mixtures of only four diastereomers (**10a**−**d** and **11a**−**d**), even though the creation of four new stereocenters could lead to 16 stereoisomers.

With the aim of improving the stereoselectivity, we carried out the cyclohydrostannations at lower temperature. The reactions between chlorohydride **3** and the unsaturated diesters of TADDOL **4**−**7** at −78 °C, using triethylborane as free radical initiator (method C), led to a dramatic increase in the stereoselectivity. Thus, in two out of the four cases studied the cyclohydrostannation proceeded with complete diastereoselectivity (reaction with esters **4** and **5**), leading to just one diastereomer, while in the other two cases (addition to diesters **6** and **7**) also a significant increase of the diastereoselectivity was observed. The results obtained are also summarized in Table 1.

In order to determine whether a change of diorganotin halohydride would affect the steric course of the cyclohydrostannation, we carried out similar studies on the reactions of TADDOL's unsaturated diesters **4**−**7** with dineophyl- (**16**) and diphenyltin (**17**) chlorohydrides, according to Scheme 2. Taking into account the previous results, we considered that method A, i.e., irradiation of the mixture of R_2SnHCl and substrate in toluene at rt, was the more convenient due to the shorter times of reaction.

We found that the ^{119}Sn NMR spectra of the crude products resulting from the addition of dineophyltin chlorohydride (**16**) and diphenyltin chlorohydride (**17**) to TADDOL diacrylate **4** indicated again the formation of just one of the two possible

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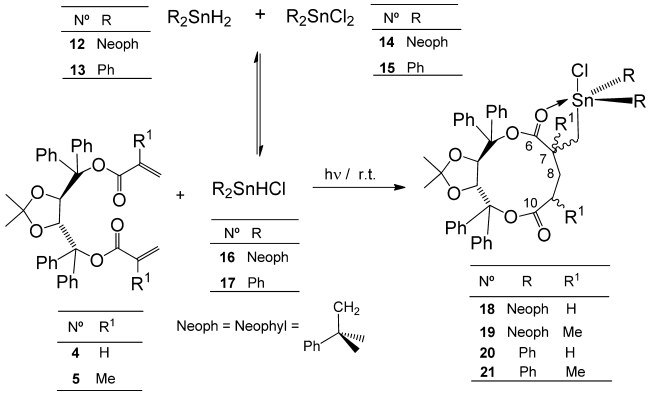
Scheme 2. Hydrostannation of TADDOL Diesters 4 and 5 with Chlorohydrides 16 and 17



diastereomeric organotin macrolides in both cases (compounds **18** and **20**, respectively, Table 2).

Table 2. Addition of Chlorohydrides 16 and 17 to TADDOL's Unsaturated Diesters 4 and 5 under Method A Conditions (irradiation at rt)

no.[b]	R (in R_2SnHCl)	substrate	D (%)[c]	^{119}Sn NMR (δ, ppm)[d]	yield (%)[e]	$[\alpha]^{20}_D$ (c, g/mL)[f]
18	neophyl[a]	**4**	100	61	69	−92 (0.75)
19a	neophyl[a]	**5**	92	67	72	−97 (0.71)
19b			8	53	[g]	
20	Ph[b]	**4**	100	−65	73	−72 (0.75)
21a	Ph[b]	**5**	60	−72	71	−78 (0.73)
21b			40	−61	[g]	

[a]Irradiation time: 14 h. [b]Irradiation time: 1 h. [c]D = % of diastereomer in the mixture (from ^{119}Sn NMR spectra). [d]In $CDCl_3$; in ppm with respect to Me_4Sn. [e]After chromatographic purification. [f]In $CHCl_3$. [g]Could not be obtained pure.

We also determined that the addition of chlorohydride **16** to TADDOL dimethacrylate **5** led to a mixture of two diastereomers, compounds **19a** (92%) and **19b** (8%), and that the cyclohydrostannation of **5** with hydride **17** led to a mixture of macrocycles **21a** (60%) and **21b** (40%).

We found that chlorohydrides **16** and **17** did not react with unsaturated diesters **6** and **7** under the conditions of methods A−C. Also, neither dineophyltin chlorohydride (**16**) nor diphenyltin chlorohydride (**17**) reacted with substrates **4** and **5** after 48 h under method B and C conditions. The results obtained are collected in Table 2.

^{1}H and ^{13}C NMR characteristics are summarized in Tables 3 and 4. The ^{13}C NMR chemical shifts (Table 1) were assigned through the analysis of the multiplicity of the signals by means of DEPT experiments, in some cases using HSQC experiments, and taking into account the magnitude of $^nJ(^1H,^{119}Sn)$ and $^nJ(^{13}C,^{119}Sn)$ coupling constants.

In macrocycles **8**−**11** and **18**−**21** the carbonyl of one of the ester groups is intramolecularly coordinated with the tin atom that has been made more electropositive because of the tin−chloro bond, as shown in Figure 1.[8] The existence of intramolecular coordination is demonstrated by the fact that the carbonyl stretching frequency of the IR spectra of compounds **8** and **9a** is the same when it was measured both in the solid state (KBr) and in acetonitrile solution (10%).

Even though the chlorodiorganotin macrocycles **8**, **9a**, **18**, **19a**, and **21a** were obtained as crystalline solids, unfortunately the crystals proved to be unsuitable for X-ray structure analysis. However, using a crystal of the chlorodiphenyltin derivative **20** it was possible to carry out an X-ray analysis, which showed that the structure might be the one depicted in Figure 2 (see X-ray data in Supporting Information).

Figure 2 shows the intramolecular coordination between the C═O and the Sn atom, and also that the configuration of the asymmetric carbon α (C-7) is *R*.

^{1}H and ^{13}C NMR data of compound **20** (Tables 3 and 4) also support the structure shown in Figure 2. The use of the Karplus-type relationship existing between the dihedral angle and the value of $^3J(^{13}C,^{119}Sn)$ and $^3J(^1H,^{119}Sn)$ coupling constants enabled us to confirm the structure of **20**. Thus, the ^3J(Sn,C═O) coupling constant of **20** with a value of 14.1 Hz is in agreement with the existence of a dihedral angle close to 60° between the C═O group and the organotin moiety.[9b] Similarly, the ^3J(Sn,C-8) coupling constant for **20** is 20.1 Hz (Table 3), indicating a dihedral angle of about 60°. On the other hand, the ^{1}H NMR spectra of compound **20** show that the ^3J(Sn−C−C−H) coupling constant between the proton attached to C-7 and the organotin substituent has a value of 101.7 Hz (Table 4), which is consistent with a dihedral angle close to 160°. Taking into account the previous discussion, it is possible to conclude that the structure of compound **8** could be represented as in Figure 3 (structure **A**).

In the case of compound **19a** the analysis of the $^3J(^{13}C,^{119}Sn)$ coupling constants also helps to establish the absolute configuration of C-7. Thus, the ^3J(Sn,C═O) coupling constant of **19a** is 45.5 Hz, suggesting a dihedral angle of 20°, indicating that the Sn moiety and the C═O group are closer than in the other cases. The ^3J(Sn,C-8) and ^3J(Sn,C-14) are 20.9 and 15.9 Hz, respectively, values consistent with angles close to 120° in both cases, suggesting that the conformation is almost eclipsed. These dihedral angles suggest that the structure of compound **19a** could be close to structure **B** of Figure 3.

In Table 5 are summarized the dihedral angles associated with the $^3J(^{119}Sn,^{13}C)$ and $^3J(^{119}Sn,^1H)$ coupling constants of compounds **8**, **9a**, **18**, **19a**, **20**, and **21a**.[9b]

Using the values included in Table 5, it could be deduced that whereas the structures of the macrocycles derived from TADDOL diacrylate (**8**, **18**, and **20**) are close to structure **A**, the macrocycles derived from TADDOL dimethacrylate (**9a**, **19a**, and **21a**) are closer to structure **B** of Figure 3.

The previous discussion suggests that, in agreement with the X-ray analysis, the configuration of C-7 in compounds **8**, **9a**, **18**, **19a**, and **21a** should be *R*, as depicted in structures **A** and **B** (Figure 3). It should be noted that in the case of compound **9a**, the HSQC experiment (included in the Supporting Information) shows that the methyl group corresponding to C-14 has a chemical shift of 29.30 ppm, but we were not able to detect the corresponding ^3J(Sn,C-14) coupling constant. However, taking into account that the ^3J(Sn,C-6) and ^3J(Sn,C-8) coupling constants of compound **9a** (11.4 and 60.0 Hz) indicate dihedral angles of around 60° and 180°, respectively, it could be considered that in this compound the configuration of C-7 is also *R* (structure **B**, Figure 3).Unfortunately, as stated before, we could not obtain the X-ray structure of any of these macrocycles, and therefore we are unable to give the absolute configuration of C-9 in compounds **9a**, **19a**, and **21a**.

We have previously proposed for these reactions a tandem mechanism similar to the one shown in Scheme 3.[5] In the case

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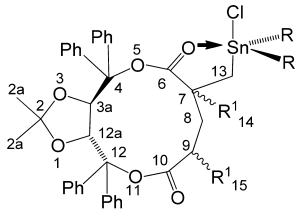
Table 3. ^{13}C NMR Spectra of Compounds 8, 9a, 18, 19a, 20, and 21a[a]

N°	R	R^1
8	*n*-Bu	H
9a	*n*-Bu	Me
18	Neoph	H
19a	Neoph	Me
20	Ph	H
21a	Ph	Me

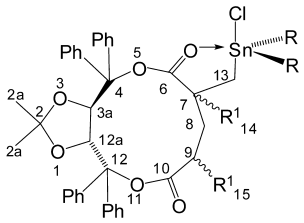


	8[b]	9a[c]	18[d]	19a[e]	20[f]	21a[g]
C-2	110.45	110.55	110.13	110.15	110.50	110.23
C-2a	27.03 and 27.10	26.90 and 27.34	27.30 and 27.33	27.29 and 27.33	26.87 and 26.90	27.46 and 27.72
C-3a and C-12a	76.04 and 76.95	75.92 and 76.81	76.81 and 76.94	76.81 and 76.94	76.78 and 76.80	75.88 and 77.11
C-4 and C-12	87.29 and 89.66	86.95 and 90.17	87.38 and 87.42	87.39 and 87.43	87.32 and 90.00	87.00 and 90.16
C-6 [^3J(Sn,C)]	180.37 (12.2)	180.96 (11.4)	175.31 (43.2)	174.61 (45.5)	179.17 (14.1)	181.02 (17.2)
C-7 [^2J(Sn,C]	44.06 (25.1)	46.52 (22.6)	43.07 (13.7)	42.91 (14.0)	43.08 (28.0)	46.56 (29.2)
C-8 [^3J(Sn,C)]	30.09 (39.2)	46.58 (60.0)	29.92 (26.0)	29.77 (20.9)	31.80 (20.1)	46.11 (76.8)
C-9	33.70	36.12	34.76	34.61	27.29	35.70
C-10	170.49	175.26	170.92	170.77	171.16	175.17
C-13 [^1J(Sn,C)]	21.10 (439.1)	26.65 (423.3)	15.70 (291.1)	15.55 (291.3)	29.73 (440.0)	26.93 (ND)
C-14 [^3J(Sn,C)]		29.13 (ND)		18.42 (15.9)		29.30 (13.6)
C-15		18.79		27.08		19.07

[a]In $CDCl_3$; chemical shifts, δ, in ppm with respect to TMS; ^nJ(Sn,C) coupling constants, in Hz (in brackets); ND = not determined. Other signals: [b]13.78; 14.03; 16.92; 19.77; 26.51 (417.9); 27.81 (28.9); 28.22 (29.4); 126.75; 126.81; 127.25; 127.51; 127.62; 127.67; 127.81; 127.85; 128.17; 128.72; 129.82; 129.91; 139.66; 140.41; 143.62; 144.71. [c]13.61; 13.92; 18.01 (423.0); 18.89 (439.4); 27.72 (29.2); 28.13 (28.5); 29.61; 126.72, 127.12; 127.26; 127.51, 127.65; 127.81; 128.13; 129.60; 129.94; 139.81; 140.41; 142.73; 144.51. [d]31.13 (316.0); 33.34 (34.7); 33.64 (36.3); 125.52; 125.66; 126.83; 127.27; 127.31; 127.55; 127.61; 127.64; 128.25; 128.61; 128.63; 130.36; 140.65; 140.90; 144.86; 144.94; 151.39 (18.5). [e]30.97 (316.0); 33.18 (34.9); 33.47 (36.4); 38.13 (18.3); 125.53; 125.67; 126.83; 127.11; 127.16; 127.39; 127.45; 127.49; 128.09; 128.45; 128.48; 130.23; 140.49; 140.73 (27.0); 144.70; 144.78; 151.23 (18.6). [f]125.66; 131.86; 133.00; 133.42; 135.63; 136.10; 136.68; 139.30; 139.75; 144.44; 144.48. [g]126.86; 127.10; 127.25; 127.45; 127.72; 127.93; 128.35; 128.68; 129.03; 129.48; 135.43 (49.7); 136.68 (47.2); 139.83; 139.95; 140.84; 141.56; 143.02; 144.98.

Table 4. ^{1}H NMR Spectra of Compounds 8, 9a, 18, 19a, 20, and 21a[a]

N°	R	R^1
8	*n*-Bu	H
9a	*n*-Bu	Me
18	Neoph	H
19a	Neoph	Me
20	Ph	H
21a	Ph	Me



no.	chemical shifts (δ, in ppm)[a] [C-No.][b]
8	0.12−0.40 (m, 2H) [C-α, *n*-Bu]; 0.59 (s, 3H) and 0.67 (s, 3H)[C-2a]; 0.79 (t, 3H) and 0.92 (t, 3H) [C-δ, *n*-Bu]; 1.00−1.90 (m, 12H) [C-α', β, δ, and C-13]; 1.92−2.61 (m, 4H) [C-8 and 9]; 2.95 (m, $^3J_{H,Sn}$ 94.8 Hz, 1H) [C-7]; 5.44 (d, $^3J_{H,H}$ 7.5 Hz, 1H) [C-3a or C-12a]; 5.51 (d, $^3J_{H,H}$ 7.5, 1H) [C-3a or C-12a]; 7.18−7.35 (m, 20H) [phenyl groups]
9a	run "i:/template/macmillan/npgeqn.3m0.03−0.16 (m, 1H) and 0.21−0.35 (m, 1H) [C-α, *n*-Bu]; 0.46 (s, 3H) and 0.70 (s, 3H) [C-2a]; 0.75−0.97 (m, 10H) [C-δ, *n*-Bu, C-13, C-15]; 1.08 (s, 3H) [C-14]; 1.10−2.00 (m, 12H) [C-β and γ, *n*-Bu, C-8, C-13]; 2.35−2.75 (m, 2H) [C-8 and C-9]); 5.48 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]; 5.56 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]
18	0.61 (s, 3H) [C-2a]; 0.63 (s, 3H) [C-2a]; 0.81 (s, 4H) [neophyl]; 1.37 (s, 12H) [neophyl]; 1.58 (d, 2H) [C-13]; 1.60−2.10 (m, 4H); 2.57−2.60 (m, $^3J_{H,Sn}$ 102.4 Hz, 1H) [C-7]; 5.53 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]; 5.56 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]; 7.09−7.27 (m, 30H) [phenyl groups]
19a	0.59 (s, 2H) [C-13]; 0.91 (s, $^2J_{Sn,H}$ 48.5 Hz, 4H) [neophyl]; 1.05 (d, 2H) [C-8]; 1.21 (s, 3H) [C-14]; 1.29 (s, 6H) [C-2a]; 1.34 (d, 3H) [C-15]; 1.37 (s, 12H) [neophyl]; 2.69 (m, 1H) [C-9]; 5.21 (d, $^3J_{H,H}$ 7.3 Hz, 1H) [C-3a or C-12a]; 5.35 (d, $^3J_{H,H}$ 7.3 Hz, 1H) [C-3a or C-12a]
20	0.50 (d, 2H) [C-13)]; 1.22 (s, 6H) [C-2a]; 1.92 (t, 2H) [C-9]; 2.32 (m, $^3J_{H,Sn}$ 101.7 Hz, 1H) [C-7]; 2.81−3.05 (m, 2H) [C-8]; 5.25 (d, $^3J_{H,H}$ 7.1 Hz, 1H) [C-3a or C-12a]; 5.42 (d, $^3J_{H,H}$ 7.1 Hz, 1H) [C-3a or C-12a]; 7.05−7.91 (m, 30H)
21a	0.55 (s, 2H) [C-13]; 0.91 (s, 3H) [C-14]; 1.05 (d, 3H) [C-15]; 1.29 (s, 3H) [C-2a]; 1.31 (s, 3H) [C-2a]; 2.61 (m, 2H) [C-8]; 2.92−3.03 (m, 1H) [C-9]; 5.42 (d, $^3J_{H,H}$ 7.2 Hz, 1H) [C-3a or C-12a]; 5.61 (d, $^3J_{H,H}$ 7.2 Hz, 1H) [C-3a or C-12a]; 6.95−7.92 (m, 30H)

[a]In $CDCl_3$; multiplicity and J values in Hz (in parentheses). [b]Carbon to which the protons are attached.

of diesters **4**−**7** the two factors that dominate the rate of addition to the olefins, i.e., electronic and steric, are both favorable: the alkene substituent (ester group) is electron withdrawing and the β-carbon of the unsaturated diesters is either unsubstituted (**4** and **5**) or monosubstituted (**6** and **7**), and therefore there is no steric hindrance or, at least, it is lower than in the disubstituted α-carbon. Taking into account the configuration of compound **19** shown in Figure 2, the possible

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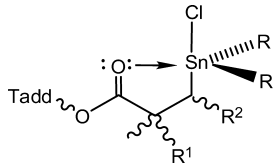

Figure 1. Intramolecular coordination between the tin atom and the carbonyl group.

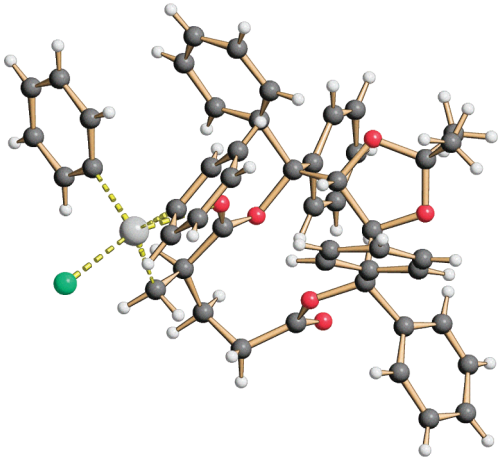

Figure 2. X-ray structure of chlorodiphenyltin-substituted macrocycle **20**.

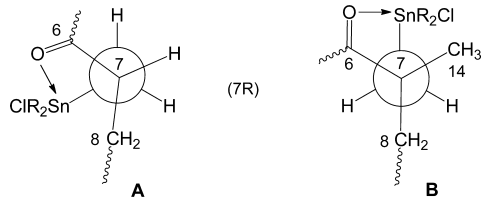

Figure 3. Configuration of C-7 resulting from the dihedral angles obtained in the analysis of the $^{3}J(^{119}Sn,^{13}C)$ and $^{3}J(^{119}Sn,^{1}H)$ coupling constants of compounds **8**, **9a**, **18**, **19a**, **20**, and **21a**.

mechanism and stereochemistry of the cyclohydrostannation of TADDOL diacrylate **4** could be the one depicted in Scheme 3.

The same should apply for the cyclohydrostannations of diesters **4** and **5** with diorganotin chlorohydrides **16** and **17**.

The very high stereoselectivity observed in these reactions could be explained as follows. The addition of chlorohydrides **3**, **16**, and **17** to TADDOL diacrylate **4** generates a new stereogenic center (C-7), and this should lead to the formation of two diastereomeric macrocycles. The formation of only one macrocycle in each case, compounds **8**, **18**, and **20**, respectively, using methods A, B, and C could reasonably be attributed to the existence of intramolecular coordination. The latter would favor the formation of an alkyl radical (**I**, Scheme 3) with a preferred conformation that will add to the other unsaturated group, leading to the cyclic radical **II**.[4a] Then, the chlorohydrides R_2SnHCl (R = *n*-Bu, neophyl, and Ph) would effect hydrogen transfer to **II**, leading to the corresponding organotin-substituted macrocyclic lactones **III**. This is confirmed by the fact that in the case of the addition of R_3SnH (R = *n*-Bu, neophyl, and Ph) to diester **4**, where the intermediate radical is not stabilized by intramolecular coordination, two diastereomeric macrocycles are obtained.[5]

Similarly, the fact that the addition of hydride **3** to diester **5** led to a mixture of two diastereomers (**9a,b**)—using methods A and B—as well as that the addition to ester **5** of hydrides **16** and **17** using method A also led to mixtures of only two diastereomers (**19a,b**, and **21a,b**), could as well be associated with the existence of intramolecular coordination between the C═O of the ester group and the Sn atom.

Here again, intramolecular coordination would favor the formation of an intermediate alkyl radical with a preferred conformation, which will add to the second olefinic group to give the product of *endo* cyclization, i.e., a cyclic alkyl radical similar to **II** (Scheme 3). Then, chlorohydrides R_2SnHCl (R = *n*-Bu, neophyl, and Ph) will effect transfer of a hydrogen atom to a preferred conformation of the cyclic radical as shown by the fact that one of the diastereomers is formed in much higher proportion (**9a**, **19a**, and **21a**) than the other (**9b**, **19b**, and **21b**).

On the other hand, radical addition of *n*-Bu_2SnHCl (**3**) to diester **5** initiated by Et_3B at −78 °C (method C) leads to the formation of diastereomer **9a** as the only reaction product. This result could be due to the fact that at −78 °C (method C) the rate of hydrogen transfer is slower than at rt, and therefore, the attack should become much more selective. The formation at rt of the second diastereomer (**9b**) could be attributed to the increase in the rate of hydrogen transfer from the tin chlorohydride to the cyclic radical, which enables the hydrogen attack to both faces of the cyclic type **II** radical (Scheme 3).

The formation of mixtures of only four macrocyclic diastereomers when chlorohydride **3** was added to TADDOL di(2-methyl-3-phenyl)- (**6**) and di(2,3-diphenyl)acrylates (**7**) under methods A (12 h), B (72 h), and C (12 h) could also be ascribed to the existence of intramolecular coordination. Thus, taking into account the previous discussion on the hydrostannation of esters **4** and **5** with *n*-Bu_2SnHCl, it should be possible that also in this case intramolecular coordination could lead to cyclic alkyl radicals stabilized in preferred conformations that would attack stereoselectively (*endo*) the C-*β* of the second olefinic system. Then, the resulting radicals on C-9 could again accept the hydrogen transfer from *n*-Bu_2SnHCl to any of its two faces. It should be added that the hydrostannations of unsaturated diesters **6** and **7** with chlorohydrides **16** and **17** do not take place due probably to steric factors.

In order to determine some chemical properties of the new organotin-substituted macrodiolides, we carried out a series of studies. In the first place, taking into account that in *β*-halodialkylstannyl esters intramolecular coordination prevents the addition of a Grignard reagent to the C═O of the ester group, which instead alkylates the tin atom,[8c] we investigated the reactions between some of the new organotin-substituted macrodiolides and RMgX (R = *n*-Bu, neophyl, Ph; X = Cl, Br) using ratios Grignard reagent/macrodiolides = 1.1 as shown in Scheme 4 (eq 1).

These reactions lead in good yields to the new triorganotin-substituted macrodiolides **22**−**24** and to the known **25** and **26** reported earlier (ref 5), thus demonstrating the existence of intramolecular coordination in the starting substrates. Two points should be noted: in the first place the ^{119}Sn NMR spectra clearly demonstrate that compounds **22**−**26** are the diastereomers present in higher proportion in the inseparable mixtures of triorganotin-substituted macrocycles obtained previously in the additions of triorganotin monohydrides (R_3SnH, R = *n*-Bu, neophyl, Ph) to the unsaturated TADDOL diesters **4** and **5**.[5] Second, whereas in the case of the addition of

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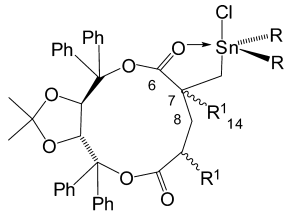
Table 5. Dihedral Angles and $^3J(^{119}Sn,^{13}C)$ and $^3J(^{119}Sn,^1H)$ Coupling Constants of Compounds 8, 9a, 18, 19a, 20, and 21a[a]

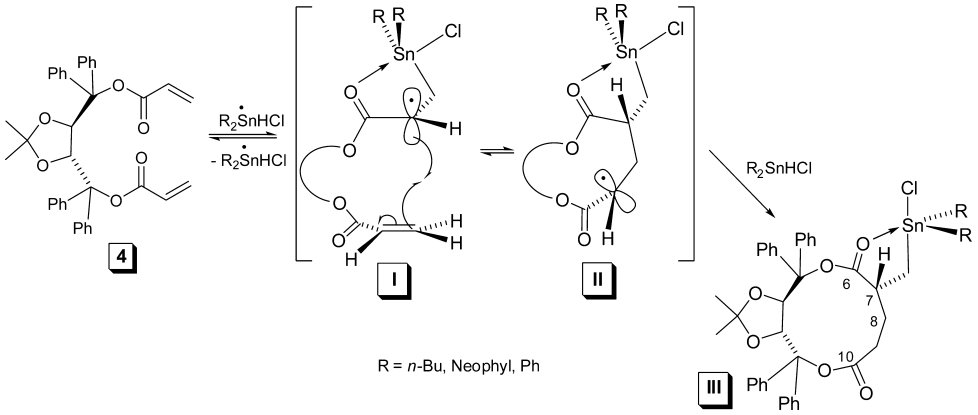
N°	R	R^1
8	*n*-Bu	H
9a	*n*-Bu	Me
18	Neoph	H
19a	Neoph	Me
20	Ph	H
21a	Ph	Me



macrocycle	δ (ppm) [^3J(Sn,R^1), Hz][b]	δ (ppm) [^3J(Sn,C-6), Hz)]	δ (ppm) [^3J(Sn,C-8), Hz]
8	2.95 (94.8)	180.37 (12.2)	30.09 (39.2)
DA	0/150°	65/105°	35/130°
9a	29.13 (ND)	180.96 (11.4)	46.58 (60.0)
DA		65/105°	180°
18	2.59 (102.4)	175.31.12 (43.2)	29.92 (26.0)
DA	160°	20/140°	45/130°
19a	18.42 (15.9)	174.61 (45.5)	29.77 (20.9)
DA	60/120°	20/140°	60/120°
20	2.32 (101.7)	179.17 (14.1)	31.80 (20.1)
DA	160°	60/110°	60/120°
21a	29.30 (13.6)	181.02 (17.2)	46.11(76.8)
DA	60/120°	60/120°	180°

[a]From Tables 3 and 4; DA = dihedral angles from ref 9b. [b]R^1 can be either H (**8**, **18**, **20**) or methyl group (**9a**, **19a**, **21a**), i.e., C-14.

Scheme 3. Mechanism of the Cyclohydrostannation of Diester 4 with Chlorohydrides 3, 16, and 17



Grignard reagents to β-chlorodialkylstannyl open-chain esters care should be taken in using the ratio ester/Grignard = 1:1.1 in order to avoid the formation of products of nucleophilic addition to the ester group,[8d] in the case of the alkylation of esters **8**, **9a**, **18**, **20**, and **21a** we found that even when using 5-fold excesses of Grignard reagents, the addition leads in all cases only to the products of tin atom alkylation. These results could be connected with the high steric hindrance generated by the phenyl groups attached to carbons C-4 and C-12 of the macrocycles.

The reduction of compounds **23**, **25**, and **26** with $LiAlH_4$ according to eq 2 (Scheme 4) led to the organostannylated diols **27**–**29**, structurally related to glutaric acid. These reactions also enabled confirming the structure of compound **28** previously reported.[5] The mixtures of optically active diols and TADDOL thus obtained were separated by column chromatography (silica gel 60), leading to the optically active stannylated diols **27**, **28**, and **29** in 56%, 75%, and 73% yield, respectively.

We were also able to obtain organotin-free macrodiolides with 11-membered rings via oxidation at room temperature of macrocycles **8**, **9a**, **18**, and **19a**, with 30% hydrogen peroxide and $KHCO_3$ according to eq 3, Scheme 4.[10] The new optically active macrodiolides **30** and **31** were obtained pure by column chromatography (silica gel 60) in 66–75% yield, as shown in Scheme 4.

In conclusion, in the case of TADDOL's unsaturated diesters the use of diorganotin chlorohydrides leads to much more stereoselective cyclohydrostannations than those carried out using triorganotin hydrides. As a result of this, a new and stereoselective two-step synthesis of organotin-substituted 11-membered macrodiolides starting from the commercially available TADDOL has been developed. The organotin macrocycles were obtained with an average total yield of 63% (from TADDOL). Another important point is that this synthetic route could also be applied to the synthesis of organotin-free 11-membered macrodiolides in three steps (from TADDOL) in an average total

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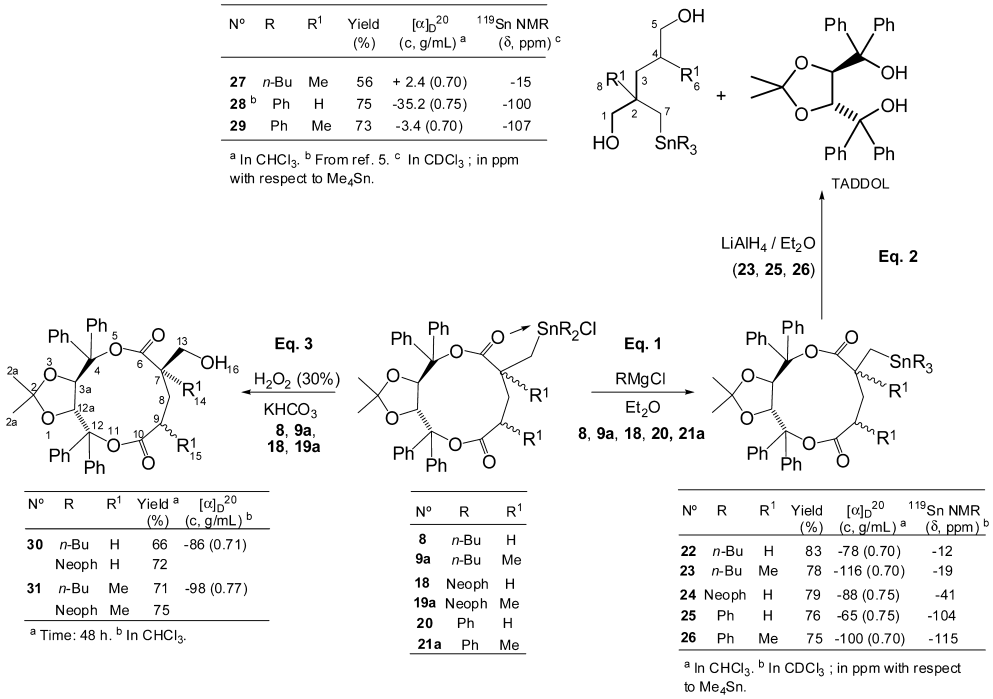
Scheme 4. Some Reactions of Chlorodiorganotin-Substituted Macrodiolides



N°	R	R^1	Yield (%)	$[\alpha]_D^{20}$ (c, g/mL) [a]	^{119}Sn NMR (δ, ppm) [c]
27	*n*-Bu	Me	56	+ 2.4 (0.70)	-15
28 [b]	Ph	H	75	-35.2 (0.75)	-100
29	Ph	Me	73	-3.4 (0.70)	-107

[a] In $CHCl_3$. [b] From ref. 5. [c] In $CDCl_3$; in ppm with respect to Me_4Sn.

N°	R	R^1	Yield [a] (%)	$[\alpha]_D^{20}$ (c, g/mL) [b]
30	*n*-Bu	H	66	-86 (0.71)
	Neoph	H	72	
31	*n*-Bu	Me	71	-98 (0.77)
	Neoph	Me	75	

[a] Time: 48 h. [b] In $CHCl_3$.

N°	R	R^1
8	*n*-Bu	H
9a	*n*-Bu	Me
18	Neoph	H
19a	Neoph	Me
20	Ph	H
21a	Ph	Me

N°	R	R^1	Yield (%)	$[\alpha]_D^{20}$ (c, g/mL) [a]	^{119}Sn NMR (δ, ppm) [b]
22	*n*-Bu	H	83	-78 (0.70)	-12
23	*n*-Bu	Me	78	-116 (0.70)	-19
24	Neoph	H	79	-88 (0.75)	-41
25	Ph	H	76	-65 (0.75)	-104
26	Ph	Me	75	-100 (0.70)	-115

[a] In $CHCl_3$. [b] In $CDCl_3$; in ppm with respect to Me_4Sn.

yield of 43.4%, i.e., a shorter route with much higher total yield than most macrolide syntheses.[2]

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker ARX 300 instrument, using $CDCl_3$ as solvent; chemical shifts (δ) are reported in ppm with respect to TMS, ^{1}H NMR, and ^{13}C NMR, and with respect to Me_4Sn in the case of ^{119}Sn NMR spectra. IR spectra were recorded on a FT-IR Nicolet Nexus 470/670/870 spectrophotometer. Mass spectra were obtained using a Finnigan MAT Incos 50 Galaxy System (DIP-MS). High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat. 900 (HR-EI-MS). Irradiations were conducted in a reactor equipped with four 250 W lamps with peak emission at 350 nm, water-cooled. Specific rotations were measured with a Polar L-μP, IBZ Messtechnik instrument. Elemental analyses (C, H) were performed in a Carlo Erba instrument. The melting points were determined with a Kofler hot stage apparatus and are uncorrected. All the solvents and reagents used were analytical reagent grade. Dineophyltin dichloride was prepared by disproportion reaction from neophylmagnesium chloride and tin tetrachloride.[8e] Di-*n*-butyl- (**3**), dineophyl- (**16**), and diphenyltin chlorohydride (**17**) were prepared by reduction of the corresponding dichloride with lithium aluminum hydride,[11] and the starting TADDOL unsaturated diesters were prepared as described previously.[7]

All hydrostannations were carried out under an argon atmosphere. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using 5% phosphomolybdic acid in ethanol.

Method A: Cyclohydrostannations Initiated by Irradiation at rt. *(a) Synthesis of Chlorodi-n-butyltin-Substituted Macrocycles **8**, **9a,b**, **10a–d**, and **11a–d**. (−)-(3aR,7R,12aS)-7-((Dibutylchlorostannyl)-methyl)-2,2-dimethyl-4,4,12,12-tetraphenyltetrahydro-3aH-[1,3]-dioxolo[4,5-c][1,6]dioxacycloundecine-6,10(4H,7H)-dione (**8**).* Di-*n*-butyltin dichloride (**2**) (0.18 g, 0.60 mmol) was dissolved in dry toluene (5 mL), and di-*n*-butyltin dihydride (**1**) (0.12 g, 0.60 mmol) was added. The mixture was stirred for about 30 min, with monitoring of the reaction by IR spectroscopy. A toluene (10 mL) solution of diester **4** (0.50 g, 0.87 mmol) was added to the mixture. The reaction mixture was irradiated for 1 h, with monitoring by TLC and IR spectroscopy. The solvent was then distilled off under reduced pressure, and the ^{119}Sn NMR spectrum of the crude product showed that the only product of reaction was macrocycle **8**. The crude product thus obtained was directly purified by column chromatography using silica gel 60. The cyclic adduct **8** (0.62 g, 0.74 mmol, 85%) was eluted with hexane/diethyl ether (80:20) as a yellow solid, mp 132−134 °C. $[\alpha]^{20}_D = -79$ (*c* 0.76, $CHCl_3$). IR (KBr): 3055; 3021; 2945; 2850; 1717; 1672; 1602; 1485; 1450; 1243; 1155; 848; 747; 690 cm^{-1}. HRMS (ESI): calcd for $C_{45}H_{53}ClO_6Sn$ 844.2553, found 844.2548 Anal. Calcd for $C_{45}H_{53}ClO_6Sn$: C, 64.03; H, 6.33. Found: C, 64.08; H, 6.29.

Using the same method, the reaction of **5** (0.50 g, 0.83 mmol) with *n*-Bu_2SnCl_2 (0.18 g, 0.58 mmol) and *n*-Bu_2SnH_2 (0.14 g, 0.58 mmol) was studied in dry toluene (10 mL) as solvent. The crude product was purified by column chromatography using silica gel 60. The cyclic adduct **9a** (0.58 g, 0.66 mmol, 80%) was eluted with hexane/diethyl ether (95:5) as a white solid, mp 121−123 °C. $[\alpha]^{20}_D = -87$ (*c* 0.77, $CHCl_3$). IR (KBr): 3060; 3024; 2955; 2923; 1719; 1676; 1605; 1492; 1448; 1239; 1160; 850; 757; 696 cm^{-1}. HRMS (ESI): calcd for $C_{47}H_{57}ClO_6Sn$ 872.2866, found 872.2872 Anal. Calcd for $C_{47}H_{57}ClO_6Sn$: C, 64.80; H, 6.48. Found: C, 64.89; H, 6.52. Diastereoisomer **9b** could not be separated pure.

Under the same conditions, the reaction of **6** (0.66 g, 0.87 mmol) with *n*-Bu_2SnCl_2 (0.19 g, 0.62 mmol) and *n*-Bu_2SnH_2 (0.14 g, 0.62 mmol) in dry toluene (4 mL) as solvent took 12 h. The crude product was purified by column chromatography using silica gel 60. The mixture of cyclic adducts (**10a–d**) (0.53 g, 0.52 mmol, 60%) was eluted with hexane/diethyl ether (95:5) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 0.61 (t, 4H); 0.82 (t, 6H); 1.23 (d, 3H); 1.33 (s, 6H); 1.30 (s, 3H); 1.34−1.61 (m, 8H); 2.52 (m, 1H); 2.81 (m, 1H); 3.62 (d, 1H); 5.25 (d, $^3J_{H,H}$ 7.3 Hz, 1H); 5.31 (d, $^3J_{H,H}$ 7.3 Hz, 1H); 7.05−7.51 (m, 30H). ^{13}C NMR ($CDCl_3$): δ 13.91; 14.13; 17.62 (167.5); 18.24 (226.8); 19.91; 21.25; 21.33; 27.12; 27.31; 29.65 (22.6); 29.82 (24.9); 52.21 (18.2); 52.31 (27.3); 79.23; 79.65; 80.40; 80.71; 89.92; 90.05; 91.22; 91.45; 109.62; 109.71; 127.96; 128.04; 128.13; 128.21; 128.42; 128.82; 128.91; 129.32; 129.85; 130.51; 130.92; 135.43; 135.51; 138.81; 138.81; 138.92; 139.53; 139.61; 142.76; 142.91; 143.33; 143.42; 143.45; 143.51; 169.15; 171.22; 180.59 (7.5); 181.53 (12.9). IR (KBr): 3050; 3031; 2949; 2852; 1720; 1675; 1600 1490; 1451; 1245; 1150; 847; 750; 695 cm^{-1}.

Under the same conditions the reaction of **7** (0.20 g, 0.23 mmol) with *n*-Bu_2SnCl_2 (0.046 g, 0.15 mmol) and *n*-Bu_2SnH_2 (0.035 g,

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0.15 mmol) in dry toluene (4 mL) also took 12 h. The crude product obtained was purified by column chromatography using silica gel 60. The mixture of cyclic adducts (**11a−d**) (0.16 g, 0.14 mmol, 62%) was eluted with hexane/diethyl ether (94:6) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 4H); 0.96 (t, 6H); 1.31 (s, 6H); 1.35−1.45 (m, 8H); 3.61 (d, 1H); 3.82 (d, 1H); 4.12 (m, 1H); 5.21 (d, $^3J_{H,H}$ 7.4 Hz, 1H); 5.3 (d, $^3J_{H,H}$ 7.4 Hz, 1H); 6.97 −7.38 (m, 40H). ^{13}C NMR ($CDCl_3$): δ 13.92; 14.02; 16.21 (205.2); 16.61 (201.3); 18.22; 18.71; 19.53; 19.71; 26.22; 26.70; 47.64 (26.5); 47.74 (27.3); 64.10 (27.1); 65.94 (18.6); 78.81; 79.42; 79.66; 80.12; 88.20; 88.31; 90.61; 90.71; 109.70; 109.79; 123.62; 126.12; 126.31; 126.44; 126.51; 126.57, 126.67; 126.91; 127.13; 127.32; 127.41; 127.71; 128.02; 128.71; 128.89; 139.49; 140.84; 142.49; 142.55; 142.73; 142.91; 143.15; 143.56; 143.77; 172.20; 173.91; 178.82 (14.1); 179.42 (4.2). IR (KBr): 3048; 3027; 2950; 2850; 1718; 1670; 1601 1495; 1450; 1250; 1151; 848; 749; 690 cm^{-1}.

*(b) Synthesis of Chlorodineophyl-Substituted Macrocycles **18** and **19a,b**.* Following the same procedure the reaction of diester **4** (0.55 g, 0.96 mmol) with dineophyltin dichloride (0.30 g, 0.65 mmol) and dineophyltin dihydride (0.25 g, 0.65 mmol) in dry toluene (18 mL) needed 14 h of irradiation. The crude product thus obtained was directly purified by column chromatography using silica gel 60. Cyclic adduct **18** (0.66 g, 0.66 mmol, 69%) was eluted with hexane/diethyl ether (85:15) as a white solid, mp 151−153 °C. $[\alpha]^{20}_D$ = −92 (*c* 0.75, $CHCl_3$). IR (KBr): 3053; 3019; 2943; 2912; 1720; 1675; 1601; 1490; 1454; 1227; 1157; 855; 755; 691 cm^{-1}. HRMS (ESI): calcd for $C_{57}H_{61}ClO_6Sn$ 996.3179, found 996.3165 Anal. Calcd for $C_{57}H_{61}ClO_6Sn$: C, 68.72; H, 6.17. Found: C, 68.67; H, 6.11.

Under the same experimental conditions, the reaction of **5** (0.55 g, 0.91 mmol) with $Neoph_2SnCl_2$ (0.30 g, 65 mmol) and $Neoph_2SnH_2$ (0.25 g, 0.65 mmol) in dry toluene (8 mL) as solvent took place in 14 h. The crude product was purified by column chromatography using silica gel 60. The cyclic adduct **19a** (0.67 g, 0.65 mmol, 72%) was eluted with hexane/diethyl ether (90:10) as a white solid, mp 170−173 °C. $[\alpha]^{20}_D$ = −97 (*c* 0.71, $CHCl_3$). IR (KBr): 3043; 3021; 2940; 2915; 1722; 1673; 1600; 1489; 1456; 1225; 1160; 857; 750; 695 cm^{-1}. HRMS (ESI): calcd for $C_{59}H_{65}ClO_6Sn$ 1024.3492, found 1024.3483 Anal. Calcd for $C_{59}H_{65}ClO_6Sn$: C, 69.18; H, 6.40. Found: C, 69.25; H, 6.50.

*(c) Synthesis of Chlorodiphenyl-Substituted Macrocycles **20** and **21a,b**.* Following the same protocol, the reaction of **4** (1 g, 1.74 mmol) with Ph_2SnCl_2 (0.42 g, 1.21 mmol) and Ph_2SnH_2 (0.33 g, 1.21 mmol) occurred in dry toluene (10 mL) as solvent; the irradiation time was 1 h. The crude product obtained was purified by column chromatography using silica gel 60. The cyclic adduct **20** (1.12 g, 1.27 mmol, 73%) was eluted with hexane/diethyl ether (93:7) as a white solid, mp 107−109 °C. $[\alpha]^{20}_D$ = −72 (*c* 0.75, $CHCl_3$). IR (KBr): 3053; 3025; 2950; 2913; 1720; 1673; 1602; 1490; 1444; 1235; 1140; 860; 750; 691 cm^{-1}. HRMS (ESI): calcd for $C_{49}H_{44}ClO_6Sn$ 883.1848, found 883.1853 Anal. Calcd for $C_{49}H_{44}ClO_6Sn$: C, 66.65; H, 5.02. Found: C, 66.70; H, 6.62.

Under the same experimental conditions, the reaction of **5** (1 g, 1.66 mmol) with Ph_2SnCl_2 (0.40 g, 1.16 mmol) and Ph_2SnH_2 (0.32 g, 1.16 mmol) occurred in dry toluene (10 mL) as solvent; the irradiation time was 1 h. The crude product obtained was purified by column chromatography using silica gel 60. The cyclic adduct **21a** (1.07 g, 1.18 mmol, 71%) was eluted with hexane/diethyl ether (94:6) as a white solid, mp 115−117 °C. $[\alpha]^{20}_D$ = −78 (*c* 0.73, $CHCl_3$). IR (KBr): 3045; 3014; 2951; 2902; 1717; 1675; 1600; 1482; 1440; 1229; 1157; 852; 758; 693 cm^{-1}. HRMS (ESI): calcd for $C_{51}H_{48}ClO_6Sn$ 911.2161, found 911.2156. Anal. Calcd for $C_{51}H_{48}ClO_6Sn$: C, 67.23; H, 5.31. Found: C, 67.18; H, 5.35. Diastereoisomer **21b** could not be separated pure.

Method B: Cyclohydrostannations at rt Initiated by AIBN. Dialkyltin dichloride (0.6 mmol) was dissolved in dry toluene (6 mL). Then the dialkylltin dihydride (0.6 mmol) was added, and the mixture was stirred for 1 h. A solution of diester (0.8 mmol) in toluene (10 mL) and AIBN (ca. 4 mg, 0.025 mmol) was added, and the reaction mixture was kept stirring for 48−72 h, with monitoring by TLC and IR spectroscopy. The solvent was distilled off under reduced pressure, and the product was purified by column chromatography on silica gel.

Using method B, the reactions with *n*-Bu_2SnHCl led to macrocycles **8** (48 h, 89% yield), **9a,b** (48 h, 87%), **10a−d** (72 h, 65%), and **11a−d** (72 h, 68%), in the same proportions as using method A.

Hydrostannation at −78 °C Initiated by Et_3B (Method C). Dialkyltin dihydride (0.12 mL, 0.60 mmol) was added to a solution of dialkyltin dichloride (0.18 g, 0.60 mmol) in dry toluene (5 mL) at 0 °C. After being stirred for 20 min, the mixture was cooled to −78 °C. A solution of diester (0.9 mmol) in toluene (4 mL) was added to the mixture. After 5 min, Et_3B (1.0 M in hexane, 0.10 mL, 0.10 mmol) was added. The mixture was stirred at −78 °C for 6 h and then 6 h at rt, with monitoring by TLC and IR spectroscopy. The solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography on silica gel.

Using method C, the reactions with *n*-Bu_2SnHCl led to macrocycles **8** (12 h, 79% yield), **9a** (12 h, 75%), **10a−d** (72 h, 65%), and **11a−d** (72 h, 68%).

Alkylation of Organotin Macrodiolides 8, 9a, 18, 20, and 21a. *(−)-(3aR,7R,12aS)-7-((Tributylstannyl)methyl)-2,2,7,9-tetramethyl-4,4,12,12-tetraphenyltetrahydro-3aH-[1,3]dioxolo[4,5-c][1,6]dioxacycloundecine-6,10(4H,7H)-dione (**23**).* The reaction was carried out under an argon atmosphere; *n*-butylmagnesium chloride (1.8 M in diethyl ether, 2.40 mL, 4.37 mmol) was added with stirring to a solution of **9a** (0.38 g, 0.44 mmol) in dry diethyl ether (6 mL). The reaction mixture was heated under reflux for 2 h. After cooling, water was added (1 mL), and the solution was acidified with diluted hydrochloric acid (10%). The organic layer was separated and then dried on $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography using silica gel 60. The cyclic adduct **23** (0.29 g, 0.34 mmol, 78%) was eluted with hexane/diethyl ether (99:1) as a white solid, mp 101−103 °C. $[\alpha]^{20}_D$ = −116 (*c* 0.70, $CHCl_3$). IR (KBr): 3035; 3010; 2945; 2858; 1740; 1602; 1485; 1450; 1235; 1152; 860; 745; 692 cm^{-1}. HRMS (ESI): calcd for $C_{51}H_{65}O_6Sn$ 893.3803, found 893.3808. Anal. Calcd for $C_{51}H_{65}O_6Sn$: C, 68.61; H, 7.34. Found: C 68.66; H 7.29.

Using the same procedure for the reaction of **8** (0.25 g, 0.29 mmol) with *n*-butylmagnesium chloride (1.75 M in diethyl ether, 0.17 mL, 0.29 mmol), the crude product obtained was purified by column chromatography using silica gel 60. The cyclic adduct **22** (0.21 g, 0.24 mmol, 83%) was eluted with hexane/diethyl ether (97:3) as a white solid, mp 112−115 °C. $[\alpha]^{20}_D$ = −78 (*c* 0.70, $CHCl_3$). IR (KBr): 3030; 3011; 2950; 2910; 2862; 1745; 1605; 1490; 1451; 1242; 1150; 850; 749; 690 cm^{-1}. HRMS (ESI): calcd for $C_{49}H_{62}O_6Sn$ 866.3568, found 866.3575. Anal. Calcd for $C_{49}H_{62}O_6Sn$: C, 67.98; H, 7.22. Found: C, 67.91; H, 7.28.

Following the same protocol for the reaction between **18** (0.30 g, 0.30 mmol) and neophylmagnesium chloride (1.80 M in diethyl ether, 0.16 mL, 0.30 mmol), the crude product obtained was purified by column chromatography using silica gel 60. The cyclic adduct **24** (0.25 g, 0.23 mmol, 79%) was eluted with hexane/diethyl ether (98:2) as a white solid, mp 107−109 °C. $[\alpha]^{20}_D$ = −88 (*c* 0.75, $CHCl_3$). IR (KBr): 3031; 3015; 2950; 2912; 2860; 1743; 1600; 1495; 1455; 1240; 1151; 853; 749; 691 cm^{-1}. HRMS (ESI): calcd for $C_{67}H_{74}O_6Sn$ 1094.4507, found 1094.4515 Anal. Calcd for $C_{67}H_{74}O_6Sn$: C, 73.56; H, 6.82. Found: C, 73.61; H, 6.87.

In the case of the reactions using phenylmagnesium halides the procedure was slightly different. Thus, phenylmagnesium bromide (1.6 M in THF, 1.4 mL, 2.2 mmol) was added with stirring to a solution of **21a** (0.34 g, 0.37 mmol) in THF (0.8 m L). The reaction mixture was heated under reflux for 24 h. After cooling NH_4Cl (4 mL) was added to quench the reaction. The aqueous layer was extracted with AcOEt. The combined extracts were washed with brine and dried on magnesium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography using silica gel 60. The cyclic adduct **26** (0.27 g, 0.28 mmol, 75%) was eluted with hexane/AcOEt (96:4) as a white solid, mp 106−110 °C, which was identified by comparison with an authentic sample (ref 5).

Similarly, the crude product obtained in the reaction of **20** (0.40 g, 0.45 mmol) with phenylmagnesium bromide (1.60 M in THF, 1.7 mL,

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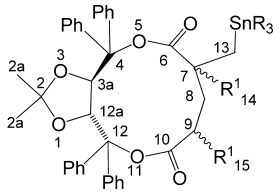
Table 6. ^{13}C NMR Spectra of Compounds 22−24[a]

N°	R	R^1
22	*n*-Bu	H
23	*n*-Bu	Me
24	Neoph	H

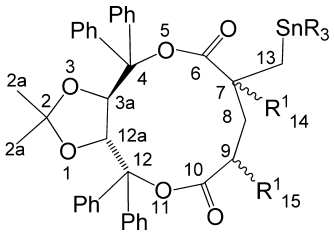


compound no.	**22**[b]	**23**[c]	**24**[d]
C-2	110.08	110.72	110.07
C-2a	27.31	27.48	27.26 and 27.30
C-3a and C-12a	76.85 and 76.90	76.02 and 77.01	76.76 and 76.90
C-4 and C-12	87.49 and 87.51	87.14 and 90.27	87.33 and 87.38
C-6 [^3J(Sn,C)]	175.61 (34.3)	181.12 (11.3)	175.18 (45.0)
C-7 [^2J(Sn,C]	43.83 (15.5)	46.74 (60.7)	42.99 (13.9)
C-8 [^3J(Sn,C)]	30.69 (25.1)	46.68 (23.0)	29.92 (21.4)
C-9	35.07	36.25	34.63
C-10	170.85	175.35	170.90
C-13 [^1J(Sn,C)]	12.51 (279.0)	18.99 (441.1)	15.61 (290.1)
C-14 [^3J(Sn,C)]		27.05 (15.7)	
C-15		18.96	

[a]In $CDCl_3$; chemical shifts, δ, in ppm with respect to TMS; ^nJ(Sn,C) coupling constants, in Hz (in brackets); NO = not observed. Other signals: [b]9.82 (327.4); 13.89; 27.50 (55.2); 29.32 (20.0); 126.82; 126.85; 127.28; 127.30; 127.53; 127.54; 127.58; 127.61; 128.61; 128.72; 130.43; 140.71; 140.87; 144.84; 144.87. [c]13.51; 13.78; 18.17 (421.9); 26.28 (83.4); 27.90 (27.84); 28.33 (27.84); 126.88; 127.31; 127.34; 127.69; 127.75; 127.94; 128.26; 129.75; 130.03; 139.82; 140.52; 142.86; 144.67. [d]31.07 (316.3); 33.32 (35.9); 33.62 (37.8); 38.23 (18.7); 125.47; 125.62; 126.78; 127.21; 127.27; 127.51; 127.55; 127.62; 128.20; 128.56; 128.60; 130.34; 140.60; 140.84 (27.5).

Table 7. ^{1}H NMR Spectra of Compounds 22−24[a]

N°	R	R^1
22	*n*-Bu	H
23	*n*-Bu	Me
24	Neoph	H



no.	chemical shifts (δ, in ppm)[a] [C-No.][b]
22	*n*-Bu groups: 0.62−0.66 (m, 6H); 0.81 (t, 9H); 1.13−1.40 (m, 12H). Protons of the cycle: 0.53 (s, 2H) [C-13]; 1.48 (s, 6H) [C-2a]; 1.96−2.62 (m, 5H) [C-7, C-8, C-9]; 5.53 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]; 5.59 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]. Phenyl groups: 7.13−7.29 (m, 20H).
23	*n*-Bu groups: 0.55−0.69 (m, 6H); 0.93 (t, 9H); 1.29−1.39 (m, 6H); 1.41−1.49 (m, 6H). Protons of the cycle: 0.42−0.45 (m, 2H) [C-13]; 0.81 (s, 3H) [C-14]; 1.01 (d, $^3J_{H,H}$ 6.8 Hz, 3H) [C-15]; 1.07 (s, 6H) [C-2a]; 2.55−2.61 (m, 3H) [C-8, C-9]; 5.56 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]; 5.83 (d, $^3J_{H,H}$ 7.6 Hz, 1H) [C-3a or C-12a]. Phenyl groups: 7.22−7.49 (m, 20H).
24	Neophyl groups: 0.81 (s, ^2J(Sn,H) 49.0 Hz, 6H); 1.07 and 1.08 (two superimposed picks, 18H). Protons of the cycle: 0.19 (d, 1H) and 0.24 (d, 1H) [C-13]; 0.61 (s, 3H) and 0.64 (s, 3H) [C-2a]; 1.60−1.79 (m, 2H) [C-9]; 1.98−2.22 (m, 2H) [C-8]; 2.24−2.40 (m, 1H) [C-7]; 5.52 (d, $^3J_{H,H}$ 7.8 Hz, 1H) [C-3a or C-12a]; 5.57 (d, $^3J_{H,H}$ 7.8 Hz, 1H) [C-3a or C-12a]. Phenyl groups: 7.04−7.31 (m, 35H).

[a]In $CDCl_3$; multiplicity and J values in Hz (in parentheses). [b]Carbon to which the protons are attached.

2.7 mmol) was purified by column chromatography using silica gel 60. The cyclic adduct **25** (0.32 g, 0.34 mmol, 76%) was eluted with hexane/diethyl ether (90:10) as a white solid, mp 96−98 °C, and was identified by comparison with an authentic sample (ref 5).

Reduction of Macrodiolides 23, 25, and 26 with $LiAlH_4$. *Synthesis of (+)-2,4-Dimethyl-2-[(tributylstannyl)methyl]pentane-1,5-diol (27).* To a solution of **23** (0.18 g, 0.22 mmol) in ether (4.0 mL) was added lithium aluminum hydride (0.055 g, 1.44 mmol) at room temperature. After stirring for 4 h, the reaction was quenched with HCl (2 N, 0.8 mL) and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over magnesium sulfate. The organic solvent was distilled off under reduced pressure to give an oily residue, which was purified by column chromatography (silica gel 60). The stannylated alcohol **27** (0.052 g, 0.12 mmol, 56%) was eluted with hexane/AcOEt (90:10) as a colorless oil. $[\alpha]^{20}_D$ = +2.4 (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.84−1.04 (m, 23H); 1.27−1.37 (m, $^2J_{H,Sn}$ 29.3 Hz, 8H); 1.45−1.51 (m, $^3J_{H,Sn}$ 31.2 Hz, 6H); 1.66−1.69 (m, 1H, H4); 3.15−3.37 (m, 2H, H1/H5)); 3.45−3.57 (m, 2H, H1/H5). ^{13}C NMR ($CDCl_3$): δ 10.44 (316.3); 13.65; 19.93 (296.1); 20.09 (195.6); 27.45 (57.6) (C-2); 27.78 (19.4); 29.19 (19.6); 30.84 (C-6); 38.73 (18.0) (C-4); 42.89 (30.0); 69.27 (C-5); 70.99 (44.2) (C-1). IR (film): 3324, 2955, 2925, 2868, 1465, 1372, 1034 cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{44}O_2Sn$ 436.2363, found 436.2358. Anal. Calcd for $C_{20}H_{44}O_2Sn$: C, 55.19; H, 10.19. Found: C, 55.15; H, 10.24.

Under the same experimental conditions, the reduction of cyclic adduct **25** gave diol **28** as a colorless oil in 75% yield. We have already reported the physical characteristics of **28** (see ref 5).

Under the same experimental conditions, the reduction of cyclic adduct **26** gave diol **29** as a colorless oil in 73% yield. $[\alpha]^{20}_D$ = −3.4 (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3H, H6); 1.03 (s, 3H, H8); 1.23−1.28 (m, 3H); 1.59 (s, $^2J_{H,Sn}$ 59.8 Hz, 2H, H7); 3.24−3.32 (m, 2H);

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3.38−3.47 (m, 2H); 7.38−7.39 (m, 9H, HAr); 7.59−7.61 (m, 6H, HAr). ^{13}C NMR ($CDCl_3$): δ 19.75 (C-6); 22.61 (291.9) (C-7); 27.32 (89.0) (C-8); 29.71 (C-4); 38.93 (20.5) (C-2); 42.90 (37.4) (C-3); 71.22 (41.2) (C-1); 69.23 (C-5); 128.41; 128.63 (10.7); 136.90 (35.6). IR (film): 3370, 3075, 2919, 1605, 1475, 1449, 1429, 1378, 1070, 1019, 722, 691 cm^{-1}. HR-MS (EI): calcd for $C_{26}H_{32}O_2Sn$ 496.1424, found. 496.1429. Anal. Calcd for $C_{26}H_{32}O_2Sn$: C, 63.06; H, 6.51. Found: C, 63.10; H, 6.56.

Oxidation of Organotin Macrocycles 8, 9a, 18, and 19a. *Synthesis of (−)-(3aR,7R,12aS)-7-(Hydroxymethyl)-2,2-dimethyl-4,4,12,12-tetraphenyltetrahydro-3aH-[1,3]dioxolo [4,5-c][1,6]-dioxacycloundecine-6,10 (4H,7H)-dione (**30**).* To a solution of **8** (0.20 g, 0.23 mmol) in methanol (1.5 mL) and THF (1.5 mL) was added $KHCO_3$ (70 mg, 0.70 mmol) and 30% H_2O_2 (0.12 mL, 1.15 mmol) at rt, and the mixture was stirred for 48 h. The mixture was quenched with a 5% aqueous sodium sulfite solution and extracted with ethyl acetate. The organic layer was washed with brine, dried, and then concentrated in vacuo to give an oil, which was purified by column chromatography on silica gel 60. Alcohol **30** (0.089 g, 0.15 mmol, 66%) was eluted with hexane/ethyl acetate (80:20) as a white solid, mp 157−159 °C. $[\alpha]^{20}_D$ = −86 (*c* 0.71, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 6H, H2a), 2.23−2.31 (m, 4H, H8/H15), 2.60−2.72 (m, 1H, H14), 3.61 (d, 2H, H13), 4.10 (s, 1H, H16), 5.43 (d, $^3J_{H,H}$ 7.5 Hz, 1H, H3a/H12a), 5.51 (d, $^3J_{H,H}$ 7.5 Hz, 1H, H3a/H12a), 7.12−7.33 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 19.50 (C-8), 26.22 (C-2a), 26.55 (C-2a), 33.41(C-9), 50.80 (C-7), 62.12 (C-13), 75.53 (C-3a/C-12a), 76.81 (C-3a/C-12a), 79.71(C-4/C-12), 108.42 (C-2), 126.21, 126.65, 126.73, 127.85, 141.40, 142.01, 172.15 (C-10), 173.72 (C-6). IR (KBr): 3615, 3025, 3011, 2950, 2910, 2865, 1744, 1600, 1485; 1451; 1243; 1155; 852; 750; 691 cm^{-1}. HRMS (ESI): calcd for $C_{37}H_{36}O_7$ 592.2461, found 592.2467. Anal. Calcd for $C_{37}H_{36}O_7$: C, 74.98; H, 6.12. Found: C, 75.01; H, 6.15.

Using the same procedure, the oxidation of **9a** led to compound **31**. The product was purified by column chromatography (silica gel 60), and macrodiolide **31** (71%) was eluted with hexane/ethyl acetate (85:15) as a white solid, mp 141−143 °C. $[\alpha]^{20}_D$ = −98 (*c* 0.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.12 (d, 3H, H15), 1.21 (s, 3H, H14), 1.28 (s, 6H, H2a), 1.63 (d, 2H, H8), 2.71−2.82 (m, 1H, H9), 3.74 (s, 2H, H13), 4.31 (s, 1H, H16), 5.35 (d, $^3J_{H,H}$ 7.4 Hz, 1H, H3a/H12a), 5.41 (d, $^3J_{H,H}$ 7.4 Hz, 1H, H3a/H12a), 7.08−7.18 (m, 20H, HAr). ^{13}C NMR ($CDCl_3$): δ 19.22 (C-15), 22.50 (C-14), 26.33 (C-2a), 26.81 (C-2a), 37.51(C-7), 38.22 (C-9), 38.80 (C-8), (C-13), 75.50 (C-3a/C-12a), 76.13 (C-3a/C-12a), 78.41 (C-4/C-12), 108.74 (C-2), 126.13, 126.51, 126.74, 127.60, 140.52, 141.61, 174.13 (C-10), 174.91 (C-6). IR (KBr): 3610; 3030; 3010; 2945; 2912; 2861; 1741; 1605; 1487; 1452; 1240; 1158; 850; 751; 695 cm^{-1}. HRMS (ESI): calcd for $C_{39}H_{40}O_7$ 620.2774, found 620.2769. Anal. Calcd for $C_{39}H_{40}O_7$: C, 75.46; H, 6.50. Found: C, 75.51; H, 6.55.

The oxidation of organotin macrodiolides **18** and **19a** under the same reaction conditions afforded the same alcohols **30** (72%) and **31** (75%), respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C, and ^{119}Sn NMR spectra as well as crystallographic data for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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