Synthesis, Characterization and *in Vitro* Cytotoxicity of Pentacoordinated Tin(IV) Complexes Derived from Aminoalcohols

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The synthesis of pentacoordinated Tin(IV) compounds derived from aminoalcohols is described. The compounds were characterized by IR, ^{1}H-, ^{13}C-, and ^{119}Sn-NMR, the mass spectrometry exhibits molecular ions corresponding to monomeric species. All compounds were evaluated for *in vitro* cytotoxic activities against five human tumor cell lines, U251 (human glioblastoma), PC-3 (human prostatic adenocarcinoma), K-562 (human chronic myelogenous leukemia), HCT-15 (human colorectal adenocarcinoma), MCF-7 (human mammary adenocarcinoma). The cytotoxic evaluation revealed that all compounds possess higher cytotoxic potency than that of the cisplatin, which was used as reference. Additionally, MT2 cells (human T-lymphocytes) were also evaluated.

Key words cytotoxicity; Tin(IV); pentacoordinated; ^{119}Sn-NMR

Since the late 1960, there have been significant advances in cancer treatment and early detection. Nonetheless, during the same period overall cancer incidence has shown an increase.[1)] This has encouraged the development of new drugs for cancer treatment. In this context the organometallic compounds have been widely investigated as potential antitumor agents. The metallocene dihalide complexes Cp2MX2 with M=titanium, vanadium, niobium or molybdenum as central metal atom were the first early transition metal that showed to have antitumor activity. The organometallic-DNA and organometallic-nucleic acids interactions have also been investigated.[2—4)] Ferricenium salts, organotin and more recently bismute complexes are also examples of organometallic compounds that have been found to exhibit interesting antitumor activity.[5)] Presently, the biological activity of organotin compounds is well known owing to their practical applications as fungicides, bactericides, biocides, and pesticides.[4,6—8)] However, one of the fields that have been more studied and reviewed is the activity of such compounds against cancer.[2,4,9,10)] Up to date several articles concerning antitumor activity of organometallic tin-containing compounds have been reported. Organotin carboxylates,[11—18)] organotin complexes derived of aminoacids and peptides are some examples.[9,19)] As part of our interest in pentacoordinated species we recently reported the synthesis and structure of a series of pentacoordinated tin compounds.[20)] As continuation of an ongoing investigation we synthesized four pentacoordinated organotin complexes derived of aminoalcohol type ligands with the aim of evaluating their *in vitro* cytotoxicity against five human tumor cell lines.

Results and Discussion

Synthesis The compounds **1a**—**d** were prepared by reaction of the corresponding epoxide and two 2-aminophenols following an efficient one pot method, the yields of compounds **1a**—**d** are in the range of 55—90%.[21)] The tin compounds **2a**—**c** were synthesized by reaction of the corresponding ligands **1a**—**c** with dibutyltin oxide in a mixture of toluene–methanol (4 : 1) as shown in Chart 1. All compounds resulted to be stable under atmospheric conditions and soluble in common organic solvents such as MetOH, EtOH, and chloroform.

Spectroscopy The IR bands due to ν(OH) centered at approximately 3200 cm^{-1} of the free ligand disappears in the complexes **2a**—**c** which indicates that the two oxygens are attached to the tin atom. The bands at 558, 547 and 567 cm^{-1} were assigned to ν(Sn–O), these values are in agreement with those found for complexes containing Sn–O bond.[22)] The mass spectrometry showed the ions m/z=439, 453, 473 which correspond to the monomeric compounds. Additionally, the fragment ions $C_6H_4NHC_6H_{10}O_2SnBu^+$, $C_6H_4NHC_6H_{10}O_2Sn^+$ and $C_6H_4NOSn^+$ were also detected.

The proton NMR parameters for **2a**—**c** are given in Table 1. A couple of triplets corresponding to the diastereotopic methyl groups were observed for all compounds. Significant changes in the chemical shifts, which might be attributed to the coordination, were not observed. The ^{13}C-NMR spectra of **2a**—**c** showed that the carbons C-1 and C-4 are shifted to higher frequencies $\Delta\delta$=8—10 and $\Delta\delta$=11—12 respectively, with respect to the free ligand, meanwhile the C-2 is less shielded than C-1 and C-4. Conversely, the carbon C-3 is shifted to low frequencies $\Delta\delta$=4—8, these changes might be associated with the coordination of the tin atom.

The ^{119}Sn-NMR spectra of **2a**, **2b**, and **2c**, obtained in $CDCl_3$, displayed singlets at −87.9, −87.0 and −81.2 ppm respectively, these chemical shift values suggest the presence of Sn→N bond and are consistent with those reported for

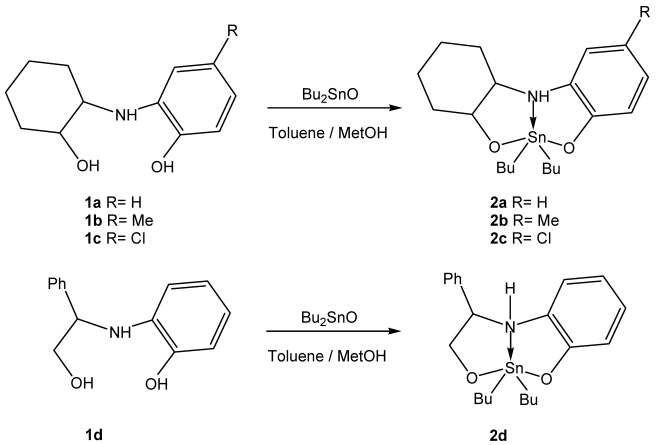

Chart 1

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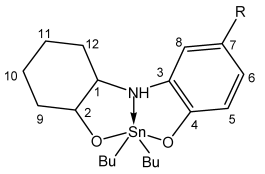
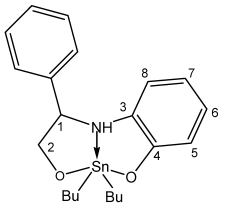
Table 1. ^{1}H-, ^{13}C- and ^{119}Sn-NMR Data

Compound	H-1	H-2	H-9	H-10/H-11	H-12	H-arom	$\underline{CH_3}(CH_2)_3Sn$
4a	2.17—2.20 (3H, m, H-1, H-12)	3.23—3.25 (1H, m)	2.30—2.38 (2H, m, H-9)	1.17—1.71 (16H, m, H-10, H-11, $CH_3(\underline{CH_2})_3Sn$)	2.17—2.20 (3H, m, H-1, H-12)	6.90—7.10 (4H, m)	0.83 (3H, t, J=6.87 Hz) 0.92 (3H, t, J=6.87 Hz)
4b	2.12—2.20 (3H, m, H-1, H-12)	3.18—3.21 (1H, m)	2.28—2.31 (2H, m)	1.1—1.58 (16H, m, H-11, H-10, $CH_3(\underline{CH_2})_3Sn$)	2.12—2.20 (3H, m, H-1, H-12)	6.79—6.87 (3H, m, H-5, H-6, H-8)	0.79 (3H, t, J=7.3 Hz) 0.84 (3H, t, J=7.3 Hz)
4c	2.13—2.28 (3H, m, H-1, H-12)	3.14—3.17 (1H, m)	1.80—2.12 (2H, m)	1.09—1.80 (14H, m, H-11, H-10, CH_2–Sn)	2.13—2.28 (3H, m, H-1, H-12)	6.78—7.20 (3H, m, H-3, H-5, H-8)	0.74—0.84 (6H, m)
4d	4.12 (1H, dd J=9.5, 3.2 Hz)	3.10 (1H, d J=12.6 Hz) 3.5—3.7 (1H, m)				6.38 (1H, d, J=7.8 Hz, H-8) 6.92 (1H, d, J=7.8 Hz, H-5) 7.01—7.07 (2H, m, H-6, H-7) 7.19—7.38 (5H, m, H-arom)	0.88 (3H, t, J=6.9 Hz, CH_3–Sn) 0.92 (3H, t, J=6.9 Hz, CH_3–Sn)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	CH_3–Sn	^{119}Sn
4a	68.7	74.2	129.1	156.7	118.5	125.9	128.6	116.7	35.5	21.5	20.3	30.9	13.7, 13.80	−87.9
4b	68.7	74.2	129.3	155.0	125.8	126.3	129.0	118.0	35.5	21.7	20.1	30.9	13.6, 13.8	−87.0
4c	68.6	74.2	133.2	155.6	121.2	125.6	128.3	119.4	35.4	22.0	20.1	30.8	13.6, 13.7	−81.2
4d	67.1	70.0	138.4	156.9	117.9	118.6	126.8	116.8	26.9	27.7	27.2		13.8	−84.1



4a R= H
4b R= Me
4c R= Cl



4d

Table 2. IC_{50} (μM) Values for **2a**—**d**

	U251	PC-3	K-562	HCT-15	MCF-7	MT2
2a	1.75±0.12	2.23±0.43	1.93±0.45	1.77±0.25	1.61±0.34	2.02±0.43
2b	3.54±0.12	2.98±0.18	1.75±0.12	2.78±0.38	2.07±0.48	3.30±0.07
2c	1.45±0.07	1.60±0.05	0.28±0.05	2.53±0.37	0.76±0.03	1.54±0.25
2d	1.88±0.11	2.41±0.43	1.12±0.21	2.69±0.25	1.77±0.31	0.28±0.08
Cisplatin	9.48±1.7	15.90±2.1	13.52±0.6	13.48±0.7	25.8±3.7	9.72±1.12

compounds with pentacoordinate geometries.[23] The ^{119}Sn-NMR experiments were also recorded using Me-d_3-alcohol-*d* as solvent, however, significant changes in the chemical shifts were not observed, which indicates that the five-coordination around the tin atom is retained whatever the solvent used.

The complex **2d** was prepared by reaction of compound **1d** with dibutyltin oxide. The IR spectra showed the band of the Sn–O vibration at 531 cm^{-1}. The formation of the monomeric complex was established by mass spectrometry which exhibited the molecular ion m/z=461, the spectrum also showed the fragment ion $C_6H_4NHOCHPhCH_2OSnBu^+$ which corresponds to ion with loss of one butyl group as well as the fragments $C_6H_4ONCHPhSn^+$ and $C_6H_4NOSn^+$. The ^{13}C-NMR spectra of C-1 and C-4 exhibit a similar pattern to that of compounds **2a**—**c**, the chemical shift values were found to be shifted $\Delta\delta$=7 and $\Delta\delta$=11 to higher frequencies for C-1 and C-4, respectively. The ^{119}Sn-NMR displayed a singlet at −84.1 ppm, which evidences pentacoordination around the tin atom.

The *in Vitro* Cytotoxicity of Organotin Derivatives of Tridentate Ligands The *in vitro* cytotoxicity was tested on five human tumor cell lines, U251 (human glioblastoma), PC-3 (human prostatic adenocarcinoma), K-562 (human chronic myelogenous leukemia), HCT-15 (human colorectal adenocarcinoma), and MCF-7 human mammary adenocarcinoma). The IC_{50} values of the four tin compounds and the cisplatin are summarized in Table 2. All compounds resulted to have lower IC_{50} values than that of the cisplatin, which indicates their high activity against the tumoral cell lines evaluated. The most outstanding results were obtained from compound **2c**, which shows the higher cytotoxic activity against four of the five cellular lines tested, whereas the less active compound was the compound **2b**. In the case of colon cancer the compound **2a** exhibits the lowest IC_{50} value. It is worth noting that the activity of tested compounds increases dramatically for the case of breast cancer in which compound **2c** showed activities from 12 to 36 times better than that of the cisplatin. Additionally, in order to discard some influence of the ligand on the cytotoxic activity displayed by the tin complexes, compound **1b** was also tested; however, the activity exhibited by this compound was negligible. Despite the fact that some studies have been aimed at elucidating the mode of the biological action of organotin(IV) complexes it has not been completely clarified. However, recent studies have shown that at low pH values Sn(IV) interacts with the phosphate groups of the DNA forming Sn–O bonds.[24—26]

Additionally, compounds **2a**—**d** were also tested against MT2 cells (human T-lymphocytes). In general, IC_{50} values determined for MT2 cells are higher than those found for cancer cell lines (Table 2), which means that this type of compounds exhibit certain selectivity towards cancer cell lines, except for compound **2d**. On the contrary, the cisplatin resulted to be more cytotoxic against MT2 cells compared to those of cancer cell lines. The compound **2c**, which is the most interesting compound, showed lower IC_{50} values for MCF-7, K-562 and U251 cell lines than those for MT2 cells.

Conclusions

The synthesis of new four organotin complexes derived from aminoalcohols has been accomplished. The *in vitro* cytotoxicity of these complexes against five cellular lines showed to be higher than that of the cisplatin, which was used as reference. Compound **2c** exhibited the highest activity against almost tumoral cell lines. The IC_{50} values determined for MT2 cells resulted to be higher than those for MCF-7, K-562 and U251 cell lines, which indicates certain selectivity towards tumoral cells. Ligand **1b** was also tested; however, the response was insignificant. This exploratory study clearly demonstrates that these tin complexes offer a promissory activity for future studies. All complexes are soluble in most of polar protic solvents, which could be an advantage in the next stage of biological studies. Investigations concerning synthesis and evaluation of optically active tin complexes are in progress and results will be published in due course.

Experimental

All reagents were commercially available from Aldrich. The reactions were carried out under nitrogen atmosphere; the solvents were carefully dried and distilled from the appropriate drying agents prior to use. ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectra were recorded on a Jeol Eclipse +300, chemical shifts (ppm) are relative to the TMS and $(CH_3)_4Sn$. Mass spectra were obtained on a Jeol JMS-AX505 HA spectrometer; Melting points were measured on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on a Nicolet FT-1 Magna 750 Fourier Transform instrument using pressed disks of KBr and powder compound. Elemental microanalyses were performed by Galbraith Laboratories, Inc.

Cell Culture and Assay for Cytotoxic Activity HCT-15, MCF-7, K-562, U-251, PC-3 and MT2 were supplied by The National Cancer Institute (NCI), U.S.A. and HIV/AIDS Services Center of Mexico City. The cytotoxicity of tumors cells with the test compounds was determined using the protein-binding dye sulforhodamine B (SRB) in microculture assay to measure cell growth.[27] The cell lines were cultured in RPMI-1640 (Sigma Chemical Co., Ltd., St. Louis, MO, U.S.A.), supplemented with 10% fetal bovine serum which was purchased from Invitrogen Corporation, 2 mM L-glutamine, 100 IU/ml penicillin G, 100 μg/ml streptomycin sulfate, and 0.25 μg/ml amphotericin B (Gibco). They were maintained at 37 °C in a 5% CO_2 atmosphere with 95% humidity. For the assay, 5×10^4 cell/ml (K562, MCF-7), 7.5×10^4 cell/ml (U251, PC-3) and 10×10^4 cell/ml (HCT-15, MT2), and 100 μl/well of these cells suspension were seeded in 96-well microtiter plates and incubated to allow for cell attachment. After 24 h, 100 μl of each test compounds and positive substances (cisplatin) were added to each well. Later 48 h, adherent cell cultures were fixed *in situ* by adding 50 μl of cold 50% (wt/vol) trichloroacetic acid (TCA) and incubated for 60 min at 4 °C. The supernatant was discarded and the plates were washed three times with water and air-dried. Cultured fixed with TCA were stained for 30 min with 100 μl of 0.4% SRB solution. Protein-bound dye was extracted with 10 mM

unbuffered tris base and the optical densities were read on an Ultra Microplate Reader (El_x 808, BIO-TEK Instruments, Inc.), with a test wavelength of 515 nm. Results were expressed as inhibitory concentration 50 (IC_{50}) values, they were calculated according to the protocol of Monks,[27] where a dose-response curve was plotted for each compound, and the concentration giving 50% inhibition (IC_{50}) was estimated from non-linear regression equations. The IC_{50} values (mean±standard error).

Synthesis of Compounds. 6,6-Dibutyl-2,3,4,4a,12,12a-hexahydro-1*H*-5,7-dioxa-12-aza-6-stanna-dibenzo[*a*,*d*]cyclooctene (2a) 0.25 g (1.2 mmol) of **1a** with 0.31 g (1.2 mmol) of di-*n*-butyltin oxide was refluxed in a mixture of toluene/methanol (4 : 1) under nitrogen atmosphere for 8 h. Then the solvent was removed under reduced pressure affording an oil which solidified after 24 h giving 0.52 g (96.6%) of a black solid, mp 120 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 (3H, t, J=6.87 Hz, $\underline{CH_3}(CH_2)_3Sn$), 0.92 (3H, t, J=6.87 Hz, $\underline{CH_3}(CH_2)_3Sn$), 1.17—1.71 (16H, m, H-10, H-11, $CH_3(\underline{CH_2})_3$-Sn), 2.17—2.20 (3H, m, H-1, H-12), 2.30—2.38 (2H, m, H-9), 3.23—3.25 (1H, m, H-2), 6.90—7.10 (4H, m, H-arom). ^{13}C-NMR (74 MHz, $CDCl_3$) δ: 13.7, 13.80 ($\underline{CH_3}$–$(CH_2)_3Sn$), 20.3 (C-11), 21.5 (C-10), 24.6, 25.3 (CH_2–CH_2–$\underline{CH_2}$–Sn), 26.7, 27.2 (CH_2–CH_2–$\underline{CH_2}$-Sn), 27.6, 27.8 (CH_2–$\underline{CH_2}$–CH_2–Sn), 30.9 (C-12), 35.5 (C-9), 68.7 (C-1), 74.2 (C-2), 116.7 (C-8), 118.5 (C-5), 125.9 (C-6), 128.6 (C-7), 129.1 (C-3), 156.7 (C-4). ^{119}Sn-NMR (112 MHz, $CDCl_3$) δ: −87.9. MS (EI) m/z: 439 (M^+) (10), 382 (100), 326 (15), 227 (45); HR-MS (FAB^+) m/z: 438.1455 (Calcd for $C_{20}H_{33}NO_2Sn$). Observed: 438.1450. *Anal.* Calcd for $C_{20}H_{33}NO_2Sn$: C, 54.81; H, 7.58; N, 3.21. Found: C, 54.01; H, 7.84; N, 2.99.

6,6-Dibutyl-10-methyl-2,3,4,4a,12,12a-hexahydro-1*H*-5,7-dioxa-12-aza-6-stanna-dibenzo[*a*,*d*]cyclooctene (2b) Complex **2b** was prepared following the procedure described for complex **2a** from 0.2 g (0.9 mmol) of ligand **1b** and 0.23 g (0.9 mmol) of di-*n*-butyltin oxide affording 0.32 g (78%) of a black solid, mp 210 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.79 (3H, t, J=7.3 Hz, $\underline{CH_3}(CH_2)_3Sn$), 0.84 (3H, t, J=7.3 Hz, $\underline{CH_3}(CH_2)_3Sn$), 1.1—1.58 (16H, m, H-11, H-10, $CH_3(\underline{CH_2})_3Sn$), 2.2 (3H, s, CH_3), 2.12—2.20 (3H, m, H-1, H12), 2.28—2.31 (2H, m, H-9), 3.18—3.21 (1H, m, H-2), 6.79—6.87 (3H, m, H-5, H-6, H-8). ^{13}C-NMR (74 MHz, $CDCl_3$) δ: 13.6, 13.8 ($\underline{CH_3}$–$(CH_2)_3Sn$), 20.1 (C-11), 20.6 (CH_3–Ph), 21.7 (C-10), 24.6, 25.3 (CH_2–CH_2–$\underline{CH_2}$–Sn), 26.7, 27.1 (CH_2–$\underline{CH_2}$–CH_2–Sn), 27.8, 27.6 ($\underline{CH_2}$–CH_2–CH_2–Sn), 30.9 (C-12), 35.5 (C-9), 68.7 (C-1), 74.2 (C-2), 118.0 (C-8), 125.8 (C-5), 126.3 (C-6), 129.0 (C-7), 129.37 (C-3), 155.0 (C-4). ^{119}Sn-NMR (112 MHz, $CDCl_3$) δ: −87.0. MS (EI) m/z: 453 (M^+), (15), 396 (100), 394 (80), 339 (20), 241 (55); HR-MS (FAB^+) m/z: 452.1612 (Calcd for $C_{21}H_{35}NO_2Sn$). Observed: 452.1609. *Anal.* Calcd for $C_{21}H_{35}NO_2Sn$: C, 55.80; H, 7.79; N, 3.11. Found: C, 55.09; H, 7.63; N, 2.87.

6,6-Dibutyl-10-chloro-2,3,4,4a,12,12a-hexahydro-1*H*-5,7-dioxa-12-aza-6-stanna-dibenzo[*a*,*d*]cyclooctene (2c) Complex **2c** was prepared following the procedure described for complex **2b** from 0.2 g (0.8 mmol) of **1c** and 0.22 g (0.8 mmol) of di-*n*-butyltin oxide, giving 0.39 g (99%) of a black solid, mp 130—140 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.74—0.84 (6H, m, $\underline{CH_3}$–$(CH_2)_3Sn$), 1.09—1.80 (16H, m, H-11, H-10, $CH_3(\underline{CH_2})_3Sn$), 1.80—2.12 (2H, m, H-9), 2.13—2.28 (3H, m, H-1, H-12), 3.15—3.17 (1H, m, H-2), 6.78—7.20 (3H, m, H-3, H-5, H-8). ^{13}C-NMR (74 MHz, $CDCl_3$) δ: 13.6, 13.7 ($\underline{CH_3}$–$(CH_2)_3Sn$), 20.1 (C-11), 22.0 (C-10), 24.5, 25.2 (CH_2–CH_2–$\underline{CH_2}$–Sn), 26.7, 26.9 (CH_2–CH_2–$\underline{CH_2}$–Sn), 27.5, 27.8 (CH_2–$\underline{CH_2}$–CH_2–Sn), 30.8 (C-12), 35.4 (C-9), 68.6 (C-1), 74.2 (C-2), 119.4 (C-8), 121.2 (C-5), 125.6 (C-6), 128.3 (C-7), 133.2 (C-3), 155.6 (C-4); ^{119}Sn-NMR (112 MHz, $CDCl_3$) δ: −81.2. MS (EI) m/z: 473 (M^+) (2), 416 (10), 301(9), 228 (100), 214 (42), 135 (15), 94 (16), 55 (18), 28 (10). HR-MS (FAB^+) m/z: 416.0439 (Calcd for fragment ion $C_{16}H_{23}NO_2SnCl$). Observed 416.0430. *Anal.* Calcd for $C_{20}H_{32}NO_2Sn$: C, 50.82; H, 6.82; N, 2.96. Found: C, 50.27; H, 6.85; N, 2.79.

6,6-Dibutyl-9-phenyl-9,10-dihydro-8*H*-5,7-dioxa-10-aza-6-stanna-benzocyclooctene (2d) Complex **2d** was prepared following the procedure described for complex **2c** from 0.2 g (0.87 mmol) of ligand **1d** with 0.23 g (0.87 mmol) di-*n*-butyltin oxide. Then the solvent was removed under reduced pressure affording 0.15 g (38%) of a black solid, mp 143—145 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.9 Hz, $\underline{CH_3}$–$(CH_2)_3Sn$), 0.92 (3H, t, J=6.9 Hz, $\underline{CH_3}$–$(CH_2)_3Sn$), 1.31—1.38 (4H, m, CH_2–Sn), 1.64—1.76 (2H, m, CH_2–Sn), 3.10 (1H, d, J=12.6 Hz, H-2a), 3.66 (1H, m, H-2a), 4.12 (1H, dd, J=9.5, 3.2 Hz, H-1), 6.38 (1H, d, J=7.8 Hz, H-8), 6.92 (1H, d, J=7.8 Hz, H-5), 7.01—7.07 (2H, m, H-6, H-7), 7.19—7.38 (5H, m, H-arom). ^{13}C-NMR (74 MHz, $CDCl_3$) δ: 13.8 ($\underline{CH_3}$–$(CH_2)_3Sn$), 26.9 (CH_2–CH_2–$\underline{CH_2}$–Sn), 27.2 ($\underline{CH_2}$–CH_2–CH_2–Sn), 27.7 (CH_2–$\underline{CH_2}$–CH_2–Sn), 67.1 (C-1), 70.0 (C-2), 116.8 (C-8), 117.9 (C-5), 118.6 (C-6), 126.8 (C-7), 127.5 (C-m), 128.8 (C-p), 129.5 (C-o), 138.4 (C-3), 156.9 (C-4). ^{119}Sn-NMR (112 MHz, $CDCl_3$) δ: −84.1. MS (EI) m/z: 461 (M^+) (12), 404 (77), 316 (96), 227 (100), 198 (65), 91 (55). HR-MS (FAB^+) m/z: 461.1381 (Calcd for $C_{22}H_{31}NO_2Sn$). Observed 461.1377 *Anal.* Calcd for $C_{22}H_{31}NO_2Sn$: C, 57.42; H, 6.78; N, 3.04. Found: C, 57.67; H, 6.86; N, 3.21.

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