[3 + n] Annulation Reactions by Means of 3-Trimethylstannyl-2-[(trimethylstannyl)methyl]propene, an Isobutene Dianion Synthetic Equivalent

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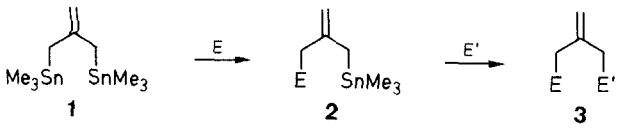
Stepwise functionalization of the two carbon–tin bonds in 3-trimethylstannyl-2-[(trimethylstannyl)methyl]propene with electrophiles (diacyl dichlorides or aldehydes and carbon dioxide, provides a promising route for [3 + n] annulation reactions.

Allylstannanes[1,2] and allylsilanes[3] are well-known allylating agents capable of reacting with a wide range of electrophiles in a regiospecific fashion. Even in the most favorable cases, however, they usually require high temperatures or catalytic activation.

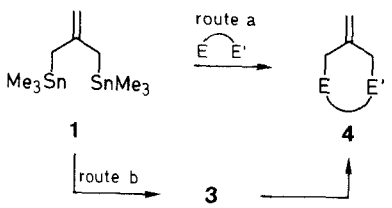
When two trialkylstannyl groups are both in an allylic position with respect to a double bond, as in the title compound **1**, which is obtained by treatment of 3-chloro-2-(chloromethyl)propene with trimethylstannyllithium,[4] reactions with carbonyl compounds and acyl chlorides are much faster[5] even in the absence of Lewis acids.

Furthermore, after the first functionalization, an allylic tin moiety still survives and allows subsequent reactions with other electrophilic centers leading to a difunctionalized open chain compound (Scheme **1**).



Scheme 1

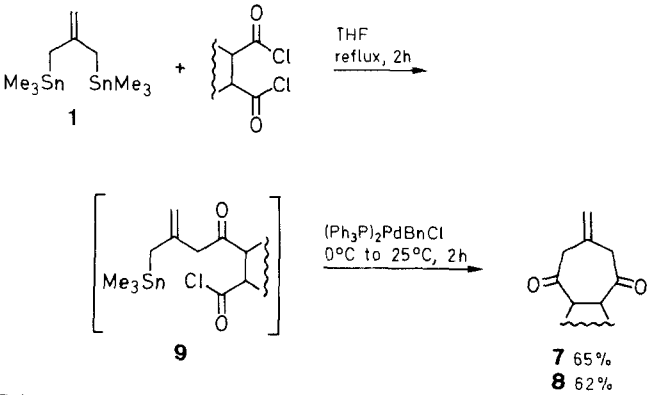
The above observations, coupled with the strong need for additional annulation approaches, prompted us to develop a general strategy for ring construction based on the use of 3-trimethylstannyl-2-[(trimethylstannyl)-methyl]propene (**1**) as an isobutene dianion synthetic equivalent: in fact if a dielectrophile is used, a cyclic product **4** could be obtained through a formal [3 + n] annulation process according to Scheme **2** (route a).



Scheme 2

Similar approaches to the synthesis of carbocycles via [3 + n]annulations have been developed mainly by Trost[6] and Molander[7] who used a 1,3-dipolar synthetic equivalent in reactions with activated olefins and a 1,3-dianionic synthetic equivalent in reactions with dielectrophiles, respectively. Alternatively, according to Scheme **2** (route b), a stepwise double functionalization of **1** with two electrophiles can be performed and the intermediate thus obtained cyclized. Allylstannanes normally couple with acyl chlorides[8] to give ketones in the presence of Pd(0) or Pd(II) catalysts. Therefore diacyol dichlorides seemed to us the substrates of choice in order to perform the process outlined in Scheme **2** (route a). Compound **1**, being much more reactive than simple allylstannanes, in several cases underwent both steps of the cyclization without any added catalyst; the reaction with oxalyl chloride, succinyl chloride and phthaloyl chloride afforded the corresponding diketones in good yield. When malonyl chloride was employed, the aromatic diphenol orcinol (5-methyl-1,3-benzenediol, **6**) was obtained, probably through aromatization of the initially formed six membered diketone.

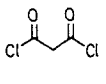
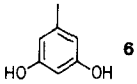
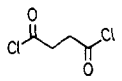
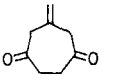
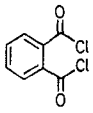
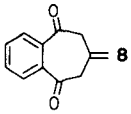
No catalyst was employed for the five- and six-membered rings while *trans*-benzyl(chloro)bis(triphenylphosphine) palladium(II) was necessary in order to obtain the seven-membered diketones: reaction with succinyl chloride and phthaloyl chloride led to the intermediate **9** in refluxing tetrahydrofuran and then cyclization occurred when the Pd(II) catalyst was added (Scheme **3**, Table).



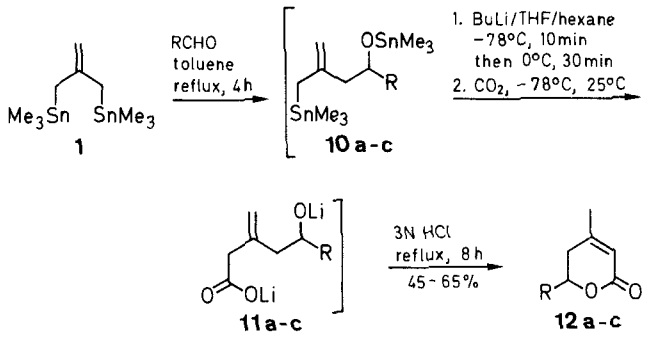
Scheme 3

The double functionalization approach has been developed mainly by using the uncatalyzed reaction of **1** with aldehydes leading to a substituted allylstannane **10** which, upon treatment with butyllithium and subsequent quench with carbon dioxide, gives the γ-hydroxy carboxylate **11** easily converted into the lactone **12**. The reaction is of a general scope: aromatic, aliphatic and α,β-unsaturated aldehydes react readily with **1** and the corresponding 6-substituted 4-methyl-5,6-dihydro-2*H*-pyran-2-ones, are obtained in good yields (Scheme **4**).

Table. [3 + n] Dianionic Annulation Reactions with Diacyl Chlorides

Diacyl-chlorides	Product	Yield[a] (%)
	 **5**	30
	 **6**	93
	 **7**	65[b]
	 **8**	62

[a] Isolated products, purified by chromatography.
[b] Not purified.



10–12	a	b	c
R	Ph	n-C_6H_{13}	(E)–CH=CHPh

Scheme 4

As a final comment we should note that the analogous 3-tributylstannyl-2-[(trimethylstannyl)methyl]propene can be used equally well in this second series of reactions but the coupling with diacyl dichloride is much slower than by using **1** and the yields are lower.

The [3 + n] annulation strategy described herein, outlines a promising new approach to highly functionalized ring systems. The use of the conjunctive reagent **1** as a trimethylenemethane dianion synthetic equivalent, compares well with and complements previous reports by Molander. Furthermore, it outlines a promising new entry into the synthesis of unsaturated lactones.

Starting materials were purchased from Fluka, Aldrich or Carlo Erba, unless literature sources or details for the preparation are given. THF and Et_2O were obtained anhydrous by distillation from Na and subsequently from $LiAlH_4$; toluene was distilled from Na.

Organotin compounds are known to be toxic[1] but hazards can be minimized taking some simple safety measures such as wearing gloves, using good hoods and cleaning used glassware with alkali solution. Chromatographic separations were performed with flash column chromatography technique using Merck silica gel 60 (230–400 mesh). Whenever reaction products were not isolated, their yields were determined by gas chromatography comparing their peak areas with that of an internal standard and correcting the ratios by calibrating factors. Gas chromatographic analyses were performed using quartz capillary columns (50 m) loaded with the following stationary phases: SE-30 (methyl-silicone polymer), OV-101 (silicon rubber), C-20M (polyethylene glycol). IR spectra were recorded with a Perkin-Elmer 881 spectrophotometer. ^{1}H-NMR spectra were recorded in the 300 MHz field on a Varian VXR-300 spectrometer. Mass spectra were obtained on a HP 5970A- HP 5790 GC-selective ion detector equipped with a high performance dimethylsilicone fluid capillary column (30 m). Microanalyses were performed on a C,H,N elemental analyzer Perkin-Elmer 240 DS.

Reaction of 3-Trimethylstannyl-2-[(trimethylstannyl)methyl]propene (1) with Diacyl Dichlorides; General Procedure:

Compound **1** (5.0 mmol) and the acyl chloride (5.0 mmol) are simultaneously added to THF (10 mL): the reaction with oxalyl chloride is complete after 10 min at – 78 °C in toluene and malonyl chloride is consumed after 4 h in THF at 0 °C. With succinyl chloride and phthaloyl chloride the reaction mixture is kept 2 h at reflux in THF and then $(Ph_3P)_2Pd$ Bn Cl (0.5 mmol) is added at 0 °C and the solution is warmed up to 25 °C over 2 h. In all cases the mixture is dissolved in Et_2O (30 mL), the organic phase washed with sat. aq NH_4Cl (20 mL), sat. aq NaCl (20 mL) and then H_2O (3 × 20 mL) in order to eliminate Me_3SnCl[9] and then dried (Na_2SO_4). The pure diketone is then obtained after chromatographic separation of the residue (eluent petroleum ether/EtOAc, 3:1).

4-Methylene-1,2-cyclopentanedione (**5**): yield: 30%; bp 58–62 °C/19 Torr.

$C_6H_6O_2$ (110.1) calc. C 65.45 H 5.49
found 64.95 5.39

IR (liquid film): ν = 1730 (s), 1590 cm^{-1} (m).

^{1}H-NMR ($CDCl_3$): δ = 3.40 (t, 4H, J = 2.3 Hz, CH_2), 5.28 (quint, 2H, J = 2.3 Hz, C=CH_2).

MS (70 eV): m/z (%) = 110 (M^+, 100), 82 (28), 81 (27), 64 (15), 54 (29), 53 (37), 42 (29).

5-Methyl-1,3-benzenediol (Orcinol) (**6**): yield: 93%; mp 59–61 °C; (Lit.[10] 56–58 °C).

IR (KBr): ν = 3450 (br s), 2940 (s), 1640 (m), 1490 (m), 1150 cm^{-1} (m).

^{1}H-NMR (acetone-d_6): δ = 2.12 (q, 3H, J = 0.7 Hz, CH_3), 3.38 (s, 2H, OH), 6.13 (q, 3H_{arom}, J = 0.7 Hz), 8.17 (s, 2H, OH).

MS (70 eV): m/z = 124 (M^+, 100), 123 (59), 95 (16), 69 (12), 67 (13), 55 (12), 51 (12).

6-Methylene-1,4-cycloheptanedione (**7**): yield: 65%.

IR (liquid film): ν = 1730 (s), 1610 cm^{-1} (m).

^{1}H-NMR ($CDCl_3$): δ = 2.78 (s, 4H, CH_2CH_2), 3.25 (t, 4H, J = 2.1 Hz, CH_2C=C), 5.21 (quint, 2H, J = 2.1 Hz, C=CH_2).

MS (70 eV): m/z (%) = 138 (M^+, 60), 110 (25), 109 (27), 96 (13), 95 (100), 83 (17), 82 (26), 67 (16), 55 (25), 54 (27).

7,8-Dihydroxy-7-methylene-5H-benzocycloheptene-5,9(6H)-dione (**8**): yield: 62%.

$C_{12}H_{10}O_2$ (186.2) calc. C 77.40 H 5.41
found 76.98 5.29

IR (liquid film): ν = 3060 (w), 1760 (s), 1680 (m), 1590 cm^{-1} (m).

^{1}H-NMR ($CDCl_3$): δ = 3.25 (t, 4H, J = 1.8 Hz, CH_2C=), 5.18 (quint, 2H, J = 1.8 Hz, C=CH_2), 7.7 (m, 4H, H_{arom}).

MS (70 eV): m/z (%) = 186 (M^+, 54), 159 (13), 158 (100), 130 (15), 129 (61), 128 (45), 127 (11), 115 (47), 76 (18).

Reaction of 3-Trimethylstannyl-2-[(trimethylstannyl)methyl]propene (1) with Aldehydes and Carbon Dioxide; General Procedure:

Compound **1** (10.0 mmol) and the aldehyde (10.0 mmol) are added to anhydr. toluene (20 mL) and the solution is heated under reflux for 4 h. Then the solvent is evaporated and the residue distilled

through a Vigreux column (**10a**: 155°C/0.07 Torr; **10b**: 130°C/0.4 Torr; **10c**: 150–155°C/0.5 Torr). The distilled intermediate (5.0 mmol) is dissolved in THF (25 mL) and, after cooling to −78°C, BuLi (20.0 mmol) in hexane solution is added. After 30 min the solution is warmed up to 0°C during 10 min and, after cooling again to −78°C, CO_2 is added. The solution is slowly warmed up to 25°C and, after adding 3 N HCl (10 mL), kept under reflux for 8 h. The mixture is then poured in sat. aq NH_4Cl, the aqueous phase extracted with Et_2O (3 × 30 mL) and dried (Na_2SO_4). The pure lactone is obtained after chromatographic separation of the residue (eluent: hexane/EtOAc, 1:1).

5,6-Dihydro-4-methyl-6-phenyl-2H-pyran-2-one (**12a**): yield: 62%; bp 109–112°C/0.02 Torr; (Lit.[11] 130°C/0.1 Torr).

IR (liquid film): ν = 3060 (w), 3020 (w), 1730 (s), 1380 (m), 1280 (s), 1250 (s), 1050 (s), 1010 cm^{-1} (s).

^{1}H-NMR ($CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 2.43 (dd, 1 H, J = 18.0, 4.5 Hz, 1 H of CH_2 of CH_2C=), 2.64 (ddq, 1 H, J = 18.0, 11.8, 1.2 Hz, 1 H of CH_2C=), 5.39 (dd, 1 H, J = 11.8, 4.2 Hz, CH-O), 5.89 (br s, 1 H, C=CH), 7.4 (m, 5 H_{arom}).

MS (70 eV): m/z (%) = 188 (M^+, 9), 82 (100), 77 (13), 54 (18).

5,6-Dihydro-6-hexyl-4-methyl-2H-pyran-2-one **12b**: yield: 45%; bp 82–85°C/0.1 Torr; (Lit.[12] 100–120°C/0.18 Torr).

IR (liquid film): ν = 2930 (s), 1730 (s), 1250 cm^{-1} (w).

^{1}H-NMR ($CDCl_3$): δ = 0.87 (t, 3 H, J = 6.9 Hz, CH_3C), 1.4 (m, 8 H, $(CH_2)_4$), 1.6 (m, 1 H, 1 H of CH_2C), 1.8 (m, 1 H, 1 H of CH_2C), 1.97 (s, 3 H, CH_3C=), 2.12 (dd, 1 H, J = 18.0, 4.6 Hz, 1 H of CH_2C=), 2.28 (ddq, 1 H, J = 18.0, 11.2, 1.2 Hz, 1 H of CH_2C=), 4.36 (ddt, 1 H, J = 11.2, 7.1, 4.6 Hz, CH-O), 5.79 (br s, 1 H, C=CH).

MS (70 eV): m/z (%) = 196 (M^+, 1), 181 (1), 111 (100), 83 (18), 82 (34), 55 (19).

5,6-Dihydro-4-methyl-6-(2-phenylethenyl)-2H-pyran-2-one **12c**: yield: 65%; bp 131–133°C/0.1 Torr.

$C_{14}H_{14}O_2$	calc.	C 78.48	H 6.59
(214.3)	found	78.02	6.31

IR (liquid film): ν = 3040 (w), 3020 (w), 1690 (s), 1370 (m), 1240 (s), 960 cm^{-1} (m).

^{1}H-NMR ($CDCl_3$): δ = 2.01 (s, 3 H, CH_3C=), 2.38 (dd, 1 H, J = 17.8, 4.8 Hz, 1 H of CH_2C=), 2.52 (ddq, 1 H, J = 17.8, 10.4, 1.2 Hz, 1 H of CH_2C=), 5.05 (dddd, 1 H, J = 10.4, 6.3, 4.8, 0.8 Hz, CH-O), 5.86 (br s, 1 H, C=CH), 6.26 (dd, 1 H, J = 15.9, 6.3 Hz, PhC=CH), 6.72 (dd, 1 H, J = 15.9, 1.2 Hz, PHCH=C), 7.3 (m, 5 H_{arom}).

MS (70 eV): m/z (%) = 214 (M^+, 10), 211 (90), 140 (13), 129 (22), 128 (28), 115 (29), 92 (17), 91 (100), 65 (16), 63 (17).

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