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Tributylstannyl 4-tributylstannylbut-3-enoate: a Useful C-4 Homologating Agent. Application to the Synthesis of Aryl Iodolactones

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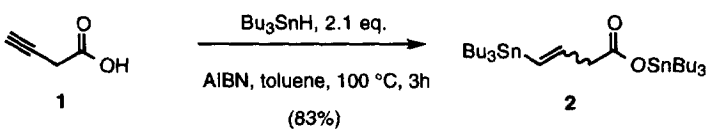
Abstract: Tributylstannyl 4-tributylstannylbut-3-enoate, readily prepared by radical hydrostannation, is used for the transfer of a but-3-enoic acid synthon. Some of the potentialities of this synthon are established by the synthesis of aryl iodolactones or tetralones (one of them is a key intermediate for ABT-200 synthesis). Copyright © 1996 Published by Elsevier Science Ltd

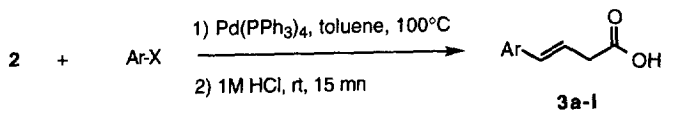
The carboxylic acid moiety can be considered as a key function for multistep syntheses.[1] On the other hand, vinyltin reagents have proved to be efficient tools for the transfer of vinyl unit with a high tolerance for numerous functionalities both on the substrate and on the reagent.[2] It is of interest to offer new organotin reagents useful for the transfer of a four carbon chain bearing such a carboxylic acid function. Until now, the most significant efforts have been related to reagents able to transfer an "umpolung" unit of d^3 type (vinyltins bearing acetal[3] or ester[4] functions) although some new vinyltin reagents like those bearing an homoallylic acetal function have been described previously.[5] Nevertheless, it should be noticed that in this particularly case the hydrolysis of the acetal function, in order to regenerate the carbonyl function, often leads to conjugated enals.

For this purpose, we planed to propose a new vinyltin bearing an homoallylic carboxylic acid function as a d^4 synthon. The required organotin precursor **2** is easily obtained by radical hydrostannation[6] of but-3-ynoic acid **1** (prepared *via* carbonatation of the corresponding allenylmagnesium bromide[7]) and is obtained in 83% yield as a thermodynamic mixture (*E*/*Z* = 85/15).



1 **2**

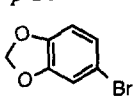
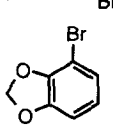
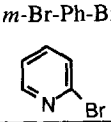
The reactivity of **2** has been examined in the case of cross-coupling with organic halides under catalysis with palladium complexes.[8] In order to find optimal experimental conditions, we tested various catalysts and we found that tetrakistriphenylphosphine palladium [0] was the most efficient.[9,10]



3a-l

According to the results reported in the table 1, the substitution reaction appears to have a mild and general character leading to substituted homocinnamic acids. With aryl or heteroaryl halides, good yields were obtained and only the (*E*)-isomer is reactive under our experimental conditions (1.3 equivalent of vinyltin).[11] The temporary protection of the carboxylic acid function is removed by simple hydrolysis at room temperature with HCl/water 1M.

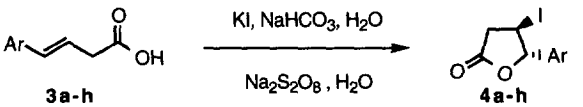
Table 1: Reactivity of **2** with arylhalides

Entry	Ar-X	Reaction time (h.)	Yield(%)	**3**
1	Ph-I	12	72	**3a**
2	*p*-F-Ph-Br	"	66	**3b**
3	*p*-MeO-Ph-Br	"	55	**3c**
4	*p*-CH_3-CO-Ph-Br	24	65	**3d**
5	*p*-CHO-Ph-Br	"	65	**3e**
6	*p*-CF_3-Ph-Br	12	73	**3f**
7	*p*-Br-Ph-Br	"	75	**3g**[a]
8		"	88	**3h**
9		"	55	**3i**
10	*m*-CF_3-Ph-Br	"	74	**3j**
11	*m*-Br-Ph-Br	"	78	**3k**[a]
12[b]		"	85	**3l**[b]

a = Only the monosubstitution adduct is recovered.
b = isolated as a stannylester.

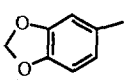
These results demonstrate the efficiency of **2** to obtain homocinnamyl skeleton in a clean fashion and more generally to transfer the d^4 but-3-enoic acid synthon onto miscellaneous substrates.

Taking into account the numerous applications of compounds **3**, we decided to apply our strategy to the synthesis of aryl-iodolactones as shown in the following scheme.

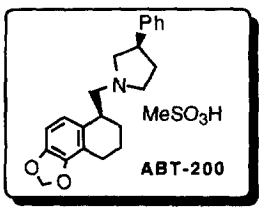


The procedure well described by Mebane *et al.* has been applied.[12] Oxidation of potassium iodide with sodium persulfate in the presence of the sodium salt of β,γ-unsaturated acids **3a-h** affords the γ-iodolactones **4a-h**. In each case, only *anti* products were obtained in good to excellent yields. The results are summarised in table 2:

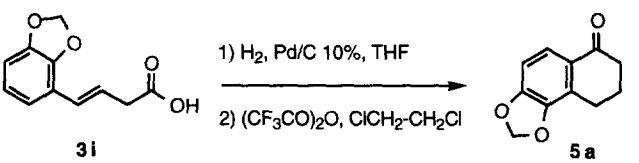
Table 2: Iodolactonisation of homocinnamic acids

Entry	Ar	Yield(%)	4
1	Ph-	93	**4a**
2	*p*-F-Ph-	67	**4b**
3	*p*-MeO-Ph-	92	**4c**
4	*p*-CH_3CO-Ph-	70	**4d**
5	*p*-CHO-Ph-	75	**4e**
6	*p*-CF_3-Ph-	70	**4f**
7	*p*-Br-Ph-	79	**4g**
8		80	**4h**

From compounds **3h** and **3i**, we were also able to prepare tetralones, especially 5,6-methylenedioxy-1-tetralone which is a key intermediate in the synthesis of ABT-200 {(±)-(1'R*, 3R*)-3-phenyl-1-[1', 2', 3', 4'-tetrahydro-5', 6'-methylene-dioxy-1'-naphtalenyl-methyl]-pyrrolidine}, an alpha-2 antagonist and a norepinephrine uptake inhibitor .[13]



Starting from compound **3i**, tetralone **5a** was obtained in 78% yield after hydrogenation over palladium oncarbon[14] followed by a Friedel Crafts acylation with trifluoroacetic anhydride.



The same approach was also applied from **3h** for the synthesis of the related isomer **5a** of tetralone in 85% yield.[15]

In conclusion, tributylstannyl 4-tributylstannylbut-3-enoate is readily prepared and useful for the transfer of a but-3-enoic acid synthon onto miscellaneous substrates under mild experimental conditions. Some of the potentialities of this synthon are shown by the syntheses of functional aryl iodolactones or 1-tetralones.

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9. Typical procedure: Preparation of compound **3h**. In a 50 mL flask are introduced 20 mL of toluene, 4 g (65 mmol) of **2**, 10.5 g (50 mmol) of aryl bromide and 25 mg of tetrakistriphenylphosphine palladium. The mixture is degassed under vacuum and stirred overnight at 100°C. After cooling, the stannyl ester is hydrolysed with 10 mL of 1N HCl solution. After ether extraction (3x30 mL), the organic layer is treated with 1N NaOH solution. The aqueous layer is washed with ether and is acidified with 1N HCl solution and extracted with ether (3x20 mL)). After removal of the solvents under reduced pressure, **3h** was recovered from the crude by crystallisation (95/5: petroleum ether/diethylether). Mp : 115°C, IR (KBr) : 3400-2300, 3018, 2903, 1710, 1655, 1604, 1498. ^{1}H NMR($CDCl_3$, 200 MHz) : 3.30 (d, $^3J_{1H}$=6.9Hz, 2H), 6.0 (s, 2H), 6.14 (dt, $^3J_{1H}$=15.8Hz, $^3J_{2H}$=6.9Hz, 1H), 6.46 (d, $^3J_{1H}$=15.8Hz, 1H), 6.76-6.86(m, 2Har), 6.96-7.0 (m, 1Har), 8.55 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) : 38.3, 101.5, 106, 108.7, 119.4, 121.4, 131.5, 133.9, 147.7; 148.4, 178.4. MS (70 eV): 206(M , 91), 161(32), 131(100), 103(85), 77(32), 51(15), 45(12).
10. The use of $PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$ in DMF gave low to moderate conversion rates (<50%).
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15. Acylation leads only to 4,5-methylenedioxy-1-tetralone.

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