An Efficient Synthesis of Conjugated Trienoic Acids *via* Stille Cross Coupling Reaction of (*E*)-1,2-Bis(tributylstannyl)ethylene

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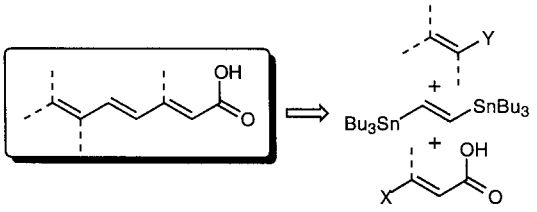
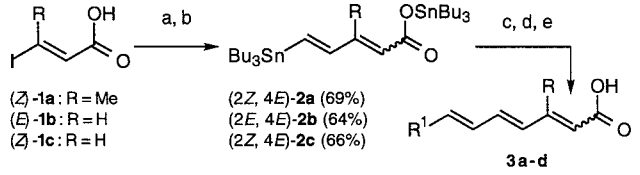
Abstract : Stereoselective construction of conjugated trienoic acids was achieved through two successive Stille reactions, coupling as the first step (*E*)-1,2-bis(tributylstannyl)ethylene and tributylstannyl-3-iodoalk-2-enoates. The second step can be conducted by two different routes: 1) cross-coupling of the stannyldienoic acid reagents **2** and vinyliodides or 2) cross-coupling of vinyltin reagents and tributylstannyl 5-iodopenta-2,4-dienoates generated by iododestannylation of stannyldienes **2**.

Polyenic compounds with fixed configuration are found in many natural products such as retinoids or polyenic macrolides (mycoticin, roxatoxin, etc.). In the past, conjugated polyene constructions have been achieved using a Wittig type of approach, Peterson olefination or Julia coupling.[1] More recently, Linstrumelle *et al.* have reported the easy construction of these compounds by successive Heck reactions using (*Z*)- or (*E*)-dichloro ethylene.[2] Identically, owing to its mild experimental conditions, the Stille cross-coupling reaction[3] has emerged as a key step in various total syntheses of natural products, such as leinamycin,[4] macrolactin A,[5] des-epoxy-rosaramycin,[6] or limocrocin,[7] etc. Nevertheless, in spite of its great potential, (*E*)-1,2-bis(tributylstannyl)ethylene has not been extensively used in the Stille approach.[7,8] We have reported recently[9] that (*Z,E*)- or (*E,E*)- dienoic acids could be prepared stereoselectively and in high yield from vinyltin reagents and unprotected iodovinylic acids by the Stille cross-coupling reaction. Unfortunately this method failed when (*E*)-1,2-bis(tributylstannyl)ethylene was used as vinyltin reagent. In addition, studies related to the synthesis of 4-arylbut-3-enoic acids through the Stille approach revealed that protection of the carboxylic acid as the tributylstannyl ester permitted a great increase in yield.[10] Taking these observations into account, we would like to report the synthesis of trienoic acids from (*E*)-1,2-bis(tributylstannyl)ethylene according to the following retrosynthetic pathway:



Scheme 1

Stille coupling of β-iodovinylic acids (protected as the tributyltin ester) with (*E*)-1,2-bis(tributylstannyl)ethylene (1.1eq.) in the presence of a catalytic amount (5%) of dichlorobis(acetonitrile) palladium(II), stereospecifically provides dienyltin **2a-c** with retention of the configuration of the two double bonds.[11] Bis coupling products[12] or tributylstannylated substituted products[13] were never observed when 1.1 equivalent of (*E*)-1,2-bis(tributylstannyl)ethylene was used. A NOESY NMR experiment on **2a** confirmed the retention of the (*Z*) stereochemistry of the α-double bond. Attention was next directed to the synthesis of trienoic acids by a second palladium mediated cross-coupling with vinyliodides (scheme 2). Conjugated trienoic acids were selectively obtained in fair to good yields (Table I). At the end of the reaction, treatment with a saturated aqueous potassium fluoride solution provides clean deprotection of the carboxylic acid function, and transformation of the tributyltin iodide that is generated into insoluble tributyltin fluoride polymer.



a) Bu_3SnOMe, ether, rt ; b) Bu_3Sn–$SnBu_3$ 1.1eq , $PdCl_2(MeCN)_2$ 5%

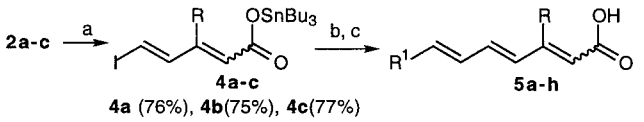
c) R^1–I , $PdCl_2(MeCN)_2$ 5% , DMF, rt, 3-6 h; d) KF sat ; e) HCl 0.1 N

Scheme 2

Table I. Synthesis of trienoic acids from **2a-c**

Entry	Dienyltin	Vinyliodide	N°	Yield (%)
1	**2a**	Ph–I	**3a**	78
2	**2b**	HOOC–I	**3b**	62
3	**2c**	Ph–I	**3c**	65
4	**2c**	HOOC–I	**3d**	60

In order to extend the potential of this approach, reverse cross-coupling reactions have been investigated. Iododestannylation of stannyldienes **2a-c** affords the more stable protected 5-iodopenta-2,4-dienoic acids **4a-c**, without isomerisation of the α double bond, and with retention of the configuration of the second one. Note that iodine treatment does not affect the tributylstannylcarboxylate function. Using a similar procedure, dienoic iodides **4a-c** were cross-coupled with vinyltin reagents, affording trienoic acids (Table II). Better yields were obtained, compared to those from **2a-c**.



a) I_2 (1 eq), ether , 0° C ; b) R^1–$SnBu_3$, $PdCl_2(MeCN)_2$ 5%, DMF

c) KF sat; d) HCl 0.1N

Scheme 3

The coupling of an alkynyltributyltin was also successfully accomplished in 79% yield, without polymerisation, proving again the mildness of these experimental conditions.

In summary, we have investigated a new general route to conjugated trienoic acids. Studies to modify the nature of the substituent in position 3 and to investigate synthetic properties of the various acids **3** and **5** are currently underway.

Table II. Stille reaction of **4a-c** with organotin reagents

Entry	Dienoic iodide **4**	Organotin reagent	Trienoic acid **5**	Yield (%)
1	**4a**	Bu_3Sn	**5a**	96
2	**4b**	Bu_3Sn	**5b**	85
3	**4c**	Bu_3Sn	**5c**	84
4	**4a**	Bu_3Sn	**5d**	74
5	**4a**	Bu_3Sn $CH(OEt)_2$	**5e**	72
6	**4a**	Bu_3Sn $SiMe_3$	**5f**	86
7	**4a**	Bu_3Sn $CH(OEt)_2$	**5g**	55*
8	**4a**	Bu_3Sn	**5h**	79

* acetal deprotection was observed during purification, affording 8-oxoocta-2,4,6-trienoic acid.

Typical procedure: Preparation of compound **5f**

To a DMF solution (15 mL), **4a** (5.28 g, 10 mmol) and 2-tributylstannyl-1-trimethylsilylethylene (4.29 g, 11 mmol), in a 50 mL flask, 129 mg (0.5 mmol) of dichloro-bis(acetonitrile)palladium(II) were added. The mixture was stirred for 3h at 25°C, then hydrolysed with 25 mL of a 1M solution of potassium fluoride and 25 mL of acetone to precipitate the tributyltin iodide formed. After strongly stirring for 2h, the reaction mixture was filtered, washed with a 0.1 N HCl solution (2x15 mL) and extracted with diethyl ether (3x30 mL). After the usual work-up, the crude acid is purified by crystallisation (petroleum ether/diethylether : 95/5).

5f: mp = 32°C ; IR: 3159, 2959, 2929, 2680, 1657, 1605, 1261 ; ^1H NMR δ (ppm) (200 MHz): 0.16 (9H, s), 2.1 (3H, s), 5.76 (1H, s), 6.19 (1H, d, J = 17Hz), 6.64 (1H, dd, J = 14.6Hz, J = 10.2Hz), 6.79 (1H, dd, J = 17Hz, J = 10.2Hz), 7.75 (1H, d, J = 14.6Hz), 11.66 (1H, s) ; ^{13}C NMR δ (ppm) (50 MHz): -1.5, 21.0, 117.0, 129.6, 138.8, 140.0, 143.9, 153.3, 171.4.

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