Stereoselective Synthesis of All-*trans*-, (13*Z*)- and (9-*nor*)-Retinoic Acids via Stille Reaction

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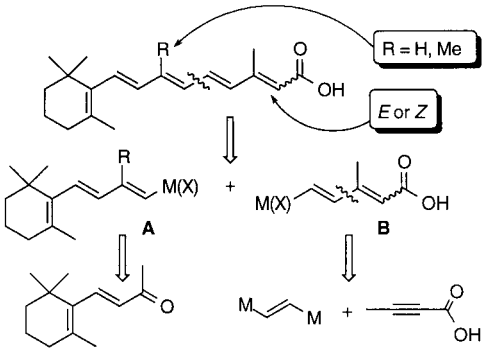
Abstract: Stereoselective construction of retinoic acid and certain analogues were achieved through two successive Stille reactions. First, the coupling of (*E*)-1,2-bis(tributylstannyl)ethene and (*Z*)- or (*E*)-tributylstannyl 3-iodoalk-2-enoates was performed followed by iododestannylation. The second step involved another vinyltin which was synthesised by stannylmetallation of the Negishi dienyne derived from β-ionone.

Key words: retinoic acids, Stille cross-coupling reaction, vinyltin reagents, (*E*)-1,2-bis(tributylstannyl)ethene, iodovinylic substitution.

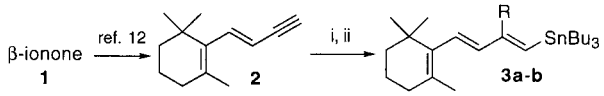
Retinoids are metabolites, derivatives and synthetic analogues of vitamin A. They bind to and activate nuclear retinoid receptors which function as ligand-dependent transcription factors.[1] All-*trans*-retinoic acid (ATRA), (13*Z*)-retinoic acid (13-*cis*-RA)[2] and other retinoids are known to modulate proliferation and differentiation of a variety of cell types through activation of their intracellular retinoid receptors. These receptors are divided into two distinct classes, retinoic acid receptors (RARs) and retinoid X receptors (RXRs) which have retinoic acids as ligands.[3] Several members of this class are in use for the treatment of dermatological diseases and certain cancers.[4,5] The search for new methods of stereocontrolled synthesis is therefore of current interest. Among these, transition metal catalysed cross coupling[6] represents an interesting alternative to Wittig[7] or sulphone-based[8] olefination. In connection with our ongoing work on the Stille reaction[9] using substrates bearing an unprotected acid function,[10] we decided to develop direct and flexible routes yielding retinoic acid and analogues. We describe here the synthesis of all-*trans*-, (13*Z*)- and (9-*nor*)-retinoic acids.[11]

Our retrosynthetic strategy (Scheme 1) is based on the coupling of two building blocks **A** and **B** and starts from commercially available and inexpensive β-ionone and tetrolic acid.

In order to minimize the number of protection and deprotection steps, we planned a method of synthesis without protection of the acid function. The synthesis of fragment **A** (Scheme 2) began with β-ionone **1** which was converted to dienyne **2** and provided 80% yield (after distillation) according to the reliable Negishi procedure.[12] Treatment of **2** with 1.1 equivalent of lithium butyltributylstannylcyanocuprate (Lipshutz reagent)[13] at -78 °C in the presence of methanol (10 eq.)[14] yielded (7*E*,9*E*)-dienylstannane **3a** mixed with the internal vinylstannane **3a'**[15] (**3a**/**3a'** = 75/25). Fortunately, we found that this ratio could be increased to 92/8 when the reaction was performed at -90 °C.



Scheme 1



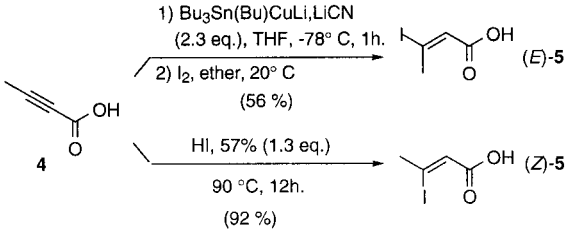
3a R = H; i) $Bu_3SnCu(Bu)CNLi_2$, THF, MeOH, - 90 °C; ii) NH_4Cl sat (85%)

3b R = Me; i) $Bu_3SnCu(Bu)CNLi_2$, THF, - 90 °C; ii) HMPA (4eq.), -90 °C, 5 mn.; iii) MeI(10 eq.), -90 °C to 25°C, 12h. (78%)

Scheme 2

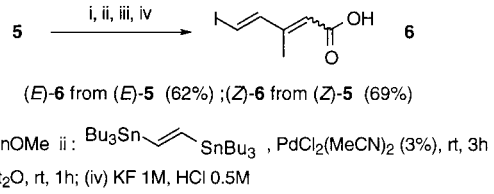
To obtain trisubstituted vinylstannane **3b**, dienyne **2** was treated with 1.1 equivalent of Lipshutz reagent in THF to yield the intermediate vinylcuprate which was trapped with an excess of methyl iodide (10 eq.) in the presence of HMPA (4 eq.). In this case, the reaction occurred with a high regioselectivity (up to 92/8 in favour to the terminal vinylstannane). Iododestannylation of **3a** and **3b** with iodine in ether at low temperature gave quantitatively the corresponding vinyliodides but these were unfortunately found to be very unstable and totally decomposed during the purification on column chromatography.[6h] We therefore chose to use vinyltin reagents rather than vinyliodides for the final step of synthesis.

Fragment **B** was obtained from tetrolic acid **4**, which was converted into pure (*E*)-vinyliodide **5** by stannylcupration reaction and iodine treatment of the generated vinylstannane,[16] while (*Z*)-**5** was more classically obtained by hydroiodination with an aqueous solution of hydroiodic acid.[17]



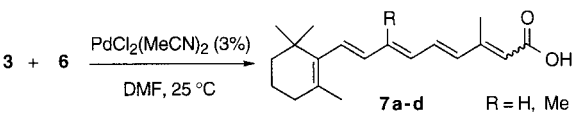
Scheme 3

Stille coupling of β-iodovinylic acids (*E*)- and (*Z*)-**5** (initially protected as the corresponding tributyltin esters) with (*E*)-1,2-bis(tributylstannyl)ethene (1.1 eq.)[18] in the presence of a catalytic amount (5%) of dichlorobis (acetonitrile)palladium(II), stereospecifically provided dienyltins with retention of the configuration of the two double bonds in fair yields. Subsequent iododestannylation of the dienyltin adducts in ether at room temperature yielded quantitatively pure dienyliodide acids (*E*)- and (*Z*)-**6**.[19]



Scheme 4

Finally, Stille coupling of iodovinylic acid **6** with vinylstannanes **3a** and **b** in the presence of a catalytic amount (3%) of dichlorobis(acetonitrile)palladium(II) stereoselectively provided retinoids **7a-d**, with good to moderate yields.[20] Crosscoupling occurred with retention of the configuration of the double bonds and no degradation products were observed. The results are summarised in Table 1. A subsequent attempt was run with **3b**, (*E*)-**6** and tetrakis(triphenylphosphine)palladium as catalyst which provided a poor yield of ATRA **7c** as already described by Negishi.[6a]



Scheme 5

It is interesting to note that, starting from the mixtures of vinylstannanes **3** and their internal isomers, only the terminal regioisomers led to the desired coupling products.

Table 1. Synthesis of retinoic acids

3	6	Retinoic Acids	Yield (%)
3a	(*E*)-**6**	All-*trans*-9-nor-retinoic acid **7a**	50
3a	(*Z*)-**6**	(13*Z*)-9-nor-retinoic acid **7b**	45
3b	(*E*)-**6**	All-*trans* -retinoic acid **7c**	73
3b	(*Z*)-**6**	(13*Z*)-retinoic acid **7d**	70

In conclusion, we have described a new stereoselective approach to the synthesis of retinoids starting from inexpensive materials and based on the Stille reaction. In contrast to the most frequently mentioned methods, the method described here uses unprotected acids, thus avoiding protection and deprotection steps.[21]

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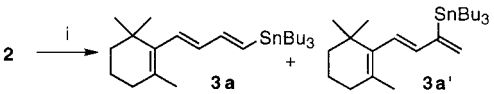

i : $Bu_3Sn(Bu)CuLi,LiCN,MeOH$ (10 eq.) THF, -78 °C

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(19) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Synlett* **1997**, 771.
(20) **Typical procedure:** To a DMF solution (15 mL), **3b** (1.20 g, 2.52 mmol) and (2*Z*,4*E*)-5-iodo-3-methylpent-2,4-dienoic acid (*Z*)-**6** (0.5 g, 2.1 mmol), 16 mg (0.063 mmol, 3%) of dichlorobis(acetonitrile)palladium(II) were added. The mixture was stirred for 3h at 25°C before the reaction mixture was washed with a saturated solution of ammonium chloride (2x15 mL) and extracted with diethyl ether (3x30 mL). After the usual workup, the crude (2*Z*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2',6',6'-trimethyl-1'-cyclohex-1'-enyl)nona-2,4,6,8-tetraenoic acid **7d** was purified by column chromatography (petroleum ether/ ether: 95/5 then 70/30) and crystallisation in ether. yield: 70%. Orange crystals; m.p. = 161 °C [m.p.(lit.) = 162-164 °C]; IR: 3062, 2956, 2921, 2851, 2581, 1682, 1605, 1562, 1276, 1225; Raman: 1594, 1163; ^{1}H NMR (400 MHz) ($CDCl_3$) δ(ppm): 1.01 (6H, s), 1.43-1.47 (2H, m), 1.58-1.61 (2H, m), 1.70 (3H, s), 1.98 (3H, s), 2.01 (2H, t, *J* = 5.7 Hz), 2.08 (3H, s), 5.64 (1H, s), 6.15 (1H, d, *J* = 16.0 Hz), 6.25 (1H, d, *J* = 11 Hz), 6.27 (1H, d, *J* = 16.0 Hz), 7.01 (1H, dd, *J* = 15.2 Hz, *J* = 11 Hz), 7.73 (1H, d, *J* = 15.2 Hz), 10.7 (1H, bs); ^{13}C NMR: 12.8, 19.1, 21.1, 21.6, 28.8 (2C), 33, 34.1, 39.5, 115.7, 128.7, 129, 130.2, 132.8, 137.2, 137.5, 138.7, 140.3, 153.5, 172; MS: *m/z* = 300 ($M^{\cdot+}$, 41), 285 (95), 239 (66), 197 (16), 185 (11), 143 (11), 133 (13), 129 (24), 99 (11), 89 (54), 88 (70), 87 (35), 85 (16), 73 (46), 72 (15), 71 (13), 61 (12), 60 (28), 59 (13), 58 (63), 57 (39), 45 (100), 44 (43).
(21) We also found that the use of acids instead of ester analogues greatly improved the purification steps for the elimination of tributyltin byproducts or impurities.