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Stereocontrolled synthesis of polyenoic acids by a Heck–Sonogashira reaction: easy access to 9,10-didehydro retinoic acids

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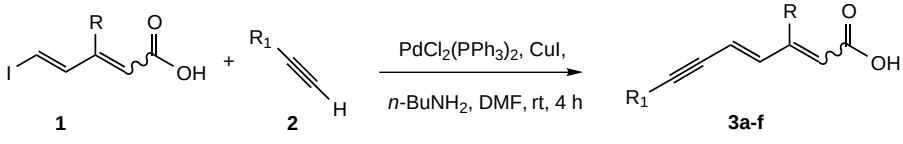
Abstract—Stereoselective synthesis of rigid 9,10-didehydro retinoic acids was achieved from (2*Z* or 2*E*,4*E*)-5-iododienoic acids through a Heck–Sonogashira cross-coupling reaction.

Organic compounds with polyenic structures are frequently found in living systems. Not unexpectedly, their ability to elicit a wide range of physiological effects often stems from a change in olefin configuration. A case in point is the family of polyenes related to retinoid acids.[1] The search for new methods of stereocontrolled synthesis is therefore of current interest, and among these, transition-metal-catalysed cross-coupling[2] represents an interesting alternative to Wittig[3] or sulphone-based[4] olefination. In connection with our ongoing work in which we succeeded in synthesising conjugated polyenes bearing an *E*,*E* or *Z*,*Z* unit under Stille reaction conditions[5] using substrates bearing an unprotected acid function,[6] we decided to develop direct and flexible routes yielding rigid retinoic acid and analogues. For this purpose, we examined the cross-coupling reaction of iodovinylic acids **1** with alkynes **2** under Heck–Sonogashira conditions[7] (Scheme 1).

We first investigated the synthesis of dienynoic acid with various alkynes from **1** using dichlorobis(triphenylphosphine)palladium(II), copper iodide, *n*-butylamine and DMF as solvent at room temperature and we obtained fair yields of the corresponding dienynoic acid **3**. In all cases, we observed a low yield of the products resulting from the duplication of terminal alkynes (<5%),[8] no protection of the carboxylic function was necessary and the configuration of the two double bonds was unchanged. In addition, no cyclisation reaction producing butenolides[9–11] or α-pyrones occurred,[12] and these products were obtained when the triple bond was located between carbons 4 and 5. Introduction of the ethynyl group was previously performed by Stille cross-coupling between for example **1a** and tributylstannylacetylene.[13] The results are summarised in Table 1.[14]

In view of the results obtained, we extended these results to retinoid chemistry. Although many papers have been published on retinoid chemistry,[2–6] only two concern the introduction of a rigid bond (i.e. triple bond) between carbons C_9–C_{10},[15] one using a Wittig



Scheme 1.

Keywords: Heck–Sonogashira reactions; retinoids; alkenyl halides.

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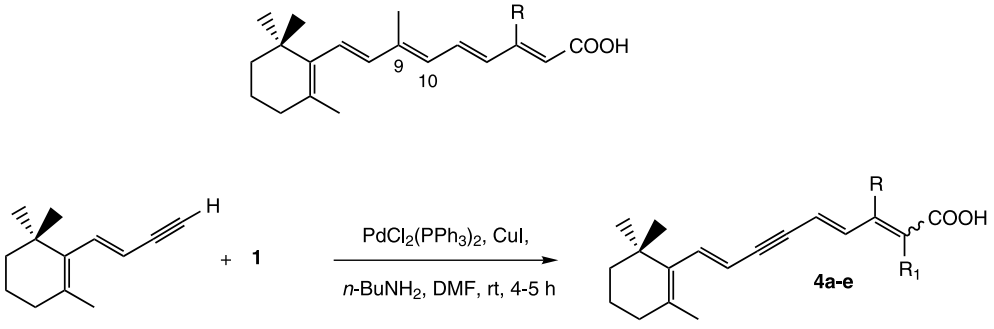
Table 1. Cross-coupling of iodovinylic acids **1** with alkynes **2**

1	R	R_1	No.	Yield (%)
(2*Z*,4*E*)-**1a**	H	Ph	**3a**	75
(2*Z*,4*E*)-**1b**	Me	Ph	**3b**	75
(2*Z*,4*E*)-**1b**	Me	Me_3Si	**3c**	77
(2*Z*,4*E*)-**1b**	Me	MeO-CH_2	**3d**	70
(2*Z*,4*E*)-**1b**	Me	BnS-CH_2	**3e**	76
(2*E*,4*E*)-**1c**	Me	Bu_3Ge	**3f**	72

reaction[16] and the second by addition of 4-methylpyrylium tetrafluoroborate[17] on appropriate substrates. Starting from the enyne derived from β-ionone (obtained in 75–80% yield according to the Negishi procedure[18]) the new 9,10-didehydro retinoid acids were obtained efficiently and a series of (7*E*,11*E*,13*Z* or 13*E*)-9,10-didehydro retinoid acids is described below (Table 2).



In conclusion, we have developed a new stereoselective synthesis approach to 9,10-didehydroretinoid acids by Heck–Sonogashira coupling. In contrast to the most frequently published methods, the method described here uses unprotected acids, thus avoiding protection and deprotection steps.

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Table 2. Synthesis of 9,10-didehydro retinoid acids

1	R	R_1	No.	Yield[b] (%)
(2*Z*,4*E*)-**1a**	H	H	**4a**	70
(2*Z*,4*E*)-**1b**	Me	H	**4b**	80
(2*Z*,4*E*)-**1b**[a]	Me	H	**4c**	78
(2*E*,4*E*)-**1c**	Me	D	**4d**	73
(2*E*,4*E*)-**1d**	Et	H	**4e**	76

[a] *t*-Bu ester was used in this case.
[b] Yields after purification.

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14. Typical procedure: Under argon atmosphere, a solution of 1 mL (10 mmol) *n*-butylamine, 6.3 mmol alkyne (**2**) and 20 mL of DMF was stirred for 15 min at room temperature, then 4.2 mmol iodovinylic dienoic acid **1**, 217 mg (0.31 mmol) dichlorobis(triphenylphosphine)palladium(II) and 59 mg (0.31 mmol) copper(I) iodide were added. After 4 h at room temperature, the mixture was poured into 20 mL of water, extracted with diethyl ether, washed with a saturated solution of NH_4Cl, and dried over $MgSO_4$. After evaporation under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: hexane/diethyl ether 30/70) or by crystallisation in ether to yield polyenes **3** or **4**. For example:

Compound **3c**: mp 112°C; IR (cm^{-1}): 3100, 2985, 2875, 2200, 1690, 1615, 1170; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.25 (s, 9H), 2.05 (d, 3H, $J=1$ Hz), 5.78 (1H, q, $J=1$ Hz), 6.08 (1H, d, $J=16$ Hz), 8.09 (d, 1H, $J=16$ Hz), 11.8 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 0.2 (3C), 21, 102, 104, 116, 119, 139, 152, 172; MS (70 eV, EI) *m*/*z*: 208 (M, 13), 193 (54), 149 (27), 105 (32), 75 (100), 73 (19), 45 (44), 43 (37).

Compound **3f**: IR (cm^{-1}): 3100, 2980, 2875, 2200, 1690, 1615, 1170; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.94 (t, 9H, $J=7$ Hz), 1.5–1.34 (m, 18H), 2.3 (s, 3H), 5.86 (s, 1H), 6.11 (d, 1H, $J=16$ Hz), 6.68 (d, 1H, $J=16$ Hz), 9.4 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 13.7, 14.2 (3C), 14.5 (3C), 26.5 (3C), 27.8 (3C), 101.5, 104.7, 116, 120, 144.3, 154, 172; MS (70 eV, EI) *m*/*z* (^{74}Ge): 323 (M−56, 22), 267 (20), 121 (11), 105 (11), 91 (44), 57 (23), 55 (33), 43 (11), 41 (100).

Compound **4d**: mp 136°C; IR (cm^{-1}): 3100, 2980, 2877, 2295, 2195, 1690, 1605, 1155; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.02 (s, 6H), 1.61–1.42 (m, 4H), 1.72 (s, 3H), 2 (t, 2H, $J=4$ Hz), 2.02 (s, 3H), 5.64 (dd, 1H, $J=16$ Hz, $J=2$ Hz), 6.18 (dd, 1H, $J=16$ Hz, $J=2$ Hz), 6.66 (d, 1H, $J=16$ Hz), 8 (d, 1H, $J=16$ Hz), 11 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm): 19, 20.6, 21.8, 29 (2C), 33.4, 34.2, 39.7, 89.4, 96.4, 111.8, 116.6, 132.6, 137, 137.2, 142.4, 151.8, 170.6; MS (70 eV, EI) *m*/*z*: 285 (M, 56), 270 (100), 224 (65), 170 (41), 129 (22), 91 (30), 55 (30), 45 (24), 43 (34), 41 (89).

Compound **4e**: mp 95°C; IR (cm^{-1}): 3095, 2980, 2878, 2185, 1685, 1605, 1165; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.07 (s, 3H), 1.19 (t, 3H, $J=7.4$ Hz), 1.6–1.47 (m, 4H), 1.78 (s, 3H), 2 (t, 2H, $J=6$ Hz), 2.45 (q, 2H, $J=7.4$ Hz), 5.7 (dd, 1H, $J=16$ Hz, $J=2$ Hz), 5.71 (s, 1H), 6.22 (dd, 1H, $J=16$ Hz, $J=2.2$ Hz), 6.68 (d, 1H, $J=16$ Hz), 7.96 (d, 1H, $J=16$ Hz), 11.1 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm): 14, 19.5, 22, 27, 29.2 (2C), 33.7, 34.5, 40, 90, 96.6, 112, 116.2, 116.4, 133, 136.4, 137.6, 142.7, 177.8, 172; MS (70 eV, EI) *m*/*z*: 298 (M, 39), 283 (97), 237 (63), 183 (31), 155 (29), 115 (47), 91 (40), 55 (38), 43 (42), 41 (100), 39 (42).

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