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Stereoselective Isomerization of 10-Arylsulfenate-11,12-Dehydroretinoids to 9-*cis*-Retinoids

Angel R. de Lera,*Alejandro Castro, Alicia Torrado and Susana López[1]

Departamento de Química Física y Química Orgánica, Universidad de Vigo, 36200 Vigo, SPAIN

[1]Departamento de Química Orgánica, Universidad de Santiago de Compostela, 15706 Santiago, SPAIN

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Abstract: The C_7-C_{12} triene fragment of 9-*cis*-retinoids **8** was stereoselectively generated by treatment of propargylic alcohol **3** with phenylsulfenyl chloride/triethylamine at -78 °C, followed by stereospecific reduction of the resulting vinylsulfoxide (*t*-BuLi, MeLi, MeOH, -78 °C). Thus, 9-*cis*-retinoic acid **2**, the natural ligand of the retinoid X receptor (RXR) was straightforwardly synthesized from **8** in two steps.

The vitamin A aldehydes 11-*cis*-retinal and *trans*-retinal have well-known roles as chromophores in the photoreceptor proteins rhodopsin and in the membrane proteins from halobacteria, respectively.[1] More recently, the vitamin A metabolites all-*trans*-retinoic acid (**1**) and 9-*cis*-retinoic acid (**2**) have been found to be natural ligands for several nuclear receptor proteins.[2] Specifically, retinoic acid receptors (RARs) have high affinity for both **1** and its isomer 9-*cis*-retinoic acid **2**, while the latter is the natural ligand of retinoid X receptors (RXRs).[3] Details of these interactions and their role in gene trancription are now emerging,[2b] fuelling great excitement as to the possible biomedical applications of this knowledge.[3] Specially interesting is the marked tendency of RXRs to form heterodimers with RARs and with other members of the nuclear receptor superfamily, including the thyroid hormone receptor (TR), the peroxisome proliferator-activated receptor (PPARs) and the orphan receptor LXR. This is due to the recent observation that RXR-selective ligands can activate certain heterodimers (PPAR-RXR, LXR-RXR), thus modulating gene transcription under the control of that pair of heterodimer partners. Thus RXR agonists have very different pharmacological activities from retinoid activators of RAR, and constitute a new group of vitamin A derivatives denominated "rexinoids".[4] Recently, interest in rexinoids has focused on the design and synthesis of ligands selective for RXRα, RXRβ or RXRγ isoforms.[5]

A stereoselective approach to 9-*cis*-retinoic acid **2** has recently been published in which the 9-*cis*-stereochemistry was generated by addition of methylcuprate to a propargylic nitrile, and the olefin chain was completed by Horner-Emmons reaction.[6] In the present work we describe a new stereoselective synthesis of 9-*cis*-retinoids based on the isomerization of 10-arylsulfenate-11,12-dehydroretinoids generated *in situ* from propargylic alcohol **3**. The mechanism of this reaction is unclear.

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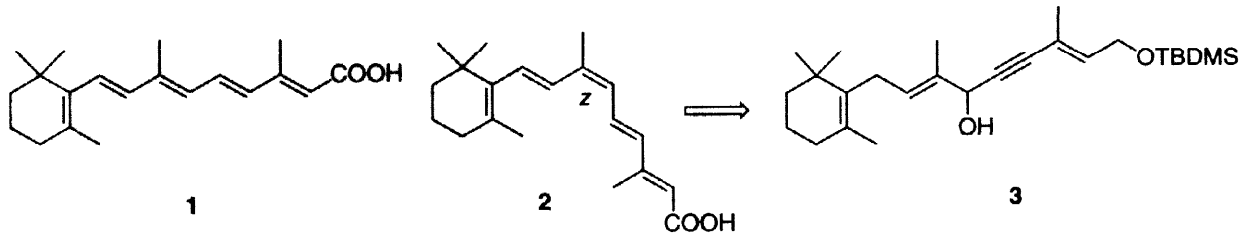
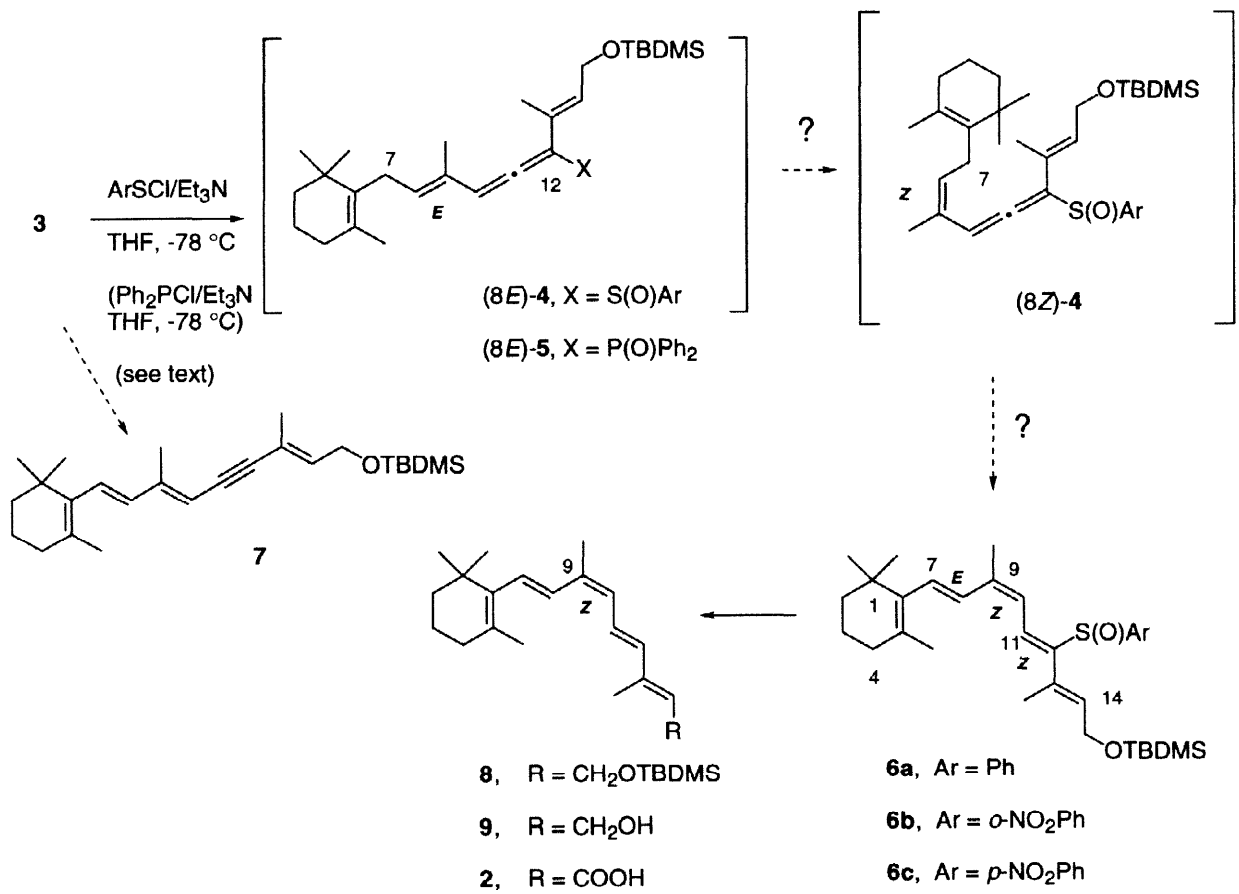


As part of our research on the electrocyclization of divinylallenes[7] to alkylidenecyclobutenes,[8] we planned to examine the effects of heteroatoms attached at the internal position (C_{12} in **4** and **5**, *vide infra*). On the basis of the known facile [2,3]-sigmatropic rearrangement of propargylic alcohols to allenyl sulfoxides,[9] we began by treating a solution of alcohol **3** (obtained in two steps from β-ionone)[8c] in CH_2Cl_2/Et_3N with freshly prepared phenylsulfenyl chloride at -78 °C, stirring it for 1 h at -78 °C and then for 1 h at ambient temperature. Work-up followed by chromatography of the residue on silica gel impregnated with Et_3N afforded 61% yield of a product that showed no ^{13}C NMR or FT-IR absorptions characteristic of allenes.[10] Moreover, its ^1H NMR spectrum lacked the signals due to the methylene at C_7 of **3**, and instead showed additional signals in the vinyl region. These observations and the results of extensive nOe experiments are compatible with the product's having the conjugated polyene structure shown in **6a**, albeit the configuration about the C_{11}-C_{12} bond was unclear. However, the (7*E*,9*Z*,11*Z*,13*E*) geometry of **6a** was unequivocally established after stereospecific desulfuration using a modification of Okamura's procedure (*t*-BuLi, MeLi, MeOH, THF, -78 °C, 68%)[11] and spectroscopic analysis of the product **8**.



Reaction of **3** with arylsulfenyl chlorides bearing an electron-withdrawing *o*-NO_2 or *p*-NO_2 substituent gave compounds **6b** (44%) or **6c** (79%), respectively, together with a second product that was easily identified as silyl ether **7** (56% and 15% yield, respectively). The latter compound was most likely formed by elimination of the 10-arylsulfenate of the 11,12-dehydroretinoid derived from **3**.

Deprotection of **6a** (TBAF, 25 °C) gave 9-*cis*-retinol **9** (83% yield), which was identical to an authentic sample, thereby providing additional proof of the validity of structure **6a**. Finally, oxidation of **9** with AgO/MnO_2/MeOH gave the desired RXR ligand 9-*cis*-retinoic acid **2** (72% yield).[12]

The mechanism of this isomerization is intriguing. It was expected that the propargylic sulfenate derived from **3** would spontaneously undergo a [2,3]-sigmatropic rearrangement to the corresponding allenyl sulfoxide (8*E*)-**4**; although sulfoxide (8*E*)-**4** was not detected in the reaction mixture, support for its formation comes from the observation that treatment of **3** with Ph_2PCl/Et_3N[13] afforded allenylphosphine oxide (8*E*)-**5**.[14] Notwithstanding, the subsequent steps of the reaction mechanism are unclear. The formation of **6a** would be nicely explained by a [1,5]-sigmatropic shift of hydrogen, but (8*E*)-**4** lacks the cisoid geometry required for such a shift. We thus postulate that (8*E*)-**4** firstly undergoes isomerization to (8*Z*)-**4** under the reaction conditions, and then the [1,5]-sigmatropic shift. The sulfoxide group in (8*Z*)-**4** would accelerate this shift, allowing it to occur at -78 °C, and would also control facial selectivity, directing the migrating hydrogen *anti*, accounting for the (9*Z*,11*Z*) geometry of **6a**.[15] Confirmation of the involvement of (8*Z*)-**4** in this reaction is currently being addressed in this laboratory.

In summary, we have developed a new synthetic approach to 9-*cis*-retinoids that allows stereospecific generation of their C_7-C_{12} triene system in a one-pot reaction starting from propargylic alcohol **3**. The reaction mechanism in unclear but may involve an unprecedented cascade of pericyclic reactions, the exact sequence of which is currently being investigated in these laboratories. The potential utility of these compounds as biological tools may be enhanced by deuterium labelling in the stereospecific reduction step.[11]

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10. Spectroscopic data for **6a**: **^{1}H-RMN** (400 MHz, $CDCl_3$): δ -0.01 (6H, s, Si-2CH_3),0.85 (9H, s, Si-*t*-Bu), 1.05 (6H, s, C_1-2CH_3), 1.4-1.6 (4H, m, $2H_2$ + $2H_3$), 1.61 (3H, d, J = 0.9 Hz, CH_3), 1.75 (3H, s, CH_3), 1.83 (3H, s, CH_3), 2.04 (2H, t, J = 6.0 Hz, $2H_4$), 4.15 (2H, m, $2H_{15}$), 5.66 (1H, tq, J = 6.0, 0.9 Hz, H_{14}), 6.39 (1H, d, J = 16.0 Hz, H_7), 6.67 (1H, d, J = 16.0 Hz, H_8), 6.89 (1H, d, J = 12.1 Hz, H_{11}), 7.12 (1H, d, J = 12.1 Hz, H_{10}), 7.4-7.6 (5H, m, ArH). **^{13}C-RMN** (100 MHz, $CDCl_3$): δ -4.8 (q, Si-2CH_3), 17.3 (q), 18.7 (s), 19.6 (t), 21.8 (q), 22.3 (q), 26.3 (q, Si-*t*-Bu), 29.4 (q, 2x, C_1-2CH_3), 33.5 (t), 34.6 (s), 39.9 (t), 60.7 (t), 121.6 (d), 124.7 (d, 2 x Ar), 129.1 (d, 2 x Ar), 129.3 (d), 129.9 (d), 131.1 (s), 131.4 (s), 132.0 (d), 132.3 (d), 133.4 (d), 138.3 (s), 142.0 (s), 144.1 (s), 144.2 (s). **FTIR** (NaCl): υ 2955 (s, C-H), 2928 (s, C-H), 2857 (s, C-H), 1582 (w), 1443 (m), 1378 (w), 1257 (m), 1051 (s), 836 (s), 777 (m), 747 (m) cm^{-1}. **MS**: *m/z* (%) 526 ($M+2^+$, 16), 525 ($M+1^+$, 41), 524 (M^+, 100), 508 (18), 507 (19), 467 (11), 399 (26), 398 (30), 379 (26), 270 (26), 267 (51), 231 (31), 197 (38), 185 (43), 145 (33), 119 (41). **HRMS**: calcd for $C_{32}H_{48}O_2SSi$: 524.3144; found: 524.3141.

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14. Allenyl phosphine oxide **5** was thermally stable, being recovered unaltered after heating it at 140 °C in C_6D_6 (^{1}H NMR monitoring), thus providing evidence of the rate-retarding effect of a heteroatom at C_4 on the electrocyclization of these model divinylallenes (see ref. 8c).

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