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AN EXPEDIENT STEREOCONTROLLED SYNTHESIS OF 7-CIS-RETINOIDS

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AN EXPEDIENT STEREOCONTROLLED SYNTHESIS OF 7-*CIS*-RETINOIDS

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ABSTRACT

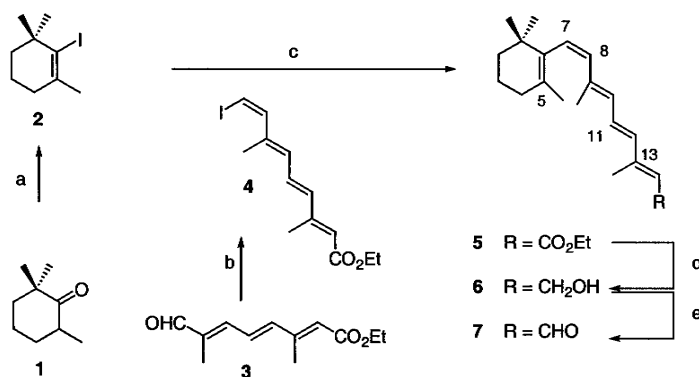
Ethyl (7*Z*)-retinoate **5** has been efficiently synthesized using as key step the Suzuki coupling of an *in situ* generated alkenylboronic acid and the geometrically homogeneous tetraenyl iodide with (*Z*)-geometry, itself obtained by yodomethylation according to Stork's conditions. Functional group manipulation then afforded (7*Z*)-retinal **7**.

The studies on the visual cycle performed by Wald and coworkers in the early fifties highlighted the importance of the retinal side-chain geometry upon its biological activity.¹ Geometric isomers of retinal have since then been extensively used in bioorganic studies aimed at understanding the stereoselectivity of the binding site in retinal proteins, in particular the visual pigments. These studies have stimulated the development of synthetic approaches to all sixteen possible geometric isomers of retinal.² For the synthesis of the more hindered 7-*cis* isomers, Liu developed a general route which uses a photosensitized isomerization of *trans*- β -ionyl derivatives

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in the presence of 2-acetonaphthone,³ an effort which culminated in the preparation of the 7-*cis* isomers,⁴ including the highly twisted all-*cis*-retinal.^{4d}

We felt that the straightforward approach to 9-*cis*-retinoids that we recently developed, based on the Suzuki cross coupling⁵ of an *in situ* generated C₉-cyclohexenylboronic acid and a C₁₁-side chain tetraenyl iodide,⁶ might be extended to the stereocontrolled synthesis of the 7-*cis* isomers. Two requisites had to be met, namely the generation of a tetraenyl iodide with the desired Z-configuration, and the preservation of that geometry during the coupling reaction. The realization of this scheme culminated an efficient synthesis of the sterically hindered 7-*cis*-retinoids.⁷



a. *i.* NH₂NH₂·H₂O, Et₃N, EtOH, 100 °C. *ii.* I₂, DBU, Et₂O, 100 °C, 80% combined yield (ref. 6); b. Ph₃PCH₂I₂, NaHMDS, HMPA, THF, -78 °C. c. *i.* ^tBuLi, B(OMe)₃, THF, -78 °C. *ii.* Pd(PPh₃)₄, 10% TIOH, THF, 25 °C, iodide **4**, 76% combined yield; d. DIBAL-H, THF, -78 °C; e. MnO₂, Na₂CO₃, CH₂Cl₂, 25 °C, 89% combined yield.

Cyclohexenyl boronate was best obtained immediately prior to the palladium-catalyzed cross-coupling reaction (in order to avoid premature decomposition) by treatment of iodide **2**⁶ with *t*-BuLi in THF at -78 °C for 30 min, followed by addition of trimethylborate.⁶ For the C₁₁-functionalized side chain, the Wittig condensation of trienal ester **3**, a common building block in retinoid synthesis,² with iodomethylenetriphenylphosphorane according to Stork's procedure⁸ remarkably provided the unstable (*Z*)-tetraenyl iodide ester **4** essentially as a single geometric isomer, as shown by ¹H-NMR analysis of the crude reaction mixture. This iodide **4** was immediately added to the freshly prepared boronate, followed by the sequential addition of 10% aq TIOH and Pd(PPh₃)₄. The palladium-catalyzed cross-coupling, accelerated by thallium hydroxide,⁹



took place at room temperature, affording the pentaene ethyl (7*Z*)-retinoate **5** in 76% yield. A two-step reduction-oxidation sequence without isolation of the unstable alcohol **6** then afforded 7-*cis*-retinal **7**.

EXPERIMENTAL

Ethyl 7-*cis*-retinoate 5. Sodium bis-trimethylsilylamide (1.17 mL, 0.6 M in toluene, 0.7 mmol) was added to a suspension of (Ph₃PCH₂I)I (0.397 g, 0.75 mmol) in THF (1 mL) and stirred at room temperature for 30 min. The reaction mixture was cooled to −60°C, and hexamethyl phosphoramidate (0.35 mL) was added. After 10 min stirring, the mixture was cooled down to −78°C, and a solution of aldehyde **3** (0.104 g, 0.5 mmol) in THF (1 mL) was added. After stirring for 2 h, the reaction mixture was poured into H₂O (5 mL) and extracted with hexane (3 × 5 mL). The combined organic extracts were dried over MgSO₄, concentrated in vacuo and the residue was used in the next step without further purification.

t-BuLi (0.88 mL, 1.7 M in THF, 1.5 mmol) was added dropwise to a cooled (−78°C) solution of iodide **4** (0.188 g, 0.75 mmol) in THF (2 mL). After stirring for 1 h, B(OMe)₃ (0.13 mL, 1.125 mmol) was added and the resulting mixture was stirred at 0°C for 1 h. Then, 10% aqueous TIOH (4.9 mL, 2.25 mmol) and a solution of the above residue and Pd(PPh₃)₄ (0.087 g, 0.075 mmol) in THF (3 mL) were added sequentially and the mixture was stirred at room temperature for 12 h. The reaction was extracted with ethyl ether (2 × 10 mL) and the combined organic extracts were washed with brine (3 × 10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by chromatography (SiO₂, 97:3 hexane:ethyl acetate) to afford 0.125 g (76%) of ethyl 7-*cis*-retinoate **5** as a yellow oil. ¹H-NMR (400.14 MHz, CDCl₃): δ 6.95 (dd, *J* = 15.3, 12.2 Hz, 1H, H₁₁), 6.28 (d, *J* = 15.3 Hz, 1H, H₁₂), 6.25 (d, *J* = 12.6 Hz, 1H, H₇), 6.13 (d, *J* = 12.6 Hz, 1H, H₈), 5.96 (d, *J* = 12.2 Hz, 1H, H₁₀), 5.81 (s, 1H, H₁₄), 4.20 (q, *J* = 7.1 Hz, 2H, OEt), 2.37 (s, 3H, CH₃), 1.9–2.0 (m, 1H, 2H₃), 1.94 (s, 3H, CH₃), 1.7–1.8 (m, 2H, 2H₄), 1.6–1.7 (m, 2H, 2H₅), 1.55 (s, 3H, CH₃), 1.33 (t, *J* = 7.1 Hz, 3H, OEt), 0.97 (s, 6H, C₁-2CH₃). ¹³C-NMR (100.62 MHz, CDCl₃): δ 167.2 (s), 152.7 (s), 140.5 (s), 136.5 (s), 135.3 (s), 135.2 (d), 134.5 (d), 131.2 (d), 130.9 (d), 128.8 (d), 118.7 (s), 59.6 (t), 39.2 (t), 34.6 (s), 32.1 (t), 29.9 (q, 2x), 28.8 (q), 21.6 (q), 19.2 (t), 14.6 (q), 13.8 (q). IR-FT (NaCl): ν. 3000–2800 (s), 1700 (s), 1580 (w), 1240 (w), 1149 (s). MS (EI⁺) *m/z* (%): 329 (M⁺ + 1, 25), 328 (M⁺, 100), 255 (37), 185 (20), 171 (16), 145 (14), 133 (14), 119 (16), 109 (16), 105 (19), 91 (17), 69 (21). HMRS (EI⁺): calcd for C₂₂H₃₂O₂, 328.2402; found, 328.2404. ¹H-NMR data for methyl 7-*cis*-retinoate has been reported.^{4c}



7-*cis*-retinal 7. To a solution of ethyl 7-*cis*-retinoate **5** (0.097 g, 0.296 mmol) in THF (5 mL) at -78°C , was added DIBALH (0.734 mL, 1 M in toluene, 0.734 mmol) and the resulting suspension was stirred for 1 h at -78°C . After careful addition of 10% aqueous NH_4Cl , the mixture was extracted with ethyl ether (3×10 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. The residue was used in the next step without further purification.

MnO_2 (0.463 g, 5.33 mmol) and Na_2CO_3 (0.565 g, 5.33 mmol) were added to a solution of the residue obtained above in CH_2Cl_2 (10 mL). After stirring at 25°C for 12 h, the reaction mixture was filtered through Celite, and the solvent was removed. The residue was purified by HPLC (Prep. Nova-Pak[®], HR silica 60A, 19×300 mm; 5:95 ethyl acetate:hexane; 8 mL/min; $t_R=28.5$ min) to afford 0.075 g (89%) of 7-*cis*-retinal **7**. **¹H-NMR** (400.14 MHz, CDCl_3): δ 10.08 (d, $J=8.2$ Hz, 1H, H_{15}), 7.04 (dd, $J=15.1$, 11.5 Hz, 1H, H_{11}), 6.31 (d, $J=15.1$ Hz, 1H, H_{12}), 6.23 (d, $J=11.5$ Hz, 1H, H_{10}), 6.10 (d, $J=12.6$ Hz, 1H, H_8), 5.9–6.0 (m, 1H, $\text{H}_7 + \text{H}_{14}$), 2.29 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.8–1.9 (m, 2H, 2H_3), 1.58 (s, 3H, CH_3), 1.5–1.6 (m, 2H, 2H_4), 1.49 (s, 3H, CH_3), 1.4–1.5 (m, 2H, 2H_5). **¹³C-NMR** (100.62 MHz, CDCl_3): δ 189.8 (s), 152.9 (s), 141.1 (s), 137.9 (s), 136.9 (s), 135.7 (d), 135.1 (d), 132.1 (d), 131.4 (d), 130.4 (d), 129.9 (d), 39.4 (t), 33.3 (s), 32.3 (t), 29.1 (q), 21.8 (q), 19.6 (t), 14.6 (q), 12.4 (q). **IR-FT** (NaCl): ν . 3000–2800 (s), 1660 (s), 1450 (w). **MS** (EI^+) m/z (%): 285 (23), 284 (M^+ , 100), 173 (36), 159 (18), 145 (18), 133 (18), 131 (14), 119 (30), 107 (16), 105 (26), 95 (18), 91 (23), 69 (18). **HMRS** (EI^+): calcd for $\text{C}_{20}\text{H}_{28}\text{O}$, 284.2140; found, 284.2150. ¹H-NMR data for 7-*cis*-retinal has been reported.^{2a}

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