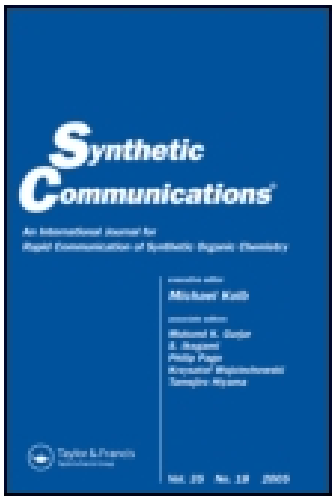

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AN EXPEDIENT STEREOCONTROLLED SYNTHESIS OF 7-*CIS*-RETINOIDS

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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 tetraenyliodide with (*Z*)-geometry, itself obtained by yodomethylenation 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 photosensitised isomerization of *trans*-β-ionyl derivatives

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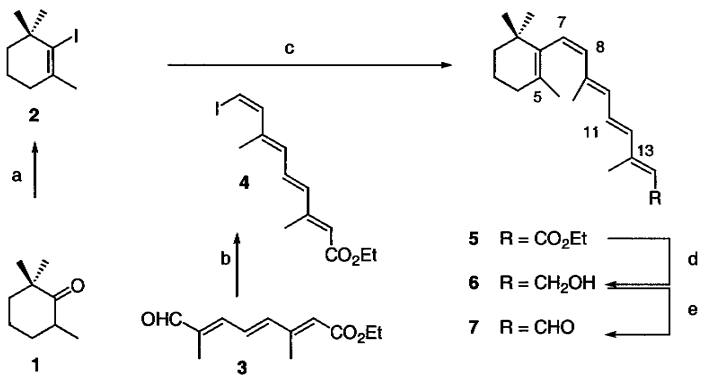
in the presence of 2-acetonaphthone,[3] an effort which culminated in the preparation of the 7-*cis* isomers,[4] including the highly twisted all-*cis*-retinal.[4d]

We felt that the straightforward approach to 9-*cis*-retinoids that we recently developed, based on the Suzuki cross coupling[5] of an *in situ* generated C_9-cyclohexenylboronic acid and a C_{11}-side chain tetraenyliodide,[6] might be extended to the stereocontrolled synthesis of the 7-*cis* isomers. Two requisites had to be met, namely the generation of a tetraenyliodide 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.* $NH_2NH_2.H_2O$, Et_3N, EtOH, 100 °C. *ii.* I_2, DBU, Et_2O, 100 °C, 80% combined yield (ref. 6); b. $Ph_3PCH_2I_2$, NaHMDS, HMPA, THF, -78 °C. *c. i.* ^{t}BuLi, $B(OMe)_3$, THF, -78 °C. *ii.* $Pd(PPh_3)_4$, 10% TlOH, THF, 25 °C, iodide **4**, 76% combined yield; d. DIBAL-H, THF, -78 °C; e. MnO_2, Na_2CO_3, CH_2Cl_2, 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 C_{11}-functionalized side chain, the Wittig condensation of trienal ester **3**, a common building block in retinoid synthesis,[2] with iodomethylenetriphenylphosphorane according to Stork's procedure[8] remarkably provided the unstable (*Z*)-tetraenyliodide ester **4** essentially as a single geometric isomer, as shown by ^{1}H-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 TlOH and $Pd(PPh_3)_4$. The palladium-catalyzed cross-coupling, accelerated by thallium hydroxide,[9]

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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 $(Ph_3PCH_2I)I$ (0.397 g, 0.75 mmol) in THF (1 mL) and stirred at room temperature for 30 min. The reaction mixture was cooled to $-60^{\circ}C$, and hexamethyl phosphoramide (0.35 mL) was added. After 10 min stirring, the mixture was cooled down to $-78^{\circ}C$, 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 H_2O (5 mL) and extracted with hexane (3×5 mL). The combined organic extracts were dried over $MgSO_4$, 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 ($-78^{\circ}C$) 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 $0^{\circ}C$ for 1 h. Then, 10% aqueous TlOH (4.9 mL, 2.25 mmol) and a solution of the above residue and $Pd(PPh_3)_4$ (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 $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, 97:3 hexane:ethyl acetate) to afford 0.125 g (76%) of ethyl 7-*cis*-retinoate **5** as a yellow oil. **^{1}H-NMR** (400.14 MHz, $CDCl_3$): δ 6.95 (dd, $J = 15.3$, 12.2 Hz, 1H, H_{11}), 6.28 (d, $J = 15.3$ Hz, 1H, H_{12}), 6.25 (d, $J = 12.6$ Hz, 1H, H_7), 6.13 (d, $J = 12.6$ Hz, 1H, H_8), 5.96 (d, $J = 12.2$ Hz, 1H, H_{10}), 5.81 (s, 1H, H_{14}), 4.20 (q, $J = 7.1$ Hz, 2H, OEt), 2.37 (s, 3H, CH_3), 1.9–2.0 (m, 1H, $2H_3$), 1.94 (s, 3H, CH_3), 1.7–1.8 (m, 2H, $2H_4$), 1.6–1.7 (m, 2H, $2H_5$), 1.55 (s, 3H, CH_3), 1.33 (t, $J = 7.1$ Hz, 3H, OEt), 0.97 (s, 6H, C_1-$2CH_3$). **^{13}C-NMR** (100.62 MHz, $CDCl_3$): 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 $C_{22}H_{32}O_2$, 328.2402; found, 328.2404. ^{1}H-NMR data for methyl 7-*cis*-retinoate has been reported.[4c]

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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**. **^{1}H-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, $H_7 + H_{14}$), 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, $2H_5$). **^{13}C-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 $C_{20}H_{28}O$, 284.2140; found, 284.2150. ^{1}H-NMR data for 7-*cis*-retinal has been reported.[2a]

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