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Synthesis of new cyclic retinoids via base induced self-condensation of C-13, C-14 and C-15 units

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Abstract

New cyclic retinoids from β-ionone and C-14 and C-15 derivatives were synthesised by self-condensation promoted by strong bases. © 2000 Published by Elsevier Science Ltd. All rights reserved.

The past decade of retinoid synthesis has witnessed the emergence of novel structures far removed from that of the natural product, and some of them have totally lost the terpenoid structure.[1] In relation to the success of vitamin A and related compounds, especially *all trans* retinoic acid (ATRA) for the treatment of skin disorders, novel synthetic derivatives were sought.[2] Moreover, new molecules are desired to improve and expand the treatment of malignant diseases. Novel molecules are also needed to overcome ATRA-resistance which usually occurs during treatment of acute promyelocytic leukemia (APL).[3]

In previous years, we have been involved in the development of useful synthons for vitamin A synthesis.[4–7] In this work, we have synthesised new retinoids with olefinic moieties incorporated into a ring. These compounds are obtained from β-ionone **1** and related C-14 and C-15 derivatives **2**, **3**[6,7] and **4**[4] (Fig. 1).

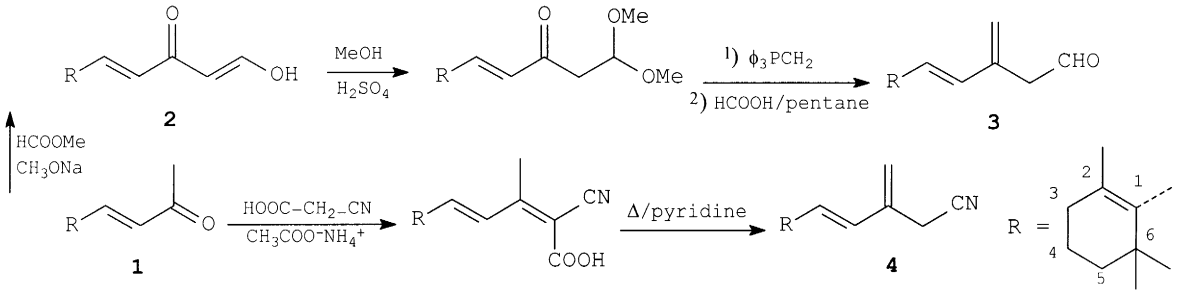

Fig. 1.

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Starting from β-ionone **1**, the new cyclohexenone **5** could be obtained by Michael addition of the ionone enolate to a second molecule of ionone [(a) MeONa, pentane, 0°C then rt; (b) HCl N]. After rearrangement of the intermediary 5-keto-enolate to the less hindered enolate, internal ring closure by aldol condensation and dehydration (Robinson annulation),[8] the cyclohexenone **5** is obtained nearly quantitatively (Fig. 2).

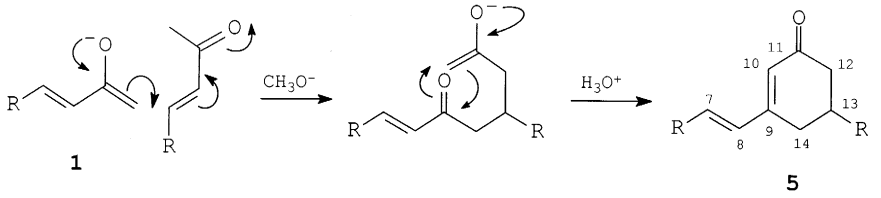

Fig. 2.

The unstable hydroxymethylenic derivative of β-ionone **2** [(a) **1**+MeONa, pentane, 0°C, >90%; (b) CH_3COOH], leads to the corresponding triacylbenzene **6** (50%). The formation of the triacylbenzene could be explained by successive base-induced condensations followed by dehydration of the intermediate trihydroxy cyclohexane (Fig. 3).

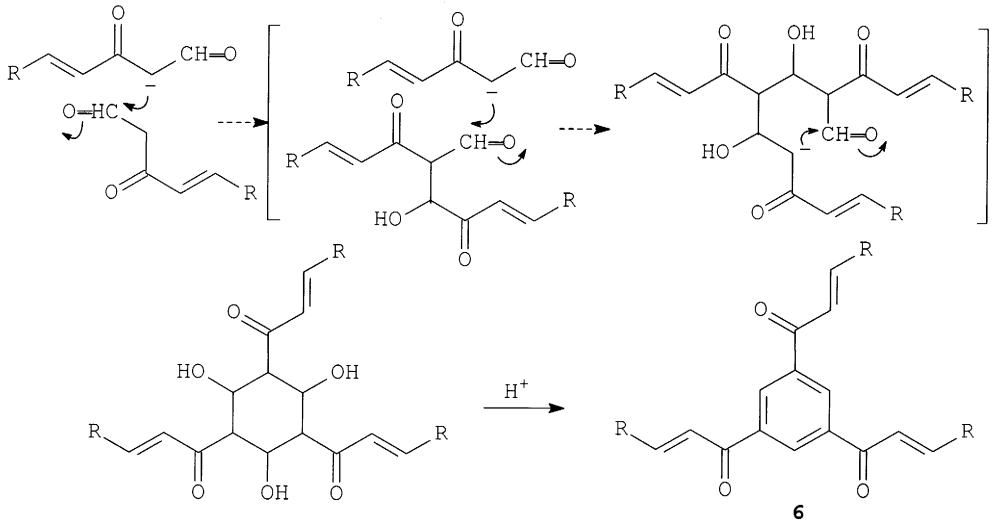

Fig. 3.

In cases **3** and **4**, the reaction plausibly first proceeds by partial conjugation of the aldehyde or nitrile [(a) *t*-but-OK, ether, −10°C, 50%; (b) HCl N]. Michael addition of the β-methylenic enolate to a second molecule leads to a dimeric intermediate. Ring closure takes place as in the first case and is followed by concomitant dehydration to the aldehyde **7** and tautomeric rearrangement to the aminonitrile **8**[9] (Figs. 4 and 5).

These new compounds are under biological evaluation.

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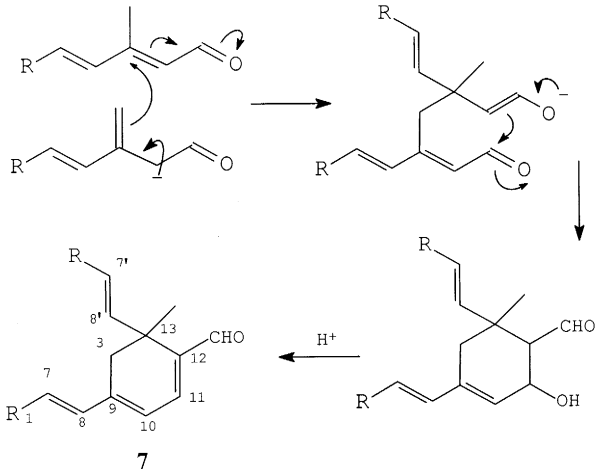

Fig. 4.

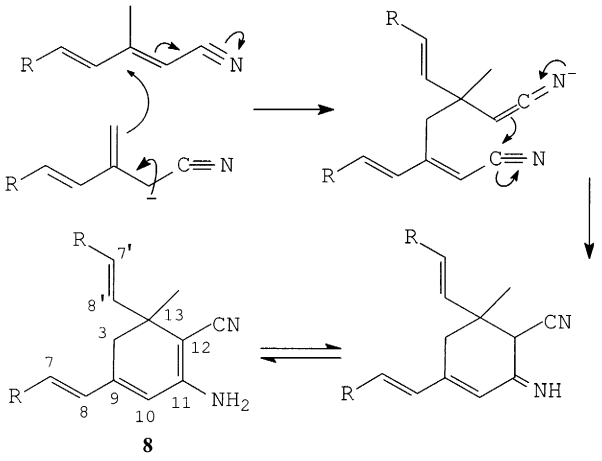

Fig. 5.

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9. Compound **5**: IR (KBr): 1662 cm$-^{1}$. ^{1}H NMR [300 MHz, $CDCl_3$, *J* (Hz)]: 6.58 (d, 1H, *J*=16, H_7), 6.15 (d, 1H, *J*=16, H_8), 5.75 (s, 1H, C-10-H), 2.80 (m, 3H, C-12-Ha, C-13-H and C-14-Ha), 2.50 (dd, 1H, *J*=12, *J′*=<1, C-12-Hb), 2.32 (d, 1H, *J*=12, <1, C-14-Hb), 2.05 and 1.95 (m, 2H, C-3-H and C-3′-H), 1.71 and 1.70 (s, 6H, C-2-CH_3 and C-2′-CH_3), 1.82 (m, 4H, C-4-H and C-4′-H), 1.30 (m, 4H, C-5-H and C-5′-H), 0.95, 0.90, 0.87 and 0.85 (s, 12H, C-6-CH_3 and C-6′-CH_3). ^{13}C NMR ($CDCl_3$): 200.8 (C-11), 157.6 (C-1), 138.1 and 137.0 (C-1′ and C-2), 134.7 and 133.6 (C-7 and C-10), 132.3 and 129.6 (C-2′ and C-9), 126.1 (C-8), 42.3 (C-12), 39.8 and 39.3 (C-3 and C-3′), 36.0 (C-6′), 34.7 (C-6), 34.3 (C-13), 34.1 and 33.1 (C-4 and C-4′), 30.1 (C-14), 28.8 and 28.7 (C-2-CH_3 and C-2′-CH_3), 22.0 and 21.7 (C-6-CH_3 and C-6′-CH_3), 19.2 and 19.0 (C-5 and C-5′). Compound **6**: IR (KBr) 1659 cm^{-1}. ^{1}H NMR [300 MHz, $CDCl_3$, *J* (Hz)]: 1.13 s, 6H, 2CH_3-C-6), 1.53 (m, 2H, CH_2-5), 1.64 (m, 2H, CH_2-4), 1.86 (s, 3H,CH_3-2), 2.12 (t, 2H, *J*=6.1, CH_2-3), 7.03 (d, 1H, *J*=15.8, H-8), 7.68 (d, 2H, *J*=15.8, H-7; 8.64, 1H, H-Ar). ^{13}C NMR ($CDCl_3$) 19.0 (CH_2-5), 22.15 (CH_3-C-6), 29.09 (CH_3-C_2), 34.14 (CH_2-C-4), 34.27 (CH-6), 40.03 (CH_2-C-3), 125.4 (CH-8), 131.6 (CH-7), 136.9 (C-1), 136.6 (C-2), 139.4 (C-10), 146.2 (CH-Ar), 189.6 (CO). Compound **7**: IR (KBr): 1674 cm^{-1}. ^{1}H NMR [400 MHz, $CDCl_3$, *J* (Hz)]: 9.51 (s, 1H, CHO), 6.86 (d, 1H, *J*=6, H_{11}),

6.54 and 6.23 (2d, 2H, *J*=16.2), 5.66 and 5.36 (2d, 2H, *J*=16.1) (H_7+H_8+$H_{7'}$+$H_{8'}$), 6.13 (dd, 1H, *J*=5.9, *J′*=1.8, H_{12}), 2.69 (d, 1H, *J*=17) and 2.42 (dd, 1H, *J*=17, *J′*=1.8) (C_{14}), 2.05, 1.92, 1.63, 1.60, 1.49 (m, 12H) (C_3+C_4+C_5+$C_{3'}$+$C_{4'}$+$C_{5'}$), 1.73, 1.57 (2s, 6H, 2-CH_3+2′-CH_3), 1.44 (s, 2H, 9-CH_3), 1.05, 1.04, 0.89, 0.88 (4s, 12H, 6-CH_3+6′-CH_3). ^{13}C NMR ($CDCl_3$): CHO: 192.7; HC═: 145.2, 137.6, 13.2, 132.0, 125.0, 122.0; CH_3: 29.4, 29.3, 29.0, 25.5, 22.2, 21.5; CH_2: 39.9, 39.6, 38.2, 33.6, 32.9, 19.7, 19.5. Compound **8**: IR (KBr): 2170, 1637 cm^{-1}. ^{1}H NMR [400 MHz, $CDCl_3$, *J* (Hz)]: 6.45 (d, 1H, *J*=16, 1), 6.13 (d, 1H, *J*=16, 1), 5.76 (d, 1H, *J*=16), 5.23 (d, 1H, *J*=16) (C_7+C_8+$C_{7'}$+$C_{8'}$), 5.72 (s, 1H, H_{12}), 4.34 (s, 2H, NH_2), 2.61 and 2.33 (2d, 2H, *J*=17C_{14}), 2.05, 1.94, 1.67, 1.6, 1.5, 1.44 (m, 12H) (C_3+C_4+C_5+$C_{3'}$+$C_{4'}$+$C_{5'}$), 1.70, 1.58 (2s, 6H, 2-CH_3+2′-CH_3), 1.38 (s, 2H, 9-CH_3), 1.02, 1.01, 0.93, 0.92 (4s, 12H, 6-CH_3+6′-CH_3). ^{13}C NMR ($CDCl_3$): HC═: 138.8, 133.6, 132.0, 125.4, 119; CN: 79.5; CH_3: 29.3, 29.2, 29.0, 28.9, 27.6; CH_2: 39.8, 39.6, 37.0, 33.5, 32.8, 19.7, 19.5.