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A New Biomimetic-Like Aromatization of the Cyclic End Groups of Terpenoids with Stereospecific Migration of One of the Methyl Groups: A Convenient Route to Isorenieratene (ϕ,ϕ-Carotene)

Alain Valla,*[a] Zo Andriamialisoa,[a] Benoist Valla,[a] Roger Labia,[a] Régis Le Guillou,[a] Laurent Dufossé,[b] and Dominique Cartier[a]

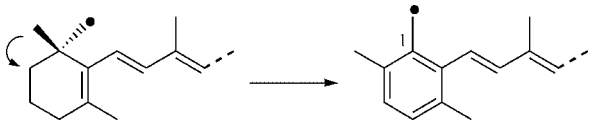
Keywords: Isorenieratenes / Carotenoids / Aromaticity

The synthesis of isorenieratene, a natural carotenoid isolated from the marine sponge *Reniera japonica* and from some anoxygenic phototrophic bacteria or nonphotosynthetic actinomycetes, was performed from α-, β- and *retro*-ionones. In this series of cyclohexenes, this synthesis is the first to include a one-pot aromatization of the cyclic end group with concomitant regioselective migration of one methyl group from the *gem* dimethyl functionality.

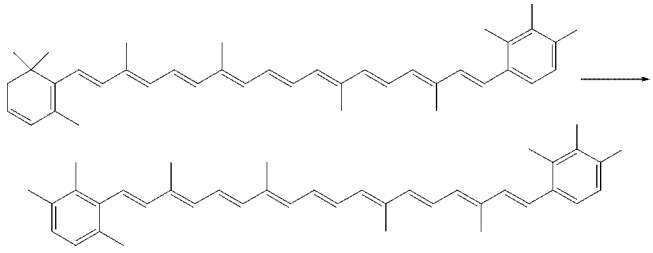
We have recently reported a new synthesis of isorenieratene, a natural carotenoid first isolated from the marine sponge *Reniera japonica*.[1] The biosynthesis of the aromatic ϕ,ϕ-carotene (isorenieratene) is restricted to green or brown phototrophic bacteria (*Chlorobium*, *Pelochromatium*, *Phaeobium*) and a few actinomycetes.[2] It is produced by *Brevibacterium linens*, a member of the leading group of coryneform bacteria[3]. This compound has also been previously extracted from *Mycobacterium aurum* A+.[4]

It was generally supposed that the aromatic rings of these compounds resulted from a classical β-ring carotenoid precursor. Formation of the phenyl end group (1,2,5-trimethylphenyl) from the original β-ring involved oxidation of the cyclohexene ring and migration of one methyl of the *gem* dimethyl group. Incubation of *Chloropseudomonas ethylica* with [2-^{14}C]-mevalonate showed that the methyl group at C-1 contained a ^{14}C label; therefore, methyl migration could proceed as outlined in Scheme 1.[5]

To the best of our knowledge, in this series of terpenes, the only related example reported in the literature is the aromatization of the end group by oxidation of 2,6,6-trimethylcyclohexa**di**ene "tethyatene" (a carotenoid isolated from a marine sponge) into ϕ,χ-carotene, by MnO_2 in a mixture of CH_2Cl_2/acetone (10% yield), Scheme 2.[6–8]



Scheme 1.



Scheme 2.

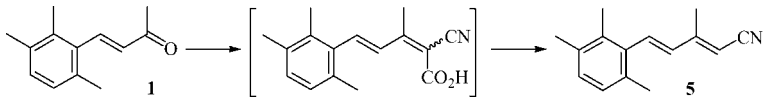
This compound was also named renieratene and has been isolated from a marine sponge, *Reniera japonica*, along with its two isomers, isorenieratene and renierapurpurine.[9]

We report herein that the oxidation of β-ionone **2** and α-ionone **3**, which have the β and the ε end group of carotenoids, respectively, leads to C_{13} aromatic ketone **1**. This reaction proceeds easily with low to moderate yields. Tables 1 and 2 show the experimental conditions for the aromatization reaction.

Improved yields, with the use of particularly mild conditions, could be obtained with *retro*-ionone **4**[10] (Table 3). It is known that among the retinoids, retro compounds are more unstable and reactive to oxidation.

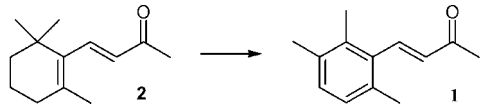
These aromatization reactions can be rationalized by a mechanism involving two hydride transfers from the same enol. In the case of *retro*-ionone, its formation may be easier, which would result in a shorter reaction time and a better yield. The first hydride transfer from the enol to the

[a] FRE 2125 CNRS, Chimie et Biologie des Substances Naturelles,
6, rue de l'Université, 29000 Quimper, France
[b] Laboratoire de Chimie des Substances Naturelles et des Sciences des Aliments, Université de La Réunion, Faculté des Sciences et Techniques, E.S.I.D.A.I.,
15 avenue René Cassin, B. P. 7151, 97715 Saint-Denis Cedex 9, La Réunion, France



Scheme 3.

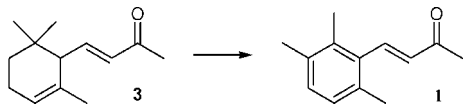
Table 1. Experimental conditions for the aromatization of **2**.



Solvent	Oxidant [equiv.]	Conditions Temp. [°C], Time [h]	Yield [%]
NMP	$CuCl_2$ 2	100, 15	30[a]
$C_2H_4Cl_2$	DDQ 3	60, 4	20[a]
Toluene	DDQ 3	reflux, 48	15[b]
Dioxane	DDQ 4	reflux, 48	43[a]
DMF	$CuCl_2$ 4, LiCl 1	120, 5	45[a]
DMF	$FeCl_3$ 4	100, 20	24[a]

[a] Yield determined from the crude product. [b] Yield determined from the purified product.

Table 2. Experimental conditions for the aromatization of **3**.

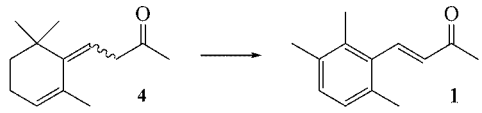


Solvent	Oxidant [equiv.]	Conditions Temp. [°C], Time [h]	Yield [%]
$C_2H_4Cl_2$	DDQ 3	60, 4	30[a]
Toluene	DDQ 3	reflux, 48	20[b]

[a] Yield determined from the crude product. [b] Yield determined from the purified product.

oxygen of quinone led to the formation of a cyclohexadiene via a carbocation or the elimination of the quinone group. The second hydride transfer occurs from the cyclohexadiene to the quinone and is followed by concomitant rearrangement of the obtained 1,1-*gem*-dimethyl carbocation to the more stable 1,2-dimethyl carbocation and the ultimate formation of trimethyl-1,2,5-benzene (Scheme 3).[11]

Table 3. Yields and reaction conditions with the use of *retro*-ionone **4**.



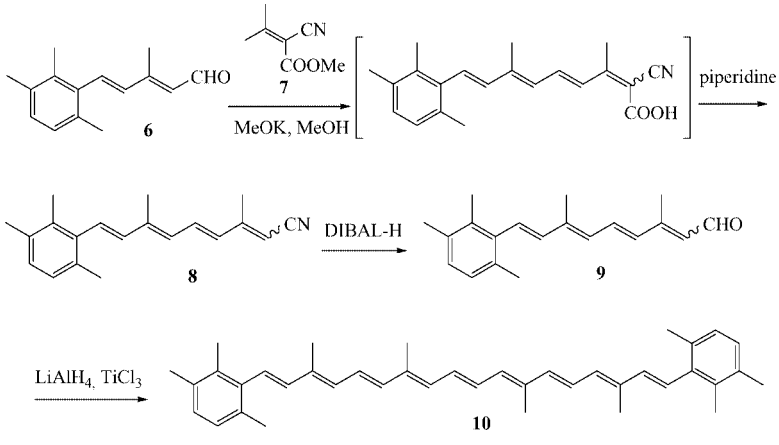
Solvent	Oxidant [equiv.]	Conditions Temp. [°C], Time [h]	Yield[a] [%]
DMF	$CuCl_2$ 4, LiCl 1	100, 3	58
DMF	$FeCl_3$ 4	100, 15	65
$C_2H_4Cl_2$	DDQ 3	60, 1	50[b]

[a] Yield determined from the crude product. [b] Yield determined from the purified product.

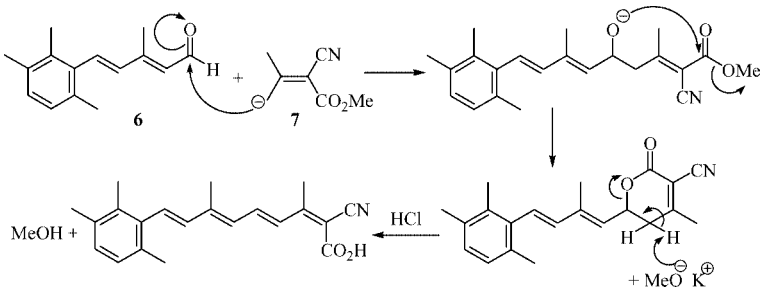
The syntheses of the C_{15} aldehyde [(2*E*,4*E*)-3-methyl-5-(2,3,6-trimethylphenyl)-2,4-pentadienal] from the C_{13} corresponding ketone, have already been depicted,[12] as well as these of the 4-methoxy analogue from the C_{14} ketone [(2*E*,4*E*)-5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-2,4-pentadienal].[13] A new improved synthesis allowed for the formation of the latter in only two steps, with excellent yield (82%). Thus, a Knoevenagel condensation of aromatic ionone **1** with cyanoacetic acid in piperidine/benzene (Dean–Stark, reflux) led to nitrile **5** [(2*E*,4*E*)-3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienenitrile] as a mixture of isomers 9*E*/9*Z*, 95:5 in nearly quantitative yield (96%).

Piperidine (as base) and benzene (as solvent) were very important in the work up of the reaction (other bases and

Scheme 4.



Scheme 5.



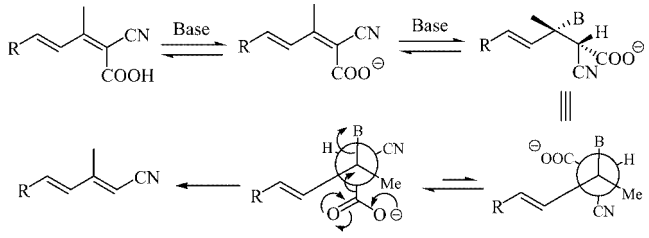
Scheme 6.

solvents led to a mixture of cyano acids and nitriles).[14] In this case, the intermediary formed cyano acid was regioselectively decarboxylated (9*E*/9*Z* 95:5) in the reaction mixture. The *all-E* nitrile was easily purified by recrystallization in a mixture of pentane/ether, 70:30 (Scheme 4).

Thus, the C_{15} nitrile was reduced by DIBAL-H in toluene (0 °C, 30 min.) into the corresponding aldehyde (86%, Scheme 5).

A Stobbe-like condensation with methyl isopropylidene cyanoacetate **7** (reported in ref.[1]) followed by decarboxylation of the crude cyanoacid, resulted in nitrile **8** (13*E*/13*Z*, 80:20). The good stereoselectivity of the reaction can be explained by the mechanistic pathway. The opening of the obtained intermediary lactone (under kinetic conditions) led to a cyano acid which possesses a specific configuration[15] (Scheme 6).

This latter compound was further decarboxylated into nitrile **8** with the use of Corey's pathway (Scheme 7).[16]



Scheme 7.

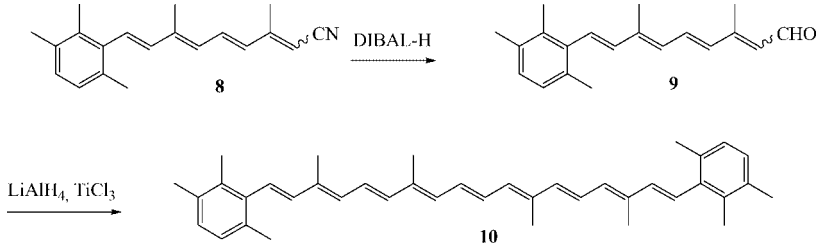
Nitrile **8** was reduced into C_{20} aldehyde **9** (13*E*/13*Z*, 80:20) by DIBAL-H. The *all-E* isomer was easily separated by column chromatography and the reductive coupling of the latter gave isorenieratene **10**[17] (Scheme 8).

Experimental Section

All reactions were carried out under an argon atmosphere. ^{1}H- and ^{13}C NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS. IR spectra were recorded with a Bruker IF 55 spectrometer.

4-(2,3,6-Trimethylphenyl)-3-buten-2-one (1): A mixture of *retro*-α-ionone (9.62 g, 50 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (34 g, 3 equiv.) in 1,2-dichloroethane (100 mL) were heated at 65 °C for 1 h. The mixture was filtered, and the solvent was removed under reduce pressure. The crude product was purified by column chromatography on silica gel, with the use of pentane/1,2-dichloroethane, 1:1, as the eluent. The product (4.72 g, 50%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 16 Hz, 1 H, C_7H), 7.05 and 6.95 (2d, J = 7 Hz,2 H, C_3H, C_4H), 6.25 (d, J = 16 Hz, 1 H, C_8H), 2.40, 235, 2.30, 2.25 (4s, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.0 (CO), 134.6 (Cq), 134.5, 133.5, 143.1 (CH), 133.4, 129.8, 127.5, 27.4 (CH_3), 20.8, 16.9 ppm. IR (film): $\tilde{\nu}$ = 1680 cm^{-1}.

(2*E*,4*E*)-3-Methyl-5-(2,3,6-trimethylphenyl)-2,4-pentadienenitrile (5): In a flask equipped with a Dean–Stark trap, cyanoacetic acid (8.21 g, 96 mmol, 3 equiv.) was added to a solution of ketone **1** (6 g, 32 mmol) in benzene (30 mL). The mixture was cooled to 0 °C and piperidine (25.43 mL, 256 mmol, 8 equiv.) was slowly added. The mixture was then heated at reflux for 4 h. Benzene was removed under reduced pressure, and the crude product was extracted with diethyl ether, the organic layer was washed with brine, water and dried with $MgSO_4$. After removing the ether under reduced pressure, the crude product was extracted with CH_2Cl_2 and quickly filtered through a mixture of basic alumina and silica (gel) (40:60), to provide 6.49 g (96%) of yellow ochre crystals of the major isomer 2*E*,4*E*-nitrile **6** (ratio determined by ^{1}H NMR) which was purified by recrystallization (ether/pentane, 30:70). F: 62 °C (2*E*,4*E*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, J = 16.3 Hz, 1 H, H^7), 6.98 (d, J = 7.5 Hz, 1 H, H^3), 6.96 (d, J = 7.5 Hz, 1 H, H^4), 6.28 (d, J = 16.3 Hz, 1 H, H^8), 5.25 (s, 1 H, H^{10}), 2.32 (s, 3 H, 2-CH_3),



Scheme 8.

2.26 (s, 3 H, 9-CH_3), 2.25 (s, 3 H, 5-CH_3), 2.2 (s, 3 H, 1-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.0 (CN), 157.1 (Cq), 136.0, 134.9, 134.7, 133.8, 135.9 (CH), 134.5, 129.7, 127.8, 98.3, 21.2 (CH_3), 20.7, 17.4, 16.9 ppm. IR (film): $\tilde{\nu}$ = 2206 cm^{-1}.

(2*E*,4*E*)-3-Methyl-5-(2,3,6-trimethylphenyl)-2,4-pentadienal (6): At 0 °C, DIBAL-H (1.2 M in toluene, 24 mL, 1.2 equiv.) was slowly added under vigorous stirring to nitrile **6** (5 g) in toluene. The solution was stirred for 2 h and hydrolyzed by a solution of 2 M H_2SO_4. After filtration of the aluminium salts, ether (50 mL) and water (50 mL) were added, and the organic layer was then washed with brine, water and dried with $MgSO_4$. The solvent was distilled under reduced pressure, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2) to yield the major isomer (*E*,*E*) of aldehyde **5**, as a yellow oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.20 (d, *J* = 8.1 Hz, 1 H, H^{11}), 7.18 (d, *J* = 16.4 Hz, 1 H, H^7); 7.01 (2d, *J* = 7.6 Hz, 2 H, H^3, H^4), 6.36 (d, *J* = 16.4 Hz, 1 H, H^8), 6.14 (d, *J* = 8.1 Hz, 1 H, H^{10}), 2.44 (s, 3 H, 9-CH_3), 2.26 (s, 6 H, 1-CH_3, 2-CH_3), 2.23 (s, 3 H, 5-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3 (CO), 154.1 (Cq), 135.9, 134.5, 134.4, 133.5, 137.2 (CH), 135.2, 129.7, 129.2, 127.5, 20.8 (CH_3), 20.4, 13.0, 9.7 ppm. IR (film): $\tilde{\nu}$ = 1659 cm^{-1}.

Methyl 2-Cyano-3-methyl-2-butenoate (7): In a flask equipped with a Soxhlet apparatus containing $CaCl_2$, methyl cyanoacetate (177 mL, 1.986 mol), β-alanine (0.88 g, 9.9 mmol, 0.005 equiv.), acetone (294 mL, 3.972 mol, 2 equiv.) and acetic acid (37.5 mL, 655.4 mmol, 0.33 equiv.) were heated at reflux for 19 h. After cooling to room temperature, the crude mixture was neutralized with a saturated solution of $NaHCO_3$. The solvent was removed under reduced pressure, and the crude product was rectified to provide **7** (133 g, 49%) as a colourless oil. B.p. (2 mm): 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, CO_2CH_3), 2.41 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3) ppm. IR (film): $\tilde{\nu}$ = 2259, 1734 cm^{-1}.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenenitrile (8): At 0 °C, MeOK (2.1 g, 3 mmol) in methanol (10 mL) was added to a mixture of **6** (1 mmol) and **7** (1 mmol). After 2 d at r.t., the crude mixture was poured into water (100 mL) and extracted with diethyl ether. The aqueous layer was acidified with a solution of 10% HCl and extracted with diethyl ether. The solvent was removed under reduced pressure, and the crude cyanoacid (80%) was dissolved in piperidine (20 mL) and heated at reflux for 4 h. The piperidine was distilled under reduced pressure, and the crude mixture was extracted with diethyl ether and successively washed with a solution of 5% HCl and water. The solvent was evaporated, and the major isomer (*all-E*) was separated from crude nitrile **8** (13*E*/13*Z*, 80:20, 98%) by column chromatography on silica gel with CH_2Cl_2 (63%). *All-E*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (m, 3 H, H^3, H^4, H^7), 6.77 (d, *J* = 16.4 Hz, 1 H, H^8), 6.32 (m, 2 H, H^{11}, H^{12}), 6.19 (d, *J* = 11.5 Hz, 1 H, H^{10}), 5.21 (s, 1 H, H^{14}), 2.27 (s, 6 H, 2-CH_3, 5-CH_3), 2.24, 2.23 (2s, 6 H, 1-CH_3, 13-CH_3), 2.10 (s, 3 H, 9-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 118.1 (CN), 157.8 (Cq), 140.7, 137.0, 134.4, 133.5, 138.3 (CH), 132.2, 130.0, 129.4, 128.5, 127.3, 97.4, 20.9 (CH_3), 20.5, 17.0, 16.6, 13.0 ppm. IR (film): $\tilde{\nu}$ = 2206 cm^{-1}.

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,3,6-trimethylphenyl)-2,4,6,8-nonatetraenal (9): As described above for the preparation of **6**, aldehyde **9** was obtained as a brown oil. The major isomer (*all-E*) was separated from the crude product (13*E*/13*Z*, 80:20, 98%) by column chromatography on silica gel with CH_2Cl_2 (80%). *All-E*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (d, *J* = 8.1 Hz,1 H, H^{15}), 6.98–7.36 (m, 4 H, H^3, H^4, H^7, H^{11}), 6.77 (d, *J* = 15.2 Hz, 1 H, H^8), 6.42 (d, *J* = 15.0 Hz, 1 H, H^{12}), 6.28 (m, 1 H, *J* = 11.8, H^{10}), 5.99 (d, *J* = 8.1 Hz, 1 H, H^{14}), 2.33 (s, 3 H, 13-CH_3), 2.28 (s, 3 H, 2-CH_3), 2.23 (s, 3 H, 5-CH_3), 2.14 (s, 3 H, 1-CH_3), 1.55 (s, 3 H, 9-CH_3) ppm. IR (film): $\tilde{\nu}$ = 1660 cm^{-1}.

10: The synthesis employed for the reductive coupling of **8** was carried out as described by Paust and Manchand.[13] Under an atmosphere of argon, powdered $LiAlH_4$ (190 mg, 5 mmol) was added to $TiCl_3$ (1.53 g, 10 mmol) in anhydrous THF (30 mL). After 2 h at room temperature, **9** (5 mmol) in THF (10 mL) was added. The mixture was stirred overnight and HCl (2 M, 50 mL) was slowly added, at 0 °C. The crude mixture was extracted with diethyl ether and washed with brine. The solvent was distilled under reduced pressure, and the crude product was purified by rapid column chromatography (neutral Al_2O_3, pentane/dichloromethane, 50:50) to yield 85% of **10**. A pure sample was obtained by HPLC (Lichro 5 µm CART RP 18 Merck, methanol/hexane, 80:20). ^{1}H NMR spectrum was identical to the one previously described.[18]

Acknowledgments

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