

New Synthetic Analogs of Retinoids: Synthesis of Aromatic Analogs of 9-Methylidene- and 13-Demethyl-9-methylidene-retinol, -retinal, and Ethyl 13-Demethyl-9-methylideneretinoate

by Alain Valla^{*1}), Virginie Prat, Alain Laurent, Zo Andriamialisoa, Dominique Cartier, Michel Giraud, Roger Labia

Chimie et Biologie des Substances Naturelles, FRE 2125 CNRS, 6, rue de l'Université,
F-29000 Quimper

and Pierre Potier

Institut de Chimie des Substances Naturelles, UPR 2301 CNRS Avenue de la Terrasse,
F-91198 Gif-sur-Yvette Cedex

Aromatic analogs of 9-methylidene and 13-demethyl-9-methylideneretinol, -retinal, and ethyl 13-demethyl-9-methylideneretinoate were synthesized *via* a new β -methylidene-aldehyde synthon.

Introduction. – Retinoids are known to modulate proliferation and differentiation of various cell types through activation of their intracellular receptors [1–3]. Presently, several aromatic retinoids are used for the treatment of cancers and skin diseases [3][4]. The search for new analogs with better therapeutic indices is still of current interest.

Standard methodologies for the preparation of synthetic retinoids have generally been based on established methods or on previously reported compounds rather than on development of new synthons.

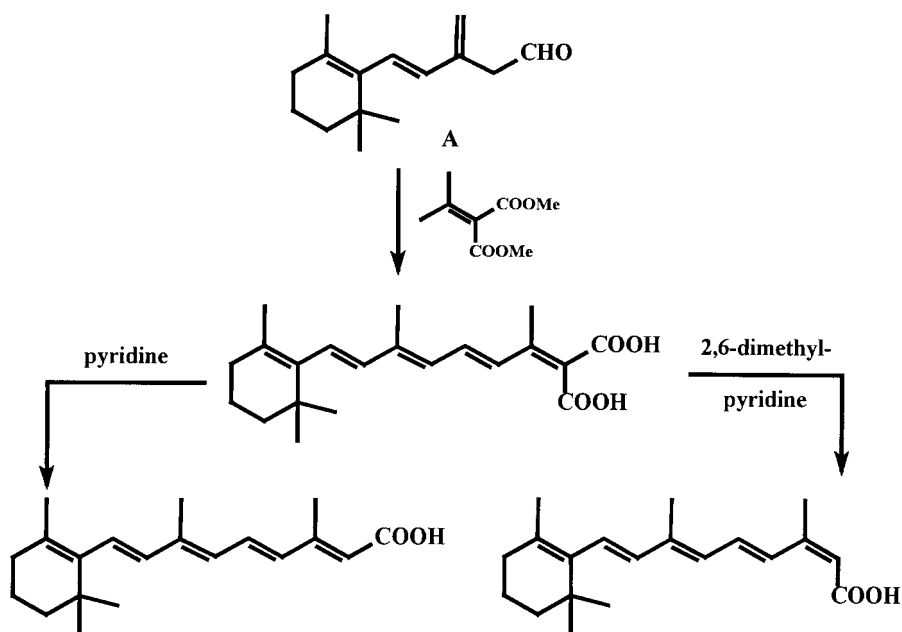
We recently reported the synthesis of β -methylidenealdehyde synthons, and their use in the synthesis of (13*Z*)- or (13*E*)-retinoic acids [5][6] (*Scheme 1*).

Results and Discussion. – Use of β -methylidene aldehyde **A** as an alternative to β -ionylideneacetaldehyde [7–9] enabled synthesis of the standard substituted chain of retinoids (*Scheme 1*). Moreover, the '9-methylidene' configuration could be preserved under *Horner-Emmons* conditions, prompting us to synthesize the new aromatic 9-*exo*-methylidene retinoids *via* the new β -methylidene aldehyde **1** (*Scheme 2*).

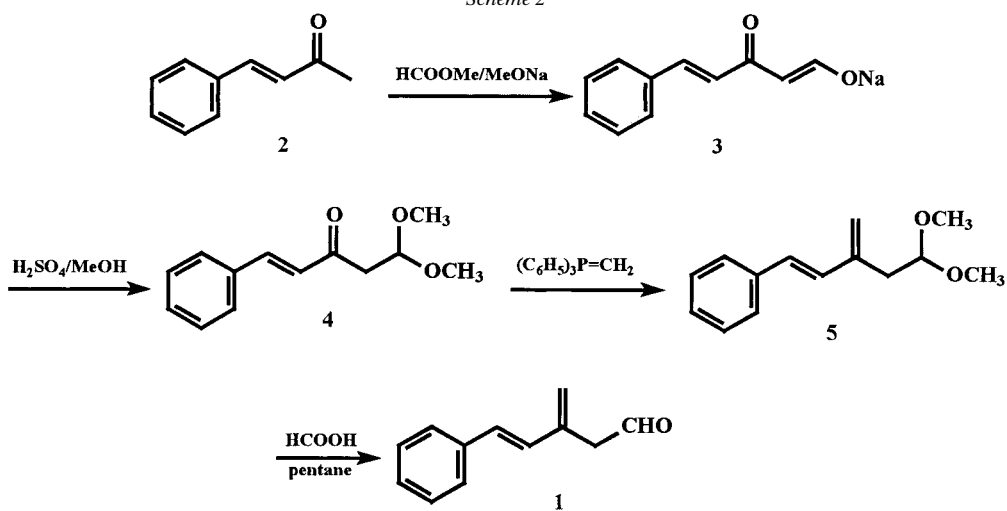
This new synthon **1** was synthesized from (*E*)-4-phenylbut-3-en-2-one (**2**). Formylation (MeONa, HCOOMe, pentane) and acetalization of Na salt of the hydroxymethylidene compound **3** (MeOH, H₂SO₄) furnished the β -acetal **4**. *Wittig* reaction (*t*-BuOK, (C₆H₅)₃P⁺CH₃ Br[–], cyclohexane) and mild acidic hydrolysis of the β -methylideneacetal **5** (HCOOH, pentane), provided the β -methylidene aldehyde **1** (20% from **2**).

¹) E-mail: Valla@iutquimp.univ-brest.fr; fax: (33)298908048

Scheme 1



Scheme 2

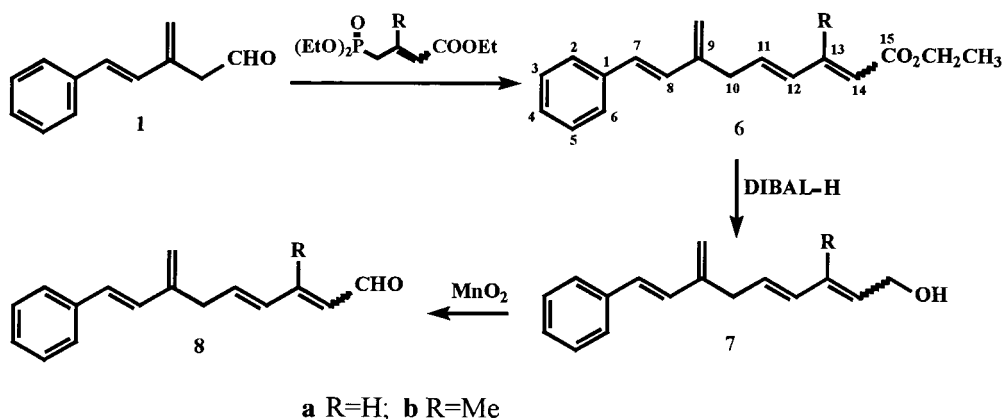


Reaction of compound **1** with ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (NaH , DME, -60°) afforded the 9-methylidene derivative **6a** (Scheme 3). Thus, this *Horner-Emmons*-based synthesis led stereoselectively (99%) to the new (7*E*,11*E*,13*E*)-13-demethyl-9-methylidene analog of ethyl retinoate. Under the same

conditions, reaction of **1** with ethyl (*E*)-4-(diethoxyphosphoryl)-3-methylbut-2-enoate (or the mixture (*E*)/(*Z*) 50:50) led to the aromatic 9-methylidene analog of ethyl retinoate **6b**, as a mixture of (13*E*)- and (13-*Z*)-isomers (50:50).

The retinol analogs **7** could be easily obtained from the latter by reduction (DIBAL-H, -5° , the room temperature, 30 min.). Oxidation of alcohols **7** (MnO_2 , pentane, room temperature, 12 h) then afforded the retinal analogs **8** (Scheme 3).

Scheme 3



The new aromatic 9-methylidene and 13-demethyl-9-methylidene analogs of retinol, retinal, and ethyl retinoate were obtained with no detectable amounts of conjugated isomers.

Experimental Part

General. All reactions were carried out under Ar. Pure anal. samples of compounds **6–8** were obtained by anal. TLC performed on Merck silica gel (60 F_{254}) plates. IR Spectra: Bruker IF-55 spectrometer. ^1H - and ^{13}C -NMR spectra were recorded at 400 and 100 MHz, resp., on a Bruker Avance DPX-400 instrument. The chemical shifts (δ) are reported in ppm relative to TMS (J in Hz).

(*E*)-3-Methylidene-5-phenylpent-4-enal (**1**). Yellow oil (20% from 4-phenylbut-3-en-2-one). IR (film): 1722. ^1H -NMR (CDCl_3): 9.70 (*t*, $J=2.4$, CHO); 7.44 (*d*, $J=7.3$, H-C(2), H-C(6) of Ph); 7.35 (*t*, $J=7.3$, H-C(3), H-C(5) of Ph); 7.25 (*m*, H-C(4) of Ph); 6.93, 6.50 (*dd*, $J=16.3$, H-C(4), H-C(5)); 5.47, 5.27 (2s, CH_2); 3.41 (*d*, $J=2.4$, $\text{CH}_2(10)$). ^{13}C -NMR (CDCl_3): 199.9 (C(1)); 137.3, 136.4 (C(1) of Ph, C(3)); 130.0, 129.8, 128.6, 127.9, 126.5 (C(2), C(3), C(4), C(5), C(6) of Ph, and C(4) and C(5)); 120.8 ($\text{CH}_2=$); 47.4 (C(10)). Anal. calc. for $\text{C}_{12}\text{H}_{12}\text{O}$: C 83.69, H 7.02, O 9.29; found: C 83.53, H 7.12, O 9.35.

Compounds 6a and 6b: Typical Procedure. To a suspension of NaH (5.8 mmol) in 1,2-dimethoxyethane (DME, 10 ml) was added at -10° a DME soln. (20 ml) of ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (for **6a**) or ethyl (*E*)/(*Z*)-4-(diethoxyphosphoryl)-3-methylbut-2-enoate (for **6b**) (50:50; 5.8 mmol). The soln. was stirred for 15 min, and a DME solution (20 ml) of **1** (5.8 mmol) was added slowly at -60° . The mixture was then warmed to r.t. and hydrolyzed with aq. sat. NH_4Cl soln. The mixture was extracted with Et_2O , and the org. layers were washed with H_2O and dried (MgSO_4). The residue was purified by chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$ 60:40 to provide compounds **6a** or **6b** as yellow oils.

Ethyl 7-Methylidene-9-phenylnona-2,4,8-trienoate (6a). Yield 35%. IR (film): 1710, 1642. ^1H -NMR (C_6D_6): 7.57 (*dd*, $J=15.4$, 10.8, H-C(13)); 7.37 (*d*, $J=7.4$, H-C(2), H-C(6)); 7.24 (*t*, $J=7.4$, H-C(3), H-C(5)); 7.17 (*t*, $J=7.4$, H-C(4)); 6.86 (*dd*, $J=16.2$, H-C(7), H-C(8)); 6.04 (*dd*, $J=15.2$, 10.8, H-C(12)); 5.99 (*d*, $J=15.4$, H-C(14)); 5.90 (*dt*, $J=15.2$, 6.7, H-C(11)); 5.17, 5.00 (2s, $\text{CH}_2=$); 4.18 (*q*, $J=7.1$, MeCH_2);

2.90 (*d*, *J* = 6.7, CH₂(10)); 1.11 (*t*, *J* = 7.1, MeCH₂). ¹³C-NMR (CDCl₃)²: 167.0 (C(15)); 144.3, 140.8, 130.1, 129.8, 128.8, 128.5, 127.6, 126.4, 120.0 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(13), C(14)); 143.3, 136.9 (C(1), C(9)); 117.8 (CH₂=); 60.1 (MeCH₂); 35.5 (C(10)); 14.2 (MeCH₂). Anal. calc. for C₁₈H₂₀O₂: C 80.56, H 7.51, O 11.93; found: C 80.43, H 7.63, O 11.94.

Ethyl 3-Methyl-7-methylidenenona-2,4,8-trienoate (6b): (13E)/(13Z) 50 : 50. Yield 40%. Yellow oil. Anal. calc. for C₁₉H₂₂O₂: C 80.82, H 7.85, O 11.33; found: C 80.68, H 7.86, O 11.46.

Data of (13E)-6b: IR (film): 1712, 1636, 1612. ¹H-NMR (D₆)DMSO)²: 7.52 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.35 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.25 (*t*, *J* = 7.3, H–C(4)); 6.98, 6.69 (2*d*, *J* = 16.4, H–C(7), and H–C(8)); 6.36 (*d*, *J* = 15.6, H–C(12)); 6.28 (*dt*, *J* = 15.6, 6.3, H–C(11)); 5.79 (*s*, H–C(14)); 5.29, 5.12 (2*s*, CH₂=); 4.08 (*q*, *J* = 7.1, MeCH₂); 3.21 (*d*, *J* = 6.3, CH₂(10)); 2.22 (*s*, Me–C(13)); 1.20 (*t*, *J* = 7.1, MeCH₂). ¹³C-NMR (CDCl₃)²: 167.1 (C(15)); 152.0, 143.7, 137.0 (C(1), C(9), C(13)); 135.1, 134.0, 130.3, 128.7, 128.5, 127.5, 126.4, 118.3 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(14)); 117.6 (CH₂=); 59.6 (MeCH₂); 35.5 (C(10)); 14.2, 13.8 (Me–C(13), MeCH₂).

Data of (13Z)-6b: IR (film): 1707, 1636, 1603. ¹H-NMR ((D₆)DMSO)²: 7.59 (*d*, *J* = 15.8, H–C(12)); 7.51 (*d*, *J* = 7.4, H–C(2), and H–C(6)); 7.35 (*t*, *J* = 7.4, H–C(3), H–C(5)); 7.25 (*t*, *J* = 7.4, H–C(4)); 6.98, 6.69 (2*d*, *J* = 16.4, H–C(7), H–C(8)); 6.31 (*dt*, *J* = 15.8, 6.8, H–C(11)); 5.68 (*s*, H–C(14)); 5.30, 5.13 (2*s*, CH₂=); 4.08 (*q*, *J* = 7.1, MeCH₂); 3.23 (*d*, *J* = 6.8, CH₂(10)); 1.98 (*s*, Me–C(13)); 1.19 (*t*, *J* = 7.1, MeCH₂). ¹³C-NMR (CDCl₃)²: 166.2 (C(15)); 150.7, 143.9, 137.1 (C(1), C(9), C(13)); 135.7, 130.3, 129.3, 128.8, 128.5, 127.5, 126.4, 116.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), and C(14)); 117.5 (CH₂=); 59.6 (MeCH₂); 36.0 (C(10)); 21.0, 14.2 (Me–C(13), MeCH₂).

Compounds 7a and 7b: *Typical Procedure*. DIBAL-H (20% in toluene, 10 mmol) was slowly added at –5° to 5 mmol of **6a** or **6b** in toluene (10 ml). After stirring 30 min at –5°, the reaction was quenched with aq. sat. NH₄Cl soln. The resulting crude product was extracted with Et₂O. The org. layers were washed with H₂O and dried (MgSO₄). The combined extracts were concentrated, and the oily product was purified by chromatography on silica gel eluting with CH₂Cl₂ (for **7a**) or CH₂Cl₂/MeOH: 98 : 2 (for **7b**) to furnish the alcohols **7a** or **7b** as yellow oils.

7-Methylidene-9-phenylnona-2,4,8-trien-1-ol (7a). Yield 60%. Anal. calc. for C₁₆H₁₈O: C 84.91, H 8.02, O 7.07; found: C 84.76, H 8.08, O 7.16. IR (film): 3302. ¹H-NMR (CDCl₃)²: 7.45 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.35 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.26 (*t*, *J* = 7.3, H–C(4)); 6.87, 6.61 (2*d*, *J* = 16.3, H–C(7), H–C(8)); 6.29, 6.19 (2*dd*, *J* = 15.0, 10.4, H–C(12), H–C(13)); 5.86 (*dt*, *J* = 15.0, 6.8, H–C(11)); 5.80 (*dt*, *J* = 15.0, 6.0, H–C(14)); 5.23, 5.11 (2*s*, CH₂=); 4.19 (*d*, *J* = 6.0, H–C(15)); 3.16 (*d*, *J* = 6.8, CH₂(10)). ¹³C-NMR (CDCl₃)²: 144.2, 137.1 (C(1), C(9)); 132.1, 131.5, 131.0, 130.4, 130.2, 128.6, 128.5, 127.4, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(13), and C(14)); 117.3 (CH₂=); 63.3 (C(15)); 35.2 (C(10)).

3-Methyl-7-methylidene-9-phenylnona-2,4,8-trien-1-ol (7b): (13E)/(13Z) 50 : 50. Yield 70%. Anal. calc. for C₁₇H₂₀O: C 84.96, H 8.39, O 6.66; found: C 84.83, H 8.44, O 6.73.

Data of (13E)-7b: IR (film): 3356. ¹H-NMR (CDCl₃)²: 7.45 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.35 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.26 (*t*, *J* = 7.3, H–C(4)); 6.87, 6.63 (2*d*, *J* = 16.3, H–C(7), and H–C(8)); 6.21 (*d*, *J* = 15.6, H–C(12)); 5.83 (*dt*, *J* = 15.6, 6.8, H–C(11)); 5.64 (*t*, *J* = 6.9, H–C(14)); 5.22, 5.11 (2*s*, CH₂=); 4.30 (*d*, *J* = 6.9, CH₂(15)); 3.18 (*d*, *J* = 6.8, CH₂(10)); 1.83 (*s*, Me). ¹³C-NMR (CDCl₃)²: 144.5, 137.2, 136.2 (C(1), C(9), C(13)); 135.6, 130.5, 128.6, 128.5, 128.4, 127.4, 127.2, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(14)); 117.2 (CH₂=); 59.3 (C(15)); 35.4 (C(10)); 12.6 (Me).

Data of (13Z)-7b: IR (film): 3384. ¹H-NMR (CDCl₃)²: 7.45 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.35 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.26 (*t*, *J* = 7.3, H–C(4)); 6.90, 6.63 (2*d*, *J* = 16.2, H–C(7), H–C(8)); 6.57 (*d*, *J* = 15.5, H–C(12)); 5.92 (*dt*, *J* = 15.5, 6.8, H–C(11)); 5.54 (*t*, *J* = 7.0, H–C(14)); 5.24, 5.12 (2*s*, CH₂=); 4.32 (*d*, *J* = 7.0, CH₂(15)); 3.21 (*d*, *J* = 6.8, CH₂(10)); 1.90 (*s*, Me). ¹³C-NMR (CDCl₃)²: 144.3, 137.1, 135.4 (C(1), C(9), C(13)); 130.5, 129.6, 128.6, 128.5, 128.0, 127.4, 126.8, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), and C(14)); 117.3 (CH₂=); 58.3 (C(15)); 35.7 (C(10)); 20.5 (Me).

Compounds 8a and 8b: *Typical Procedure*. A mixture of alcohol **7a** or **7b** (10 mmol) and 100 mmol of MnO₂ in 60 ml of pentane was stirred at r.t. for 3 h. After filtration, the org. layer was concentrated, and the oily product was purified by chromatography on silica gel eluting with CH₂Cl₂ to provide the aldehydes **8** as yellow oils.

7-Methylidene-9-phenylnona-2,4,8-trienal (8a). Yield 65%. Anal. calc. for C₁₆H₁₆O: C 85.68, H 7.19, O 7.13; found: C 85.50, H 7.35, O 7.14. IR (film): 1687, 1637. ¹H-NMR (CDCl₃)²: 9.57 (*d*, *J* = 8.0, H–C(15)); 7.45 (*d*, *J* =

²) For C-atom numbering, see formula **6** in Scheme 3.

7.3, H–C(2), H–C(6)); 7.36 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.27 (*t*, *J* = 7.3, H–C(4)); 7.14 (*dd*, *J* = 15.3, 10.0, H–C(13)); 6.87, 6.58 (*2d*, *J* = 16.3, H–C(7), H–C(8)); 6.45 (*m*, H–C(11), H–C(12)); 6.13 (*dd*, *J* = 15.3, 8.0, H–C(14)); 5.29, 5.13 (*2s*, CH₂=); 3.29 (*d*, *J* = 5.2, CH₂(10)). ¹³C-NMR (CDCl₃)²: 193.8 (C(15)); 152.0, 143.5, 130.6, 130.0, 129.9, 129.0, 128.6, 127.7, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(13), and C(14)); 142.9, 136.8 (C(1), C(9)); 118.1 (CH₂=); 35.7 (C(10)).

3-Methyl-7-methylidene-9-phenylnona-2,4,8-trienal (**8b**); (13*E*)/(13*Z*) 50:50; Yield 70%. Anal. calc. for C₁₇H₁₈O: C 85.67, H 7.60, O 6.71; found C 85.50, H 7.62, O 6.88.

Data of (13E)-8b: IR (film): 1666, 1632. ¹H-NMR (CDCl₃)²: 10.13 (*d*, *J* = 8.2, CHO); 7.45 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.36 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.27 (*t*, *J* = 7.3, H–C(4)); 6.88, 6.60 (*2d*, *J* = 16.3, H–C(7), H–C(8)); 6.42 (*dt*, *J* = 15.8, 6.4, H–C(11)); 6.33 (*d*, *J* = 15.8, H–C(12)); 5.95 (*d*, *J* = 8.2, H–C(14)); 5.28, 5.13 (*2s*, CH₂=); 3.27 (*d*, *J* = 6.4, CH₂(10)); 2.28 (*s*, Me). ¹³C-NMR (CDCl₃)²: 191.4 (C(15)); 154.3, 143.3, 136.9 (C(1), C(9), C(13)); 136.2, 134.8, 130.1, 128.9, 128.8, 128.6, 127.6, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(14)); 117.9 (CH₂=); 35.7 (C(10)); 13.0 (Me).

Data of (13Z)-8b: IR (film): 1666, 1633. ¹H-NMR (CDCl₃)²: 10.20 (*d*, *J* = 8.1, CHO); 7.45 (*d*, *J* = 7.3, H–C(2), H–C(6)); 7.36 (*t*, *J* = 7.3, H–C(3), H–C(5)); 7.27 (*t*, *J* = 7.3, H–C(4)); 7.22 (*d*, *J* = 15.4, H–C(12)); 6.88, 6.61 (*2d*, *J* = 16.3, H–C(7), H–C(8)); 6.33 (*dt*, *J* = 15.4, 6.7, H–C(11)); 5.87 (*d*, *J* = 8.1, H–C(14)); 5.29, 5.14 (*2s*, CH₂=); 3.31 (*d*, *J* = 6.7, CH₂(10)); 2.11 (*s*, Me). ¹³C-NMR (CDCl₃)²: 191.1 (C(15)); 154.4, 143.2, 136.8 (C(1), C(9), C(13)); 137.3, 130.1, 128.9, 128.6, 127.8, 127.6, 126.8, 126.4 (C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(11), C(12), C(14)); 117.9 (CH₂=); 35.9 (C(10)); 21.3 (Me).

We are indebted to Dr. R. H. Dodd for helpful discussions.

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Received May 19, 2001