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

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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, H_2SO_4) furnished the β-acetal **4**. *Wittig* reaction (*t*-BuOK, $(C_6H_5)_3P^+CH_3\,Br^-$, cyclohexane) and mild acidic hydrolysis of the β-methylideneacetal **5** (HCOOH, pentane), provided the β-methylidene aldehyde **1** (20% from **2**).

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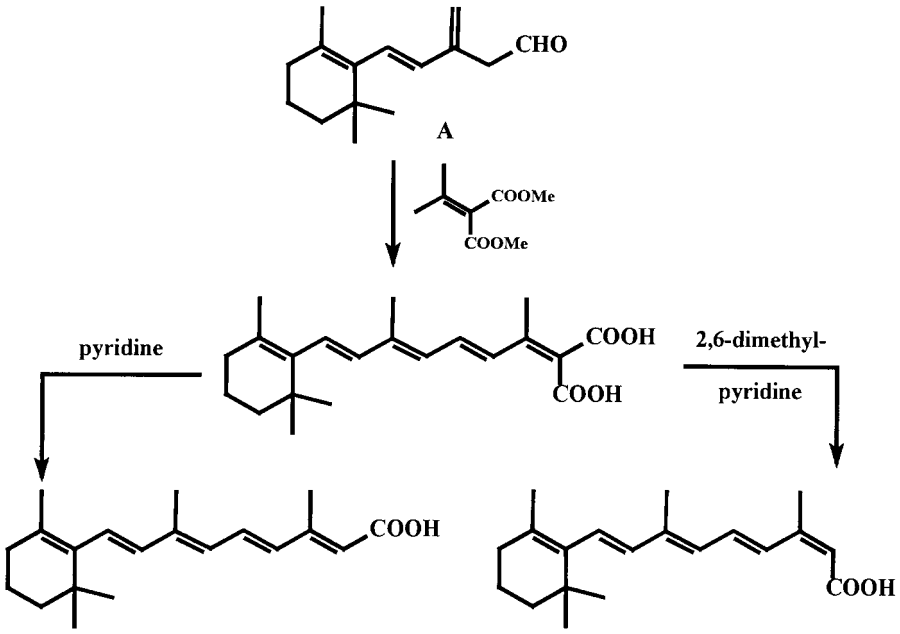
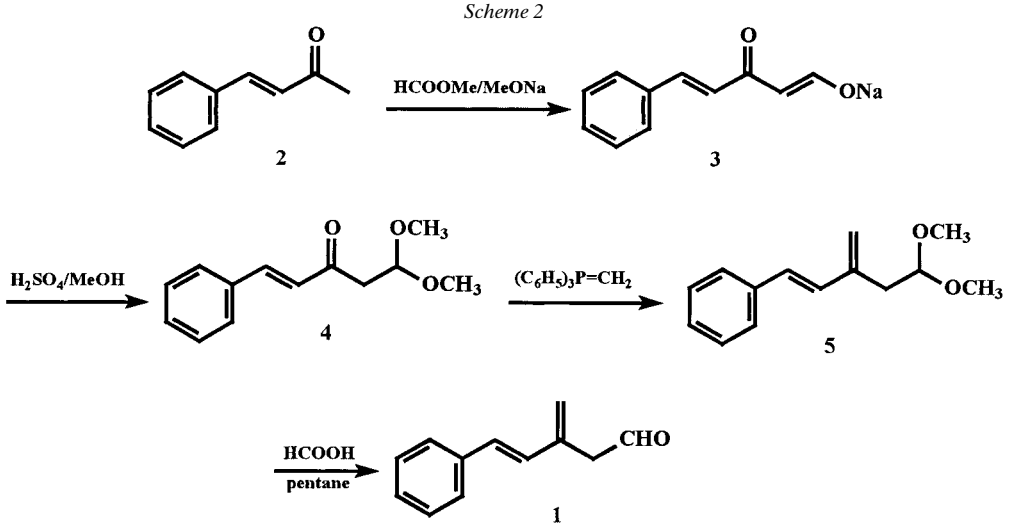
Scheme 1



Scheme 2

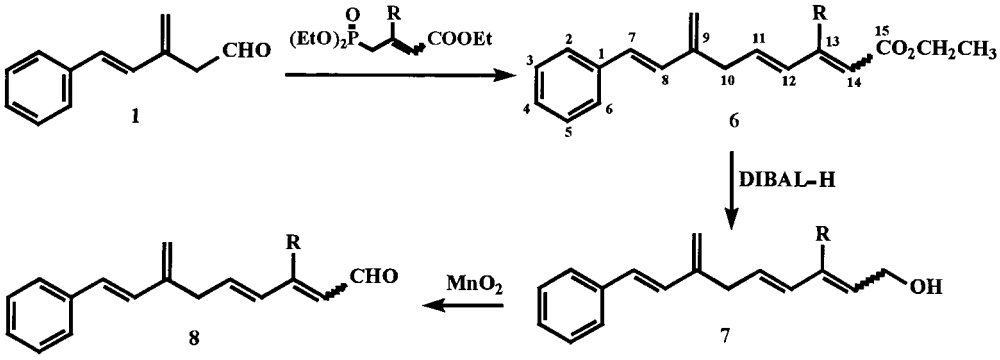


Reaction of compound **1** with ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (NaH, DME, $-60°$) afforded the 9-methylidene derivative **6a** (*Scheme 3*). Thus, this *Horner-Emmons*-based synthesis led stereoselectively (99%) to the new (7*E*,11*E*,13*E*)-13-demethyl-9-methylidene analog of ethyl retinoate. 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. ^{1}H- 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. ^{1}H-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 (2*d*, *J* = 16.3, H–C(4), H–C(5)); 5.47, 5.27 (2*s*, CH_2); 3.41 (*d*, *J* = 2.4, 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 (CH_2=); 47.4 (C(10)). Anal. calc. for $C_{12}H_{12}O$: 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 CH_2Cl_2/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. ^{1}H-NMR (C_6D_6)^2): 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 (2*d*, *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 (2*s*, CH_2=)); 4.18 (*q*, *J* = 7.1, MeCH_2);

2.90 (*d*, *J* = 6.7, CH_2(10)); 1.11 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 60.1 (Me*C*H_2); 35.5 (C(10)); 14.2 (*Me*CH_2). Anal. calc. for $C_{18}H_{20}O_2$: 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**; (13*E*)/(13*Z*) 50 : 50). Yield 40%. Yellow oil. Anal. calc. for $C_{19}H_{22}O_2$: C 80.82, H 7.85, O 11.33; found: C 80.68, H 7.86, O 11.46.

*Data of (13*E*)-***6b***: IR (film): 1712, 1636, 1612. ^{1}H-NMR (D_6)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*, CH_2=); 4.08 (*q*, *J* = 7.1, MeC*H*$_2$); 3.21 (*d*, *J* = 6.3, CH_2(10)); 2.22 (*s*, Me−C(13)); 1.20 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 59.6 (Me*C*H_2); 35.5 (C(10)); 14.2, 13.8 (*Me*−C(13), *Me*CH_2).

*Data of (13*Z*)-***6b***: IR (film): 1707, 1636, 1603. ^{1}H-NMR ((D_6)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*, CH_2=); 4.08 (*q*, *J* = 7.1, MeC*H*$_2$); 3.23 (*d*, *J* = 6.8, CH_2(10)); 1.98 (*s*, Me−C(13)); 1.19 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 59.6 (Me*C*H_2); 36.0 (C(10)); 21.0, 14.2 (Me−C(13), *Me*CH_2).

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. NH_4Cl soln. The resulting crude product was extracted with Et_2O. The org. layers were washed with H_2O and dried ($MgSO_4$). The combined extracts were concentrated, and the oily product was purified by chromatography on silica gel eluting with CH_2Cl_2 (for **7a**) or CH_2Cl_2/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 $C_{16}H_{18}O$: C 84.91, H 8.02, O 7.07; found: C 84.76, H 8.08, O 7.16. IR (film): 3302. ^{1}H-NMR ($CDCl_3$)[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−(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*, CH_2=); 4.19 (*d*, *J* = 6.0, H−C(15)); 3.16 (*d*, *J* = 6.8, CH_2(10)). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 63.3 (C(15)); 35.2 (C(10)).

3-Methyl-7-methylidene-9-phenylnona-2,4,8-trien-1-ol (**7b**; (13*E*)/(13*Z*) 50 : 50). Yield 70%. Anal. calc. for $C_{17}H_{20}O$: C 84.96, H 8.39, O 6.66; found: C 84.83, H 8.44, O 6.73.

*Data of (13*E*)-***7b***: IR (film): 3356. ^{1}H-NMR ($CDCl_3$)[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*, CH_2=); 4.30 (*d*, *J* = 6.9, CH_2(15)); 3.18 (*d*, *J* = 6.8, CH_2(10)); 1.83 (*s*, Me). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 59.3 (C(15)); 35.4 (C(10)); 12.6 (Me).

*Data of (13*Z*)-***7b***: IR (film): 3384. ^{1}H-NMR ($CDCl_3$)[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*, CH_2=); 4.32 (*d*, *J* = 7.0, CH_2(15)); 3.21 (*d*, *J* = 6.8, CH_2(10)); 1.90 (*s*, Me). ^{13}C-NMR ($CDCl_3$)[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 (CH_2=); 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 MnO_2 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 CH_2Cl_2 to provide the aldehydes **8** as yellow oils.

7-Methylidene-9-phenylnona-2,4,8-trienal (**8a**). Yield 65%. Anal. calc. for $C_{16}H_{16}O$: C 85.68, H 7.19, O 7.13; found: C 85.50, H 7.35, O 7.14. IR (film): 1687, 1637. ^{1}H-NMR ($CDCl_3$)[2]): 9.57 (*d*, *J* = 8.0, H−C(15)); 7.45 (*d*, *J* =

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[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 (2*d*, *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 (2*s*, CH_2=); 3.29 (*d*, *J* = 5.2, CH_2(10)). ^{13}C-NMR ($CDCl_3$)^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 (CH_2=); 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 $C_{17}H_{18}O$: C 85.67, H 7.60, O 6.71; found C 85.50, H 7.62, O 6.88.

*Data of (13*E*)-***8b***:* IR (film): 1666, 1632. ^{1}H-NMR ($CDCl_3$)^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–(C3), H–C(5)); 7.27 (*t*, *J* = 7.3, H–C(4); 6.88, 6.60 (2*d*, *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 (2*s*, CH_2=); 3.27 (*d*, *J* = 6.4, CH_2(10)); 2.28 (*s*, Me). ^{13}C-NMR ($CDCl_3$)^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 (CH_2=); 35.7 (C(10)); 13.0 (Me).

*Data of (13*Z*)-***8b***:* IR (film): 1666, 1633. ^{1}H-NMR ($CDCl_3$)^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 (2*d*, *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 (2*s*, CH_2=); 3.31 (*d*, *J* = 6.7, CH_2(10)); 2.11 (*s*, Me). ^{13}C-NMR ($CDCl_3$)^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 (CH_2=); 35.9 (C(10)); 21.3 (Me).

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