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Efficient preparation of 9-*Z*-11-methylretinal and 11-*Z*-11-methylretinal

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ABSTRACT

[2-(β-Ionylidene)propyl]triphenylphosphonium bromide is reacted with 3-methyl-4-oxobut-2-enenitrile in refluxing 1,2-epoxybutane to give a mixture of 11-*Z*- and all-*E*-11-methylretinal via DIBAL-H reduction. In an analogous fashion, β-ionyl triphenylphosphonium bromide is reacted with 3,5-dimethyl-6-oxohexa-2,4-dienenitrile in 1,2-epoxybutane followed by subsequent DIBAL-H reduction to afford a mixture of new products consisting of 9-*Z*-11-methylretinal, its all-*E* isomer and 1-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)-6-(buten-2″-al-3″-yl)-3,5-dimethylcyclohexa-1,3-diene. These molecules were obtained in pure form by HPLC.

For our investigations on rhodopsin chemistry we needed an easy access to 11-*Z*-11-methylretinal and its 9-*Z*-isomer. The preparation of 11-*Z*-11-methylretinal and its all-*E* isomer has been reported via complicated reactions that did not fulfill our requirements.[1] We were aware that retinoids and carotenoids are produced on an industrial scale via Wittig reaction of triphenylphosphonium ylides.[2–4] In these reactions an appreciable amount of the 11-*Z* isomer is formed. A similar situation holds for the preparation of retinoic acids and their metabolites.[5] Thus, we reasoned that a scheme based on Wittig chemistry between [2-(β-ionylidene)propyl]triphenylphosphonium bromide (**3**) and 3-methyl-4-oxobut-2-enenitrile (**4**) should give 11-methylretinonitrile with a high contribution of 11-*Z*-11-methylretinal in the product mixture.

All-*E* β-ionylideneacetaldehyde (**2**) (prepared from β-ionone[4]) was reacted with methyllithium in THF to give the corresponding alcohol, and then treated with triphenylphosphonium hydrobromide in ethanol to give [2-(β-ionylidene)propyl]triphenylphosphonium bromide (**3**). 3-Methyl-4-oxobut-2-enenitrile (**4**) was prepared via a known procedure[6] involving reaction of 1,1-dimethoxyacetone and diethylphosphonoacetonitrile followed by subsequent deprotection of the aldehyde function.

The reagents **3** (2.20 g, 4.0 mmol) and **4** (0.29 g, 3.0 mmol) were dissolved in 1,2-epoxybutane (50 mL) and heated at reflux (65 °C). 1,2-Epoxybutane was used as the solvent in the commercial synthesis of astaxanthin.[7] During the reaction, the concentration of base was very small; 1,2-epoxybutane (a cryptobase) reacts with the bromide anion to afford a transient alcoholate anion that further reacts with product **3**.

Base-sensitive materials such as 11-*Z*-11-methylretinonitrile did not undergo base-catalyzed conversions under these conditions. After work-up and subsequent DIBAL-H reduction, a ca. 1:1 mixture of 11-*Z*-11-methylretinal and its all-*E* isomer was obtained. Silica gel column chromatography afforded 11-*Z*-11-methylretinal (**1**) (0.20 g) and the all-*E* form (0.25 g) in pure state. The ^{1}H NMR spectra of these materials were in agreement with published data within experimental error.[1] UV spectroscopy of 11-*Z*-11-methylretinal (**1**) showed λ_{max} values at 363 nm and 250 nm. Upon treatment with light in the presence of a small amount of iodine, it was fully converted into all-*E*-11-methylretinal (**1**).

In order to prepare the novel 9-*Z*-11-methylretinal (**1**) we developed a scheme in which the C9–C10 carbon–carbon bond was formed via Wittig coupling. The required β-ionyltriphenylphosphonium bromide (**5**) was prepared according to the literature,[8] and the aldehyde precursor, 3,5-dimethyl-6-oxohexa-2,4-dienenitrile (**6**) was prepared by treating 1,1-dimethoxyacetone with the anion of 4-diethylphosphono-3-methylbut-2-enenitrile, analogous to the preparation of product **4**.

Reagents **5** (5.20 g, 10 mmol) and **6** (1.00 g, 8.1 mmol) were heated at reflux in 1,2-epoxybutane (50 mL) for 8 h. After work-up, a mixture of conjugated nitriles was isolated, which underwent subsequent DIBAL-H reduction and chromatography on silica gel. All-*E*-11-methylretinal (**1**) was isolated along with two new compounds: 9-*Z*-11-methylretinal (**1**) and aldehyde **7**, by HPLC techniques. Based on ^{1}H NMR and ^{13}C NMR spectroscopy the product **7** was identified as 1-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)-6-(buten-2″-al-3″-yl)-3,5-dimethylcyclohexa-1,3-diene. Compound **7** results from 1,4-conjugated Wittig addition of **5** to aldehyde **6**

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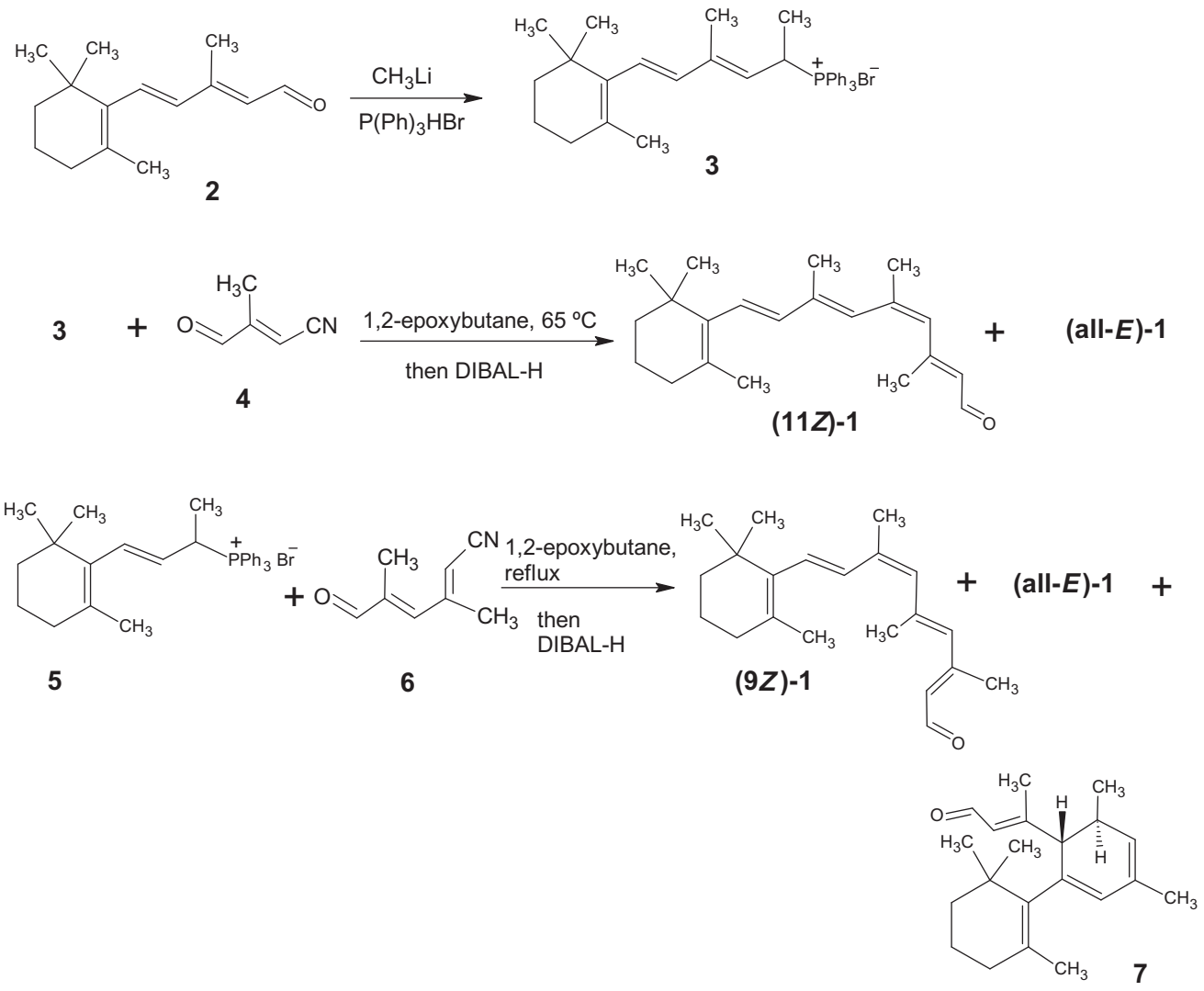
in which the charged carbon (C7) of ylide **5** reacts with C3 of the nitrile **6**. After internal proton exchange, intramolecular 1,4-conjugated Wittig reaction afforded a nitrile corresponding to the product **7**. The 1,4-conjugated Wittig reaction has been reported previously for simple conjugated aldehydes.[9] In those cases the normal Wittig component was totally absent or present only in very small amounts. In the present case, the ratio between all-*E*-**1**, 9-*Z*-**1**, and **7** is 1:1:2, making our procedure useful for obtaining sufficient quantities of 9-*Z*-11-methylretinal (**1**). Furthermore, 9-*Z*-11-methylretinal (**1**) was converted into all-*E*-11-methylretinal (**1**) upon treatment with light in the presence of a small amount of iodine.

It was clear that the reaction between **3** and **4** afforded clean products without formation of the 1,4-addition product **7**. Our present method can be adjusted easily to afford many more 11-modified all-*E* and 11-*Z* retinals via a simple isolation procedure in the absence of light. The corresponding 9-*Z* 11-modified system would be accessible via more difficult isolation procedures. Earlier, we reported a simple preparation of pure all-*E* and 9-*Z* modified retinals (modified in many positions except position 11). The corresponding 11-*Z* systems were available together with the all-*E* form as mixtures, which were isolated as described previously[10–12] (see Scheme 1).

Chemical modification of 11-*Z* and all-*E* retinals is straightforward via the chemistry described in this Letter. This provides an access to systems with modification of the substituent on the C11–C12 double bond. The influence of modification on this double bond in photochemical isomerization can now be studied systematically and we feel that this will contribute to the understanding of rhodopsin photochemistry.

[2-(β-Ionylidene)propyl]triphenylphosphonium bromide (**3**): To a cold solution (−70 °C) of β-ionylidene acetaldehyde (**2**)[13] (4.90 g, 22 mmol) in THF (100 mL) was added 1 M CH_3Li (18 mL) via a syringe. The extent of reaction was monitored by TLC. After stirring for 2 h, a saturated solution of NH_4Cl (100 mL) was added and the aqueous layer was extracted with Et_2O (100 mL × 3). The ethereal phases were combined, washed with brine (100 mL), dried over $MgSO_4$, and filtered. The solvent was evaporated under vacuum. The crude product, 1,3-dimethyl-5-(2,6,6-trimethylcyclohexa-1-enyl)-penta-2,4-dienol, was purified by silica gel column chromatography (Et_2O/petroleum ether, 1:1) to afford the pure product (22 mmol, 99%). The product was dissolved in dry EtOH (20 mL) and Ph_3PHBr (7.80 g, 23 mmol) added. The mixture was stirred for 72 h at rt in the absence of light to prevent isomerization. The solvent was removed under reduced pressure to afford a yellow oil which was crystallized from a mixture of EtOAc and Et_2O



Scheme 1. The preparation of 11-*Z*-11-methylretinal (11*Z*-**1**), 9-*Z*-11-methylretinal (9*Z*-**1**), all-*E*-11-methylretinal (all-*E*-**1**) and 1-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)-6-(buten-2″-al-3″-yl)-3,5-dimethylcyclohexa-1,3-diene (**7**) via Wittig reactions.

to afford the product **3** (7.30 g, 13 mmol). ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.44 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.66 (d, $^3J_{H-P}$ = 7 Hz, 3H, CH_3), 1.91 (d, $^5J_{H-P}$ = 3 Hz, 3H, CH_3), 1.98 (d, 2H, CH_2), 5.00 (dd, $^3J_{H-H}$ = 8.50 Hz $^3J_{H-H}$ = 9.50 Hz, 1H, CH), 5.50 (m, 1H, CH), 5.89 (d, $^3J_{H-H}$ = 16 Hz, 1H, CH), 6.15 (d, $^3J_{H-H}$ = 16 Hz, 1H, CH), 7.87–7.32 (m, 15H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 14.2 (CH_3), 16.9 (CH_3), 18.9 (CH_2), 21.4 (CH_3), 28.6 (2 × CH_3), 30.8 (d, $^1J_{C-P}$ = 47 Hz, CH), 32.6 (CH_2), 33.9 (CH_2), 39.2 (CH_2), 117.4 (d, $^1J_{C-P}$ = 82 Hz, Ph), 120.0 (d, $^2J_{C-P}$ = 7 Hz, CH), 129.3 (d, $^5J_{C-P}$ = 4 Hz, CH), 129.6 (CH_2), 130.2–134.8 (Ph), 135.3 (d, $^4J_{C-P}$ = 4 Hz, CH), 137.0 (C), 142.6 (d, $^3J_{C-P}$ = 14 Hz, CH). ^{31}P (162 MHz, $CDCl_3$/TMS) δ = 27.2.

11-Z-11-Methylretinal (**1**) *and all-E-11-methylretinal* (**1**): A solution of **3** (2.25 g, 5 mmol) and 3-methyl-4-oxobut-2-enenitrile (**4**)[6] (0.48 g, 5 mmol) in 1,2-epoxybutane (50 mL) was heated under reflux at 65 °C for 60 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Et_2O/petroleum ether, 1:4) to afford a mixture of conjugated nitriles 11-*Z*-**1** and all-*E*-**1** (0.78 g, 87%).

To a cold solution (−60 °C) of the mixture of the conjugated nitriles (0.78 g, 2.60 mmol) in petroleum ether (20 mL) was added DIBAL-H (1 M, 4 mL, 4 mmol) via a syringe. The solution was stirred for 30 min at −60 °C, then for 1 h at rt. On completion of the reaction a mixture of silica gel–H_2O (5.00 g) (prepared by mixing 20.00 g of silica gel and 0.4 mL of H_2O) was added at 0 °C and stirring continued for 1 h. The mixture was dried over $MgSO_4$ and filtered; the residue was washed with Et_2O (10 mL × 3) and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography (Et_2O/petroleum ether, 5:95) to afford a mixture of 11-*Z*-11-methylretinal (**1**) (0.20 g) and all-*E*-11-methylretinal (**1**) (0.25 g). The spectroscopic data were identical to those in Ref. 1.

3,5-Dimethyl-6-oxohexa-2,4-dienenitrile (**6**): To a cold solution (0 °C) of (diethylphosphono)-3-methyl-2-butenenitrile[14] (5.43 g, 25 mmol) in THF (125 mL) was added *n*BuLi (1.6 M in hexanes, 15.60 mL, 25 mmol) via a syringe. After stirring for 15 min at 0 °C, 1,1-dimethoxyacetone (2.36 g, 20 mmol) was added. The extent of reaction was monitored by TLC (EtOAc/petroleum ether, 1:3) with 2,4-dinitrophenylhydrazine as the staining reagent. After stirring for 2 h, a saturated solution of NH_4Cl (100 mL) was added. The aqueous layer was extracted with Et_2O (100 mL × 3) and the ethereal phases were combined, washed with brine (100 mL), dried over $MgSO_4$, and filtered. The solvent was evaporated under vacuum and the product was purified by column chromatography to afford 6,6-dimethoxy-3,5-dimethylhexa-2,4-dienenitrile (**6**) (3.12 g, 17 mmol). ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ = 1.84 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.34 (s, 6H, 2 × OCH_3), 4.55 (s, 1H, CH), 5.22 (s, 1H, CH), 6.13 (s, 1H, CH).

This product was dissolved in acetone (50 mL) and acidified with 1 M HCl (to ca. pH 2). The solution was treated with a mixture of K_2CO_3 and $MgSO_4$, filtered and evaporated under reduced pressure. The product was purified to afford 3,5-dimethyl-6-oxohexa-2,4-dienenitrile (**6**) (2.20 g, 17 mmol) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ = 2.01 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.53 (s, 1H, CH), 6.76 (s, 1H, CH), 9.50 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 11.3 (CH_3), 20.0 (CH_3), 103.3 (CH), 116.2 (CN), 141.9 (C), 146.4 (CH), 155.3 (C), 195.4 (CHO). HRMS (calculated for C_8H_9NO) *m*/*z* 135.1632, (obtained) 134.1624.

Preparation of 9-Z-11-methylretinal (**1**), *all-E-11-methylretinal* (**1**) *and 1-(2′,6′,6′-trimethylcyclohex-2′-en-1′-yl)-6-(buten-2″-al-3″-yl)-3,5-dimethylcyclohexa-1,3-diene* (**7**): A solution of β-ionyltriphenylphosphonium bromide (**5**)[8] (5.20 g, 10 mmol) and 3,5-dimethyl-6-oxohexa-2,4-dienenitrile (**6**) (1.20 g, 10 mmol) in 1,2-epoxybutane (50 mL) was heated under reflux for 60 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Et_2O/petroleum ether, 1:4) to afford a mixture of the conjugated nitriles 9-*Z*-**1**, all-*E*-**1** and **7** (2.35 g, 7.7 mmol, 82%).

To a cold solution (−60 °C) of the mixture of conjugated nitriles (2.30 g, 8 mmol) in petroleum ether (50 mL) was added DIBAL-H (1 M, 11 mL, 11 mmol) via a syringe. The solution was stirred for 30 min at −60 °C, and then for 2 h at rt. The extent of reaction was monitored by TLC. To this solution at 0 °C was added a mixture of silica gel–H_2O (20.00 g/0.4 mL) and stirring was continued for 1 h. The mixture was dried over $MgSO_4$ and filtered. The residue was rinsed with Et_2O (50 mL × 3) and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography (Et_2O/petroleum ether, 5:95) to afford a mixture of aldehydes 9-*Z*-**1** and all-*E*-**1** (0.83 g, 2.8 mmol, 41%) and aldehyde **7** (0.78 g, 2.60 mmol, 39%). The three aldehyde products were isolated in pure form after separation by HPLC.

9-Z-11-Methylretinal **1**: ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.02 (s, 6H, 2 × CH_3), 1.47 (m, 1H, CH_2), 1.61 (m, 2H, CH_2), 1.69 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 2.01 (t, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.86 (s, 1H, CH), 5.92 (s, 1H, CH), 5.99 (d, $^3J_{H-H}$ = 8.21 Hz, 1H, CH), 6.29 (d, $^3J_{H-H}$ = 16 Hz, 1H, CH), 6.48 (d, $^3J_{H-H}$ = 16 Hz, 1H, CH), 10.07 (d, $^3J_{H-H}$ = 8.21 Hz, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 18.4 (CH_3), 19.2 (CH_3), 20.6 (CH_3), 21.4 (CH_3), 21.8 (CH_3), 29.0 (2 × CH_3), 33.9 (CH_2), 34.2 (CH_2), 39.6 (CH_2), 129.7, 129.9, 131.5, 132.1, 132.3, 136.5, 137.9, 141.9, 155.9, 191.3 (CHO).

1-(2′,6′,6′-Trimethylcyclohex-2′-en-1′-yl)-6-(buten-2″-al-3″-yl)-3,5-dimethylcyclohexa-1,3-diene (**7**): ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.00 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.48 (m, 2H, CH_2), 1.50 (s, 3H, CH_3), 1.60 (m, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.90 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.74 (d, $^3J_{H-H}$ = 8.21 Hz, 1H, CH), 3.61 (m, 1H, CH), 5.24 (s, 1H, CH), 5.81 (d, $^3J_{H-H}$ = 8.21 Hz, 1H, CH), 5.85 (s, 1H, CH), 9.96 (d, $^3J_{H-H}$ = 8.21 Hz, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 19.1, 20.6, 22.3, 23.8, 28.0, 28.7, 33.4, 35.9, 39.8, 41.9, 52.9, 125.5, 125.6, 129.0, 130.0, 132.3, 135.7, 136.5, 162.5, 191.2 (CHO). HRMS (calculated for $C_{21}H_{30}O$) *m*/*z* 298.2296, (obtained) 298.2273.

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