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Novel Synthesis of the Ocular Age Pigment A2-E: New Method for Substituted Pyridine Synthesis via Azaelectrocyclization

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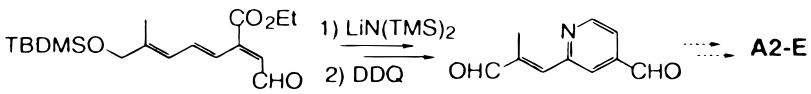
ABSTRACT



The formal synthesis of the ocular age pigment A2-E was achieved by the efficient one-pot preparation of the substituted pyridine, which involves the aza-6π-electrocyclization of the Schiff base derived from (*E*)-3-carbonyl-2,4,6-trienal followed by oxidation.

Pyridinium bisretinoid "A2-E" was isolated from over 40 aged human eyes as the major orange fluorophore of ocular age pigments called lipofuscin, and its structure was determined by Nakanishi and co-workers.[1] Lipofuscin accumulates in the human retinal pigment epithelium (RPE) cells[2] with age, and it is considered as the possible cause of age-related decline of cell functions and related eye diseases, such as age-related macular degeneration (AMD),[3] which leads to blindness in elderly people. For this reason, the main component of lipofuscin, "A2-E", which might be involved in the process of AMD, has been the potential target molecule for the remedies of this disease. Nakanishi and co-workers proposed the biosynthesis of A2-E as shown in Scheme 1.[1] Thus, 2 equiv of *all-trans*-retinal and ethanolamine would give azatriene **1**, which would produce A2-E via an aza-6π-electrocyclization reaction[4] followed by autoxidation. Furthermore, they synthesized A2-E by the double-Wittig olefination of bis-aldehyde **4** with the Wittig reagent **5**, and the bis-aldehyde **4** was synthesized from 4-methyl-2-pyridone **3** via the allylic oxidation of the 4-methyl group and the installation of the unsaturated side chain at the 2 position by Pd(0)-catalyzed Stille coupling.[5,6]

During the course of our recent studies on the syntheses of the enzyme inhibitors and then the elucidation of their inhibitory mechanism, we have found that (*E*)-3-carbonyl-2,4,6-trienal **6** inhibits the hydrolytic ability of phospholipase A_2 (PLA_2) by the formation of the dihydropyridine derivatives resulting from the reaction with the particular lysine residues of PLA_2 via the 6π-electrocyclization of the intermediary Schiff bases such as **9** (Figure 1).[7] Our finding of aza-6π-electrocyclization is compatible with Nakanishi's hypothetical metabolic pathway from *all-trans*-retinal to A2-

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(3) Tso, M. O. M. *Invest. Ophthalmol. Visual Sci.* **1989**, *30*, 2430.

(4) (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. (b) de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 4051. (c) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763 and references therein.

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(6) Nakanishi and co-workers also succeeded in the efficient synthesis of A2-E from 2 equiv of *all-trans*-retinal and ethanolamine in 49% yield in one step, and they obtained a sufficient quantity of A2-E for the elucidation of its biological properties in RPE cells: Parish, C. A.; Hashimoto, M.; Nakanishi, K.; Dillon, J.; Sparrow, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14609.

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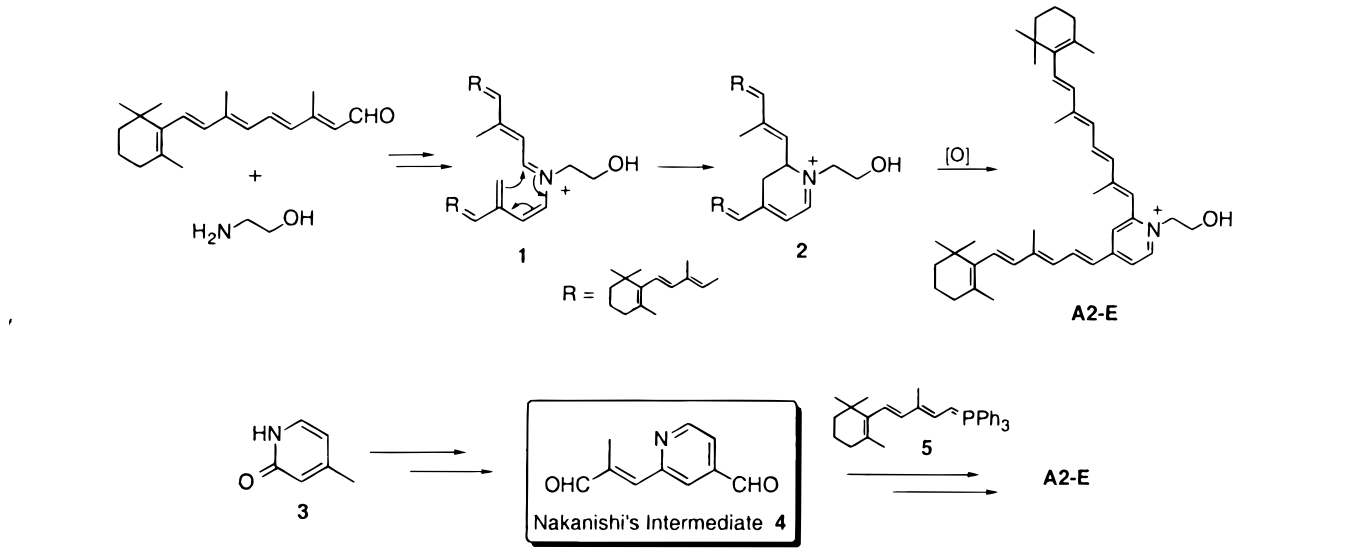
Scheme 1



E, which involves the aza-6π-electrocyclization. Moreover, we have also found that both the C4 carbonyl group and the double bond attached at C6 in 1-azatriene **9** significantly contribute to the acceleration of the aza-6π-electrocyclization. Thus, the reaction of **6** with *n*-propylamine quantitatively yielded the corresponding 1, 2-dihydropyridine derivative within 5 min at room temperature, although the derivatives **7** and **8** gave only the corresponding Schiff bases within 60 min.

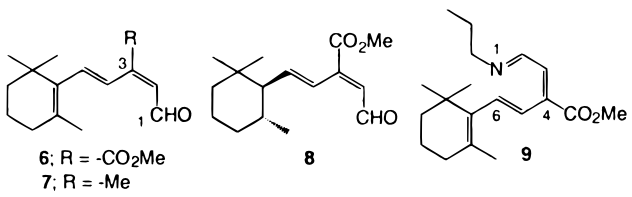
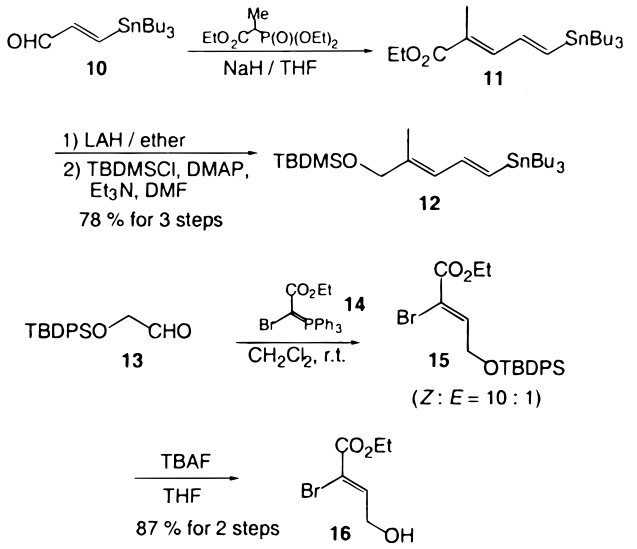


Figure 1.

Now, we report the efficient formal synthesis of A2-E based on the synthesis of pyridine bis-aldehyde **4** from (*E*)-ethoxycarbonyl-2,4,6-trienal **18** via the one-pot aza-6π-electrocyclization followed by oxidation.

Although we previously established the highly stereoselective synthesis of (*E*)-3-alkoxycarbonyl-2,4,6-trienal compounds such as **6** by hydrometalation of ethynyl acetylenes as the key step,[7,8] we felt that this method involves some limitations over the wide range of derivatives. Pd(0)-catalyzed Stille coupling[9] between (*E*)-vinylstannane **12** and (*Z*)-vinyl bromide **16** was selected as a more general method for the synthesis of such types of compounds.[10] The stannane **12** and bromide **16** were prepared as shown in Scheme 2.

Scheme 2



(*E*)-Vinylstannane **10**, which was obtained by the hydrostannylation of propargyl alcohol with tri-*n*-butyltin hydride followed by oxidation with manganese dioxide in 88% yield,[11] was subjected to the Horner−Emmons reaction with the sodium salt of triethyl phosphonoacetic acid to provide

(7) (a) Tanaka, K.; Kamatani, M.; Mori, H.; Fujii, S.; Ikeda, K.; Hisada, M.; Itagaki, Y.; Katsumura, S. *Tetrahedron Lett.* **1998**, *39*, 1185. (b) Tanaka, K.; Kamatani, M.; Mori, H.; Fujii, S.; Ikeda, K.; Hisada, M.; Itagaki, Y.; Katsumura, S. *Tetrahedron* **1999**, *55*, 1657.

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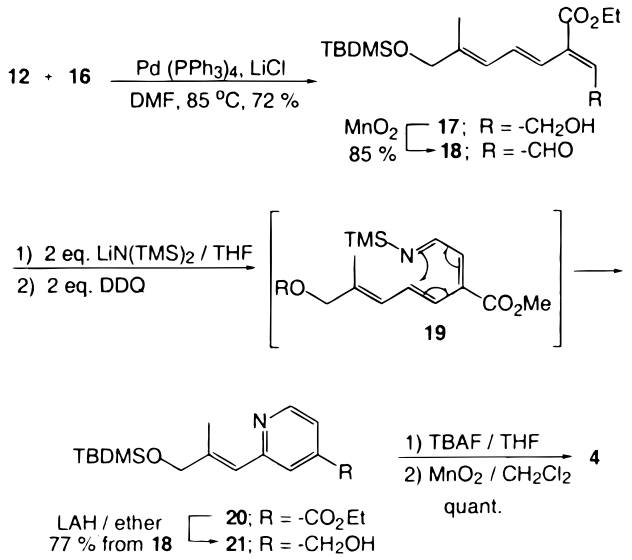
(10) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866.

11. The reduction of **11** without purification and then protection of the resulting primary alcohol with *tert*-butyldimethylsilyl chloride completed the synthesis of the vinyl stannyl fragment **12** in 78% yield in three steps. (*Z*)-Vinyl bromide **16** was synthesized by the stereoselective Wittig reaction as the key step. Thus, aldehyde **13**, which was prepared by the monoprotection of ethylene glycol as the *tert*-butyldiphenylsilyl ether followed by the Swern oxidation,[12] was reacted with the Wittig reagent, triphenylcarbethoxybromomethylenephosphorane **14**,[13] to provide **15**. The ratio of *Z* to *E* was 10:1 based on an NMR analysis. After removal of the TBDPS group by treatment with TBAF, the *Z* and *E* stereoisomers were separated by column chromatography on silica gel to give pure (*Z*)-vinyl bromide **16** in 87% yield in two steps. The Pd(0)-catalyzed Stille coupling between the stannane **12** and bromide **16** fortunately proceeded in the presence of 5 mol % tetrakis(triphenylphosphine)palladium(0) and 2 equiv of lithium chloride in dimethyl formamide at 85 °C to produce **17** in 72% yield with retention of their stereochemistry (Scheme 3). The

Scheme 3



oxidation of **17** with manganese dioxide nicely provided **18** in 85% yield.[14] Thus, the new stereoselective synthesis of 3-alkoxycarbonyl-2*E*,4*E*,6*E*-trienal was achieved. This method is believed to be more general and practical for the synthesis of (*E*)-3-alkoxycarbonyl-conjugated aldehydes. The next step is the key to the synthesis of Nakanishi's intermediate **4**. To achieve the efficient oxidation of the dihydropyridine to the corresponding pyridine, we planned to prepare the trimethylsilylimine derivative **19** by utilizing the Peterson reaction between **18** and lithium bis(trimethylsilyl)amide.[15] The treatment of the (*E*)-carbonyltrienal **18** with excess lithium bis(trimethylsilyl)amide in THF at room temperature cleanly produced the corresponding *N*-trimethylsilyl-1,2-dihydropyridine derivative within 5 min via the Peterson reaction followed by the smooth aza-6π-electrocyclization of the resulting intermediary azatriene **19**. The reaction mixture of the unstable 1,2-dihydropyridine derivative was then continuously treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant[16] to successfully yield the desired pyridine derivative **20** in one pot. The reaction of the crude **20** with lithiun aluminum hydride gave **21** in 77% total yield from **18**.[17] No Michael adducts of $LiN(TMS)_2$ to the 3-carbonyltrienal system or other byproducts were detected in the reaction mixtures. This efficient one-pot procedure of the Peterson reaction, aza-6π-electrocyclization and oxidation, provides a new entry for the synthesis of the substituted pyridine derivative. Finally, the synthesis of the bis-aldehyde **4**, mp 91 °C, was successfully realized from **21** by the deprotection of the TBDMS group followed by oxidation with manganese dioxide. The spectral characteristics (^{1}H and ^{13}C NMR) of the thus-synthesized bis-aldehyde **4** were in good agreement with those reported by Nakanishi and coworkers.[18]

In conclusion, we achieved the formal synthesis of the ocular age pigment A2-E by focusing on the efficient one-pot synthesis of the pyridine derivative by utilizing the Peterson reaction of (*E*)-3-carbonyl-2,4,6-trienal with lithium bis(trimethylsilyl)amide, the facile aza-6π-electrocyclization of the corresponding 1-azatriene derivative, and oxidation. The sequence of the reactions is compatible with Nakanishi's hypothetical metabolic pathway of A2-E. A new stereoselective synthesis of (*E*)-3-carbonyl-2,4,6-trienal compounds by the Pd(0)-catalyzed cross-coupling between vinylstannane and vinyl bromide was also established.

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(14) Data for **18**: IR (neat, cm^{-1}) 1726, 1672, 1248, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.93 (s, 9H), 1.36 (t, 3H, J = 7.1 Hz), 1.79 (s, 3H), 4.14 (s, 2H), 4.32 (q, 2H, J = 7.1 Hz), 6.32 (d, 1H, J = 11.2 Hz), 6.52 (d, 1H, J = 7.3 Hz), 6.83 (d, 1H, J = 15.4 Hz), 7.09 (dd, 1H, J = 15.1, 11.2 Hz), 10.11 (d, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.40, 14.11, 14.45, 18.40, 25.89, 61.87, 67.40, 121.34, 122.73, 130.02, 137.88, 145.75, 146.50, 166.57, 191.29; EI HRMS *m/e* calcd for $C_{18}H_{30}O_4Si$ (M^+) 338.1913, found 338.1912.
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(17) Data for **21**: IR (neat, cm^{-1}) 3385, 3218, 2955, 2930, 2895, 2857, 1603, 1472, 1254, 1111, 1078, 839, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 1.97 (s, 3H), 4.15 (brs, 2H), 4.68 (s, 2H), 6.56 (brd, 1H, J = 1.2 Hz), 7.04 (brd, 1H, J = 3.7 Hz), 7.17 (s, 1H), 8.46 (d, 1H, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.33, 15.25, 18.42, 25.93, 63.46, 68.09, 118.36, 121.34, 122.56, 142.45, 148.95, 150.10, 157.14; EI HRMS *m/e* calcd for $C_{16}H_{27}NO_2Si$ (M^+) 293.1811, found 293.1804.
(18) Data for **4**: mp 91 °C; IR (KBr disk, cm^{-1}) 2361, 1709, 1684, 1372, 1150, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 7.35 (s, 1H), 7.69 (d, 1H, J = 4.9 Hz), 7.90 (s, 1H), 9.01 (d, 1H, J = 4.9 Hz), 9.69 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.11, 121.71, 123.88, 142.02, 142.74, 145.66, 151.33, 156.11, 190.95, 195.41; EI HRMS *m/e* calcd for $C_{10}H_9NO_2$ (M^+) 175.0633, found 175.0624.