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Convergent Stereoselective Synthesis of the Visual Pigment A2E

Cristina Sicre and M. Magdalena Cid*

Departamento de Química Orgánica, Universidade de Vigo, Campus Lagoas-Marcosende, 36310 Vigo, Spain

mcid@uvigo.es

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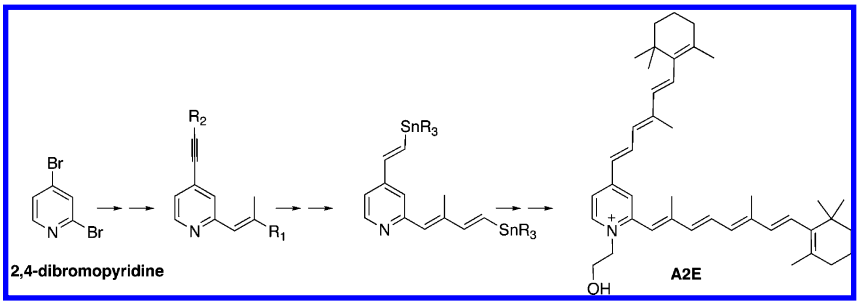
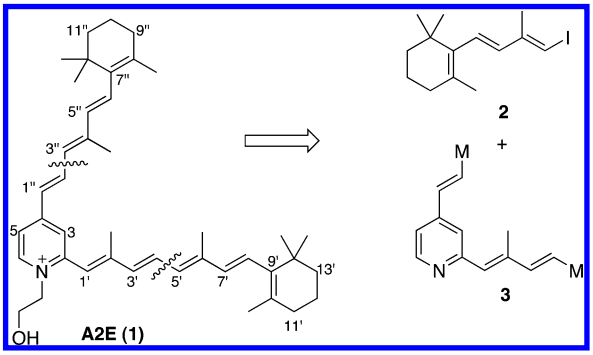
ABSTRACT



A stereoselective total synthesis of the visual pigment A2E has been achieved with use of palladium-catalyzed cross-coupling reactions in all key steps: a regioselective Suzuki or Negishi coupling of 2,4-dibromopyridine, a Sonogashira reaction, and a double Stille cross-coupling to complete the bispolyenyl skeleton.

Deposition of a fluorophoric material, known as lipofuscin, in lysosomes of retinal pigment epithelium cells has been speculated to be one of the biomarkers of age-related macular degeneration. Pyridinium bisretinoids, A2E and its 1′-*Z*-photoisomer (see Scheme 1 for numbering), iso-A2E,[1] have been characterized as fluorophores of lipofuscin. Several modes of toxicity have been suggested through which A2E can affect the health of the retinal pigment epithelium (RPE).[2]

Scheme 1. Strategy for the Synthesis of A2E



The confirmation of the role of A2E was given by recent studies on transgenic mice that have shown that accumulation of lipofuscin by the RPE is followed by RPE atrophy.[3] Its cationic nature along with two hydrophobic retinal chains suggests that it can disrupt the membrane integrity by its detergent-like activity and can thus cause cellular damage.[4] Also, it was found that A2E, at low concentrations, causes apoptosis in cultured human retinal pigment epithelial cells[5] and a possible mechanism for A2E toxicity may include photochemical processes leading to photooxidation products, mainly epoxides in the acyclic side chains,[6] through free radicals[7] or singlet oxygen intermediacy.[8]

Biosynthetic studies revealed that detectable levels of A2-PE, the A2E precursor generated from two units of *all-trans*-retinal and phosphatidylethanolamine, are formed

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(4) De, S.; Sakmar, T. P. *J. Gen. Physiol.* **2002**, *120*, 147.

(5) (a) Shaban, H.; Borrás, C.; Viña, J.; Richter, C. *Exp. Eye Res.* **2002**, *75*, 99. (b) Suter, M.; Remé, C.; Grimm, C.; Wenzel, A.; Jäättela, M.; Esser, P.; Kociok, N.; Leist, M.; Richter, C. *J. Biol. Chem.* **2000**, *275*, 39625.

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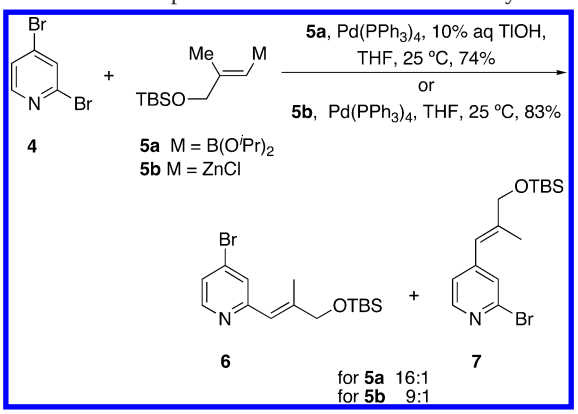
within the photoreceptor outer segments following light-induced release of endogenous *all-trans*-retinal.[9] This scheme was followed in the reported A2E biomimetic synthesis,[1,10] where A2E was prepared in 50% yield by simple mixing of *all-trans*-retinal and hydroxylamine, and also in a formal synthesis through a 6π-azaelectrocyclization reaction.[11]

The first total synthesis of the ocular pigment A2E was achieved by a nonstereoselective double Wittig-olefination of a pyridyl bisaldehyde and 2 equiv of a retinoid-C-15 phosphonium salt containing the moiety common to both sidearms.[12]

Here, we report the first stereoselective synthesis of A2E (**1**) through a convergent process involving a two-directional palladium-catalyzed C(sp^2)−C(sp^2) bond formation between the properly functionalized pyridine **3** and the trienyliodide **2** (Scheme 1).

The synthesis of the pyridine core **3** was envisioned from the corresponding bisalkynylpyridine, itself prepared from 2,4-dibromopyridine (**4**), through regioselective and sequential palladium cross couplings, under the assumption that the two halogens should exhibit differential reactivity toward palladium[0] in cross-coupling reactions due to their different electronic environments.[13]

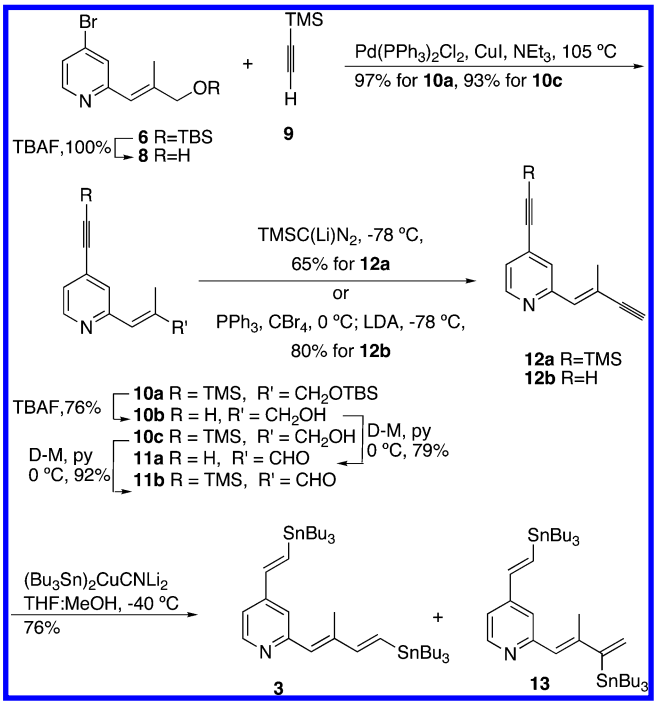
Scheme 2. Preparation of the Monosubstituted Pyridine



The reaction between 2,4-dibromopyridine (**4**)[14] and boronic ester **5a**, prepared in situ from the corresponding iodide[15] by halogen−lithium exchange and further treatment with triisopropoxyborate, in the presence of Pd[0] and TlOH at 25 °C proved to be highly regioselective (**6**:**7** ratio of 16:1) yielding the 2-alkenyl-4-bromopyridine **6** in 70% yield. Cross-coupling with zinc derivative **5b** under Negishi conditions[16] also proceeded at 25 °C and provided compound **6** (separated from ca. 10% of **7**) in 73% yield.[17]

The next target was the incorporation of the substituent at the 4-position of the pyridine nucleus and it turned out that Sonogashira cross-coupling served very well to attach the alkyne moiety at this position. So, reaction of **6** with ethynyltrimethylsilane under the usual Sonogashira conditions followed by deprotection of both silyl groups and Dess−Martin oxidation rendered **11a** in good overall yield (58%) (Scheme 3).

Scheme 3. Synthesis of the Pyridine Core **3**



The transformation of the aldehyde **11a** into the corresponding alkyne **12b** under different conditions was sluggish and yields were poor (15−20%).

To circumvent these difficulties, presumably due to the acidity of the acetylenic hydrogen, the silyl ether group of

(6) (a) Dillon, J.; Wang, Z.; Avalle, L. B.; Gaillard, E. R. *Exp. Eye Res.* **2004**, *79*, 537. (b) Radu, R. A.; Mata, N. L.; Bagla, A.; Travis, G. H. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5928. (c) Sparrow, J. R.; Vollmer-Snarr, H. R.; Zhou, J.; Jang, Y. P.; Jockusch, S.; Itagaki, Y.; Nakanishi, K. *J. Biol. Chem.* **2003**, *278*, 18207.

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(8) (a) Ben-Shabat, S.; Itagaki, Y.; Jockusch, S.; Sparrow, J. R.; Turro, N. J.; Nakanishi, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 814. (b) Roberts, J. E.; Kukielczak, B. M.; Hu, D.-N.; Miller, D. S.; Bilski, P.; Sik, R. H.; Motten, A. G.; Chignell, C. F. *Photochem. Photobiol.* **2002**, *75*, 184. (c) Kanofski, J. R.; Sima, P. D.; Richter, C. *Photochem. Photobiol.* **2003**, *77*, 235.

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(11) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099.

(12) Ren, R. X.-F.; Sakai, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1997**, *119*, 3619.

(13) 2-Bromo-4-chloropyridine was also used. But although monosubstituted pyridine **6b** was successfully obtained, the incorporation of the substituent at position 4 was hampered by the low reactivity of the chlorine atom under different Sonogashira reaction conditions. See the Supporting Information for further details.

(14) 2,4-Dibromopyridine was prepared by using a modified version of the method reported by den Hertog: den Hertog, H. J. *Recl. Trav. Chim.* **1944**, *63*, 85.

(15) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.

(16) Bach, T.; Heuser, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3184.

(17) We also tried a Stille coupling with the corresponding stannane **5** (M = $SnBu_3$) but its reactivity was low at 25 °C, and even at 95 °C after 68 h, conversion was not complete and selectivity was low, this being attributable to the methyl cis to the C−metal bond. Besides, this C−metal bond is very labile.

compound **6** was removed by treatment with TBAF in THF before running the Sonogashira coupling. Thus, reaction of pyridine **8** under Sonogashira conditions provided enynyl pyridine **10c**, which after treatment with Dess−Martin periodinane led to aldehyde **11b** in an overall 85% yield. The preparation of alkyne **12** was now successfully accomplished either directly with $TMSC(Li)N_2$[18] or through Corey−Fuchs-type conditions (Scheme 3).[19]

Subsequent treatment of the bisethynylpyridine **12b** with $(Bu_3Sn)_2CuCNLi_2$[20] at −40 °C afforded the double functionalized bisstannylpyridine **3** in 56% yield, the presence of MeOH throughout the reaction being critical for the success of the stannylcupration. Although the reaction was totally regio- and stereoselective at the alkyne at position-4 to give the *E*-stannyl derivative, at the enynyl chain at position-2 the selectivity was lower and the internal isomer **13** was also obtained in a ratio of 2.8:1. This ratio increased to 4.2:1 when the reaction was run at −10 °C, but the yield was slightly lower (50% for compound **3**) most likely as a result of decomposition processes. The structures of both stannanes **3** and **13** were assigned by using 2D NMR experiments and some characteristic NMR data along with the main $^1H-^{13}C$ long distance couplings are shown in Figure 1.

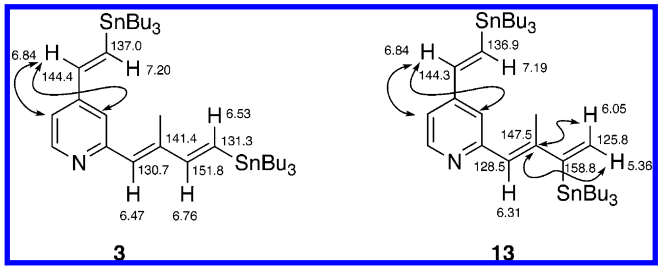
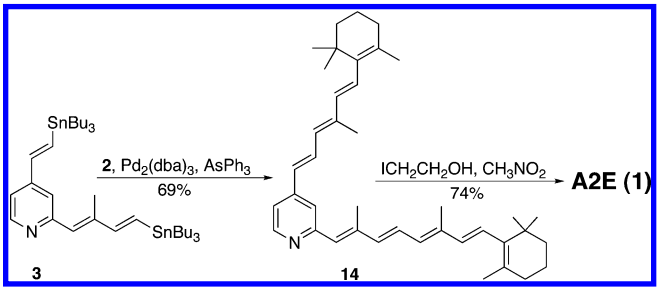


Figure 1. Structural assignments for stannanes **3** and **13**: ^1H and ^{13}C NMR shifts and crucial $^{13}C-^1H$ correlations.

Last, a double Stille coupling of the bisstannane **3**[21] with the trienyliodide **2**[22] with use of Farina conditions or $Pd(PhCN)_2Cl_2$ in the presence of Hünig base, *i*-Pr_2NEt, rendered stereoselectively the *all-trans* bispolyenyl pyridine **14** (50%) (Scheme 4). Alkylation of **14** with iodoethanol in nitromethane for 19 h gave A2E (**1**) in an overall 14% yield from 2,4-dibromopyridine. All spectroscopic data of A2E were identical with those previously reported.[1b]

Scheme 4. Preparation of the Ocular Pigment A2E



To summarize, a stereoselective total synthesis of A2E has been achieved that uses palladium-catalyzed cross-coupling reactions in all key bond-forming steps: regioselective Suzuki (or Negishi) coupling of 2,4-dibromopyridine, Sonogashira reaction, and 2-fold Stille cross-coupling to complete the bispolyenyl skeleton.

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Supporting Information Available: Experimental procedures and characterization (^1H NMR, ^{13}C NMR, HRMS, or EA) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The transformation of the 1,1-dibromoalkenyl derivative into the corresponding alkyne was achieved by using 6 equiv of LDA as the base. When *t*-BuO^- was used, instead, a complex mixture of products was obtained, probably due to its higher nucleophilic character. Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971.

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(21) Different mixtures of **13** and **3** were used as starting material. See the Supporting Information for details.

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