STEREOSELECTIVE FUNCTIONALIZATION AT C-9 OF RETINAL: SYNTHESIS OF 9-*TRANS*-19-NOR-9-HALORETINAL ANALOGS

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Stereoselective functionalization at C-9 of retinal based on the use of the C_4+X-unit is described. A sequential linkage of C_4+X-units (X=Cl, Br, and I) with ylide **8** (C_{10}) and phosphonate **12** (C_5)selectively gave 9-*trans*-19-nor-9-Cl, Br, and I-retinal derivatives.

KEY WORDS 9-haloretinal; conjugate addition; retinal proteins

Retinal proteins play an important role in the light energy converting process for vision, phototaxis, and light-driven ion pumping. It has been established that these functions are triggered by the photoisomerization of the retinal linked to apoproteins. One recent topic of interest in this field is the crucial role of the interaction between the methyl group at C-9 and the amino acid residue near the retinal, which occurs in the photoisomerization process.[1] This fact led us to explore the mechanistic details of this interaction using 9-functionalized retinal analogs. However, stereoselective functionalization at C-9 has not been extensively studied. Furthermore, most of the previous methods afforded 9-*cis*-isomers as the major product.[2] Herein we report a novel method for the stereoselective functionalization at C-9, and its successful application to the selective synthesis of 9-*trans*-19-nor-9-haloretinals. The synthetic strategy involves the use of C_4+X-units bearing halogen at the C-3 position (Chart 1). We anticipate that functionalization at C-3 of the C_4+X-units by palladium-catalyzed cross-coupling and radical reactions will provide a wide variety of C_4+R-units, which would be readily converted into 9-*trans*-19-nor-9-X(R)-retinals by the Wittig and Horner-Emmons reactions with C_{10}- and C_5-synthons.

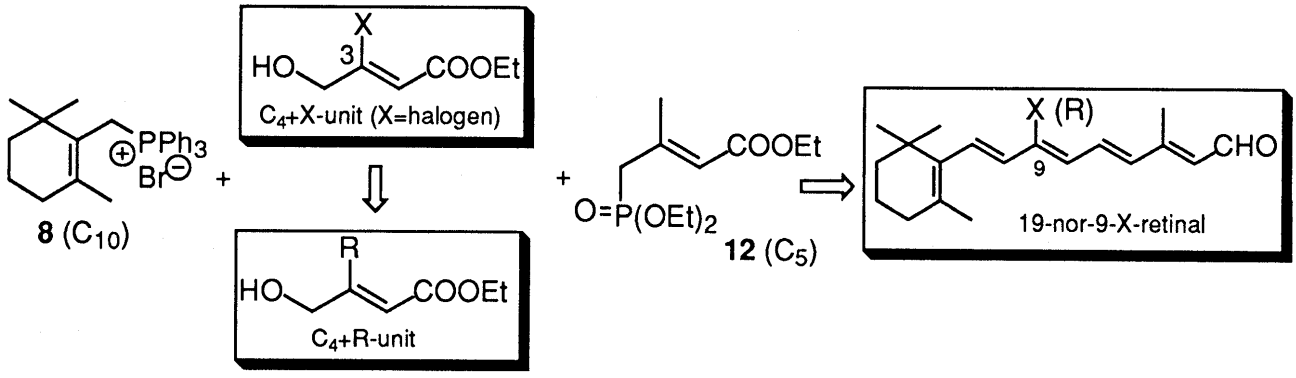

Chart 1

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The key to our strategy was the stereoselective synthesis of the Z-C_4+X-units possessing halogen at C-3. We accomplished the selective construction by the application of Lu's procedure[3] to 4-hydroxybutynoate **1** (Chart 2). Treatment of **1** with LiX (X=Cl, Br, and I) in acetic acid at 70°C afforded *Z*-adducts **2a-c**, respectively, whereas fluorine nucleophiles (CsF and KF) were inert even under drastic conditions. The limitation of this addition reaction was investigated by use of **3** having the left-half moiety of the retinal. In this case, the addition proceeded slowly to give the undesired 9*E*-adduct **4** in a moderate yield along with unidentified polymers.

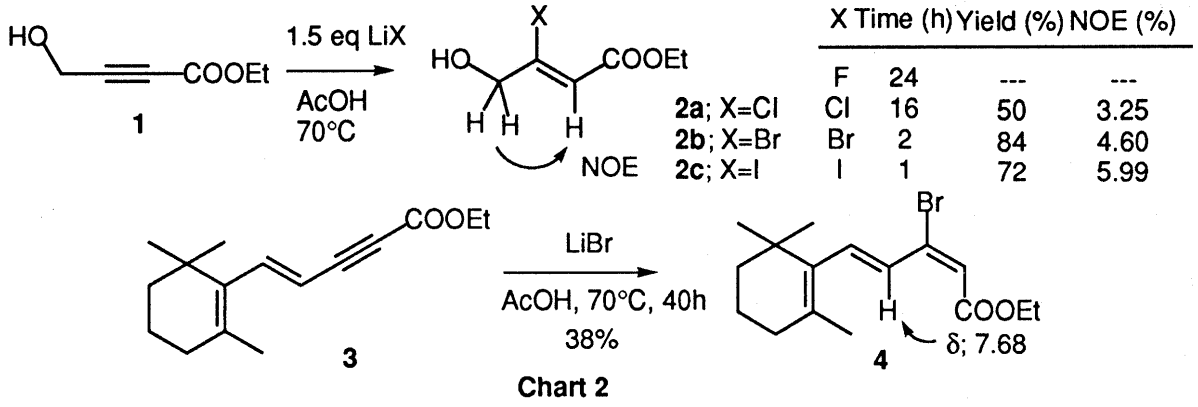

Chart 2

Further functionalization at C-3 of the C_4+X-unit was successfully exemplified in the Stille cross-coupling reaction (Chart 3).[4] Treatment of **2c** with alkyl and vinyltin reagents in the presence of $Pd(MeCN)_2Cl_2$ selectively provided the corresponding coupling products **5** and **6**. Moreover, recent progress in the specific synthesis of *Z*-alkenoic acids involving palladium-catalyzed cross-coupling reactions[5] promises a wide range of substitutions at C-3 of **2c**.

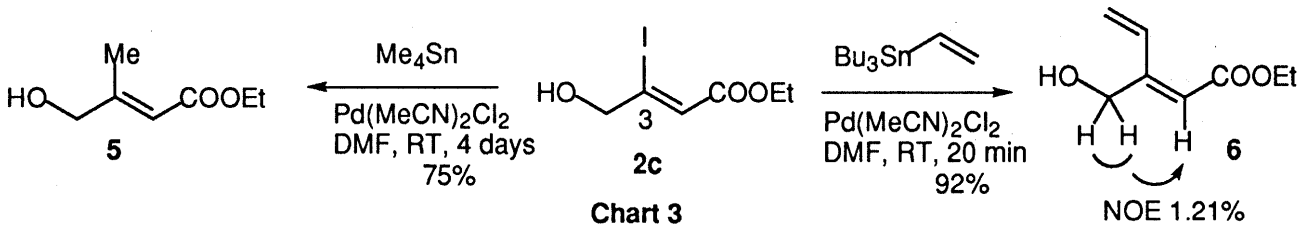

Chart 3

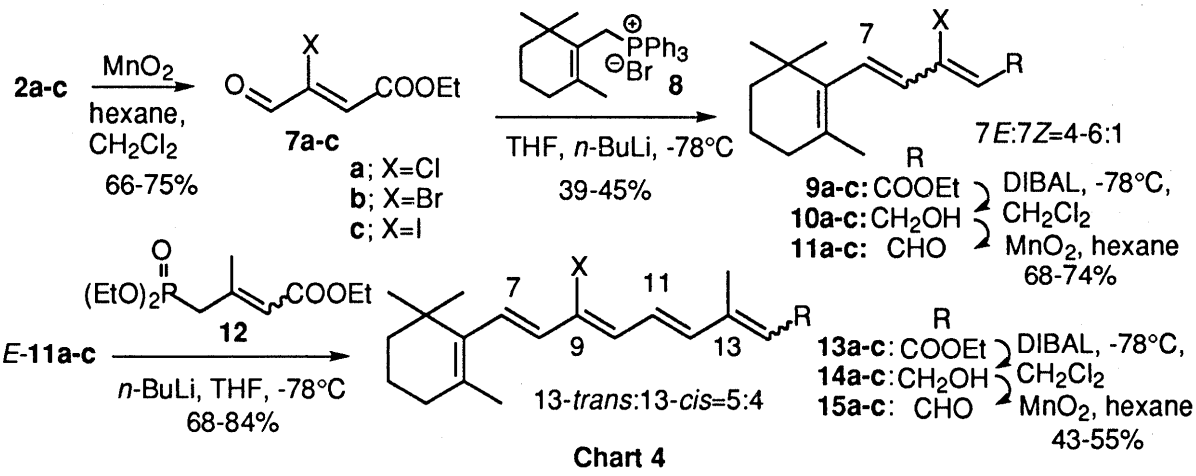

Chart 4

The C_4+X-units (X=Cl, Br, and I) were successfully converted into the corresponding 9-*trans*-19-nor-9-haloretinals[6] (Chart 4). Oxidation of **2a-c** with MnO_2 followed by the Wittig reactions of **7a-c** with ylide **8** afforded a 6~4:1 mixture of 7*E*- and 7*Z*-esters **9a-c**, which were subjected to a sequential reduction and oxidation to give **11a-c**. The 7*E*-aldehydes **11a-c** were transformed into the corresponding retinal analogs **15a-c** by a series of reactions, the Horner-Emmons olefination with phosphonate **12**, reduction with DIBAL, and oxidation with MnO_2.

In conclusion, we have developed a novel strategy for the stereoselective functionalization at C-9 of retinal based on the using the C_4+X-units as the key synthons. Biological studies using 9-*trans*-19-nor-9-X-retinals (X=Cl, Br, and I) **15a-c** are in progress.[7]

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7) All-*trans*-analogs **15a-c** were smoothly incorporated into bacterioopsin to give the corresponding bacteriorhodopsin analogs (λ_{max} 545-555 nm), respectively.

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