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Synthesis of isomeric 1,4-[$^{13}C]_2$-labeled 2-ethoxycarbonyl-1,4-diphenylbutadienes

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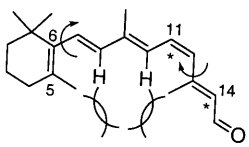
Abstract—The 1,4-bis-^{13}C-labeled isomeric compounds (*Z*,*E*)- and (*E*,*E*)-2-ethoxycarbonyl-1,4-diphenylbutadiene have been synthesized by two different methods. A double Horner–Wadsworth–Emmons (HWE) strategy was employed for the synthesis of the *Z*,*E* isomer. On the other hand, synthesis of the *E*,*E* isomer was achieved by Baylis–Hillman reaction of benzaldehyde with ethyl acrylate and subsequent rearrangement, followed by Wittig olefination with benzaldehyde. These routes provide stereoselective access to labeled compounds in good yields.

Retinal binding proteins have been the focus of many investigators, their importance in visual transduction, gene regulation control, and onset of diseases has been well documented.[1] They have also been used as models for studying protein–substrate interactions. Wavelength regulation exhibited by various rhodopsin pigments in the eye is a remarkable example of the consequences of protein–substrate interactions.[2,3] A single chromophore, namely 11-*cis*-retinal, bound to different rhodopsins is tuned to absorb at various wavelengths, which allows for the perception of color. These interactions provide a simple and elegant platform to study protein–substrate interactions.



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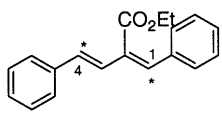
It has been suggested that conformational and/or stereoelectronic effects control wavelength regulation exhibited by different rhodopsins.[2,3] With regards to the unbound chromophore, steric interactions of the C5-CH_3/H8 and C13-CH_3/H10 in 11-*cis*-retinal (**1**) force dihedral twists of the C6/C7 and C12/C13 single bonds, respectively. However, unique environments within the retinal binding site of each rhodopsin pigment may cause different degrees of torsional twisting of the single bonds, thus causing different degrees of conjugation and ultimately different wavelength maxima.[4] We are interested in studying retinal conformational differences in different rhodopsin pigments by the binding of bis-^{13}C-labeled retinal such as 11,14-[$^{13}C]_2$-11-*cis*-retinal (**1**) (for examining the degree of C12/C13 twisting). Solid state NMR techniques will be used to probe the degree of single bond twisting within the polyene as it is bound to different rhodopsin proteins.[5,6]



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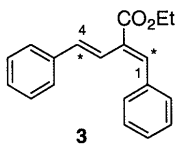

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To first establish the solid state NMR conditions and probe the limitations in sensitivity and accuracy for the measurement of dihedral angles with bis-^{13}C-labeled substrates, we have synthesized two isomers of 2-ethoxycarbonyl-1,4-diphenylbutadiene to serve as model compounds (*Z*,*E* isomer **2**, and *E*,*E* isomer **3**). These two molecules contain the same olefinic labeling pattern as the proposed 11-*cis*-retinal (**1**), i.e. 1,4-[$^{13}C]_2$-labels. The isomeric phenyl group at C1 of **2** and **3** lead to different torsional twists within the C2/C3 single bond. We have performed conformational analyses of

Keywords: 1,2,4-trisubstituted-butadienes; HWE reactions; stable radiolabeled synthesis.

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these molecules and have determined the theoretical dihedral angles between the olefinic planes (dihedral angles between C1–C2–C3–C4) for each compound. As illustrated in Fig. 1, the planes defined by the two olefins in the *Z*,*E* isomer **2** are twisted by about 20°. However, the same two planes in the *E*,*E* isomer **3** are twisted by 41°.

Herein, we report two simple and straightforward schemes for the stereospecific synthesis of **2** and **3**. Strategies for synthesis of similar compounds have been reported previously.[7,8] However, we required a procedure that would deliver the 1,4-bis-labeled butadienes from readily available and inexpensive ^{13}C-labeled precursors. The labeled carbons are incorporated from benzaldehyde in all cases, thus allowing the schemes to be modified to obtain different 1,4-substituted butadienes by changing the carbonyl species.

The *Z*,*E* isomer **2** was synthesized by employing a double Horner–Wadsworth–Emmons (HWE) strategy (Scheme 1) in a similar fashion, which was reported by Minami et al.[8] Selenation of triethyl-2-phosphonopropionate (**4**) proceeded smoothly to furnish **5**, which was oxidized promptly with *m*CPBA to yield the *syn*-eliminated product **6** in high yield. The olefinic carbons in **6** are the unlabeled carbons C2 and C3 in the final product. The double HWE reaction at these two carbon centers with ^{13}C-carbonyl-labeled benzaldehyde would deliver the 1,4-bis-^{13}C-labeled compounds. The double HWE reaction was initiated by the 1,4 addition of diethylphosphite anion to obtain the bis-phosphate **7**. Deprotonation of **7** with *s*-BuLi and addition of labeled benzaldehyde delivered intermediate **8**, which was treated with another equivalent of *s*-BuLi and labeled benzaldehyde to deliver a 6:1 isomeric mixture of **2**:**3** in 39% yield over the latter steps. The *Z*,*E* isomer **2** was purified by HPLC.[9]

Our attempts at a one pot synthesis from **6**→**2** by utilizing the enolate generated after the Michael addition of diethylphosphite with **6** for the subsequent HWE reactions produced low yields of the desired final compound and was not reproducible. It was therefore necessary to isolate **7** and proceed forward. The bis-olefination of **7** allows for the introduction of commercially available ^{13}C-labeled carbonyl compounds such as benzaldehyde or other ketones or aldehydes as the

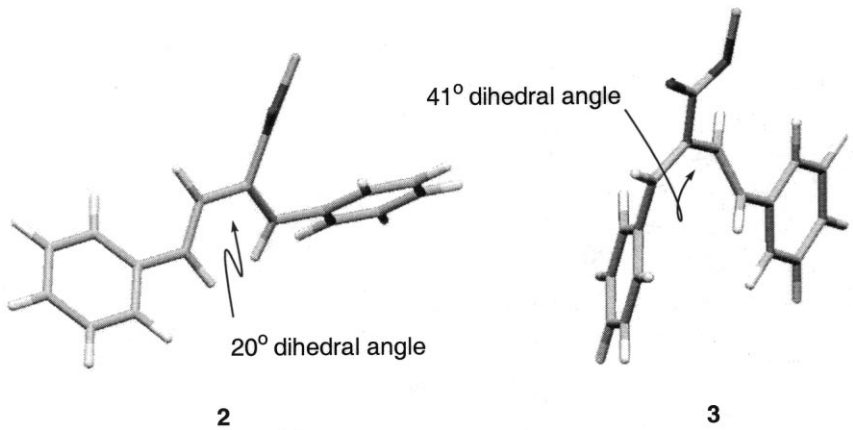
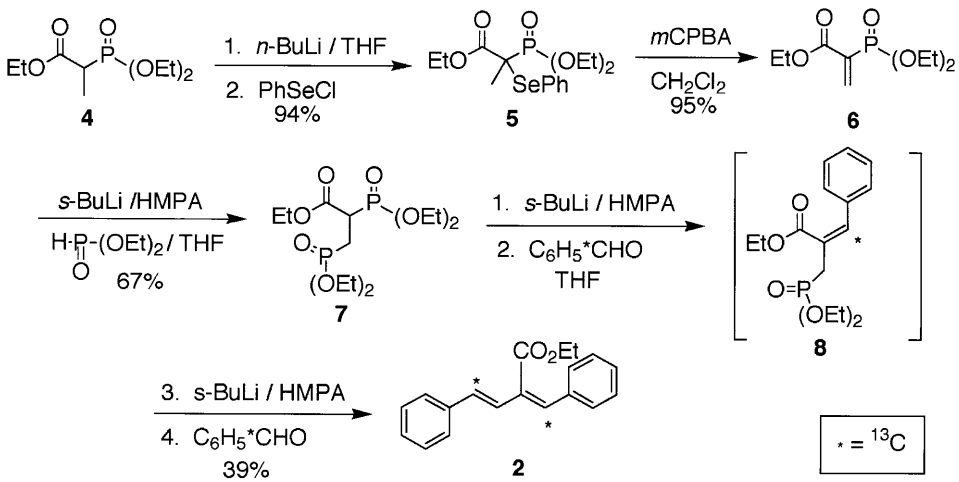
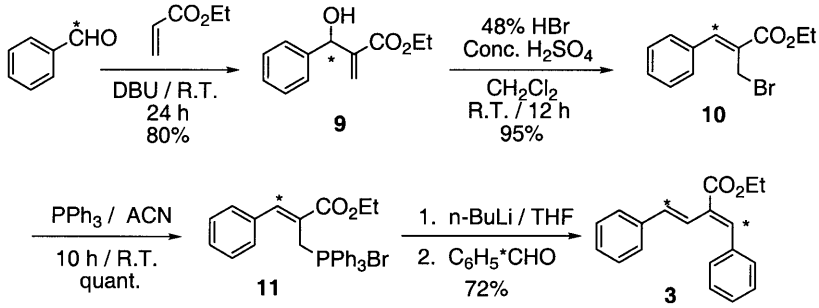


Figure 1. Structures **2** and **3** were minimized (MacroModel, version 7.0) to obtain the most stable conformation. The *Z*,*E* isomer **2** exhibits a 20° dihedral twist of the single bond which connects the olefinic planes. The *E*,*E* isomers exhibits a 41° dihedral twist of the same bond.



Scheme 1.



Scheme 2.

last step of the synthesis. In this manner, we can introduce both labels at once at the end of the scheme. This is desirable in the synthesis of labeled compounds since there are no subsequent steps that would decrease the yield of the labeled material.

Synthesis of the *E*,*E* isomer **3** is illustrated in Scheme 2. The Baylis–Hillman reaction between labeled benzaldehyde and ethyl acrylate proceeded smoothly to furnish the allyl alcohol **9**,[10] which upon treatment with HBr in concentrated sulfuric acid rearranged to yield the allyl bromide **10** in excellent yield.[11] As reported by Aggarwal and co-workers, we also noticed a substantial decrease in reaction time required for the Baylis–Hillman reaction catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 day) as compared to DABCO (7 days).[12] Ylide **11** was obtained in quantitative yield from the reaction of **10** with triphenylphosphine, which was subsequently deprotonated and reacted with labeled benzaldehyde to afford the desired *E*,*E* diene **3** in good yield and high isomeric purity (20:1 ratio of **3**:**2**).[13] Although we had to use the labeled benzaldehyde in the first step of the synthesis, we did not deem this as a major problem since the yield of subsequent reactions were high.

The stereoisomers **2** and **3** were characterized by one- and two-dimensional NMR spectroscopy. The stereochemistry of the olefinic bonds was confirmed by NOESY. In particular, strong coupling of H1 and H3 protons was observed in **2**, which was absent in **3**. ^{13}C NMR analysis of the resulting **2** revealed doubly enhanced signals at 132.7 and 131.0 ppm, while **3** displayed enhanced signals at 138.8 and 134.7 ppm, corresponding to enriched C_1 and C_4 of the 1,3-butadiene system.

In conclusion, the present procedure provides a convenient route to synthesize isomeric 1,4-substituted-butadienes. The solid state NMR studies will be reported in due course.

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9. Compound **2** was purified by HPLC with a normal phase column (Altex Ultra Sphere-Si) using a Perkin–Elmer LC-75 system under isocratic conditions (2% EtOAc/Hex, 5 mL/min, detection at 325 nm). ^1H NMR (300 MHz, $CDCl_3$): δ 1.2 (3H, t, $J=7.14$ Hz); 4.34 (2H, q, $J=7.14$ Hz); 6.65 (1H, dd, $J=16.5$ Hz, $^1J_{HC}=156$ Hz); 6.75 (1H, d, $^1J_{HC}=155.2$ Hz); 6.89 (1H, m); 7.2–7.5 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9; 61.4; 126.6 (d, $^3J_{CC}=2.3$ Hz); 127.4 (d, $^1J_{CC}=43.8$ Hz); 128.0; 128.2; 128.3; 128.5 (d, $^2J_{CC}=4.6$ Hz); 128.7 (d, $^2J_{CC}=4.6$ Hz); 131.0 (d, $^3J_{CC}=8.0$ Hz); 132.7 (d, $^3J_{CC}=9.2$ Hz); 134.2 (d, $^1J_{CC}=58.5$ Hz); 135.4 (d, $^1J_{CC}=55.5$ Hz); 136.7 (d, $^1J_{CC}=55.5$ Hz); 168.9.
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13. Compound **3** was purified by HPLC under the same conditions as compound **2**.[9] ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (3H, t, $J=7$ Hz); 4.35 (2H, q, $J=7$ Hz); 7.03 (1H, dd, $J=3.3$ Hz, 17 Hz); 7.20–7.48 (11H, m); 7.57 (1H, d, $^1J_{HC}=134$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5; 61.0; 121.6 (d, $^1J_{CC}=73.3$ Hz); 126.7; 127.8; 128.4; (d, $^2J_{CC}=4.6$ Hz); 128.6; 128.7; 130.0 (d, $^1J_{CC}=70.9$ Hz); 130.1; 134.7 (d, $^3J_{CC}=5.7$ Hz); 135.5 (d, $^1J_{CC}=55.5$ Hz); 137.5 (d, $^1J_{CC}=55.5$ Hz); 138.8 (d, $^3J_{CC}=5.7$ Hz); 167.5.