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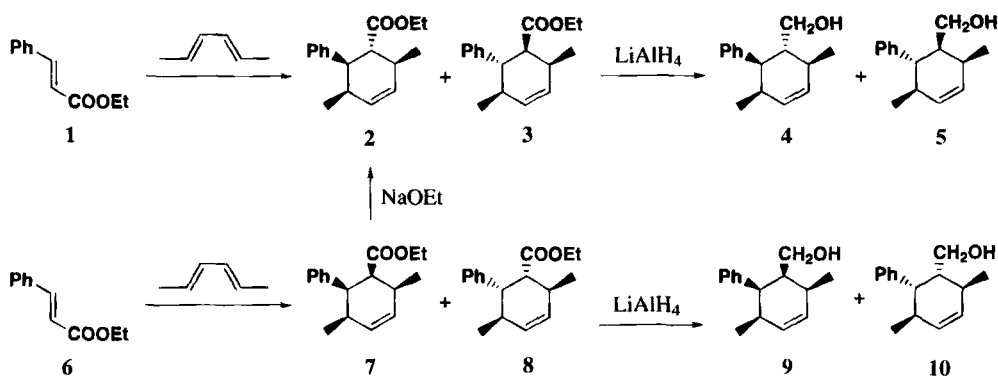
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**SYNTHESIS AND CHARACTERIZATION OF ISOMERIC
2,5-DIMETHYL-6-PHENYL-3-CYCLOHEXENE-1-METHANOL ANALOGS**

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Few if any reactions can rival the Diels-Alder cycloaddition for the construction of carbocyclic molecules. The stereochemical outcome for as many as four contiguous ring centers can usually be predicted due to the highly organized nature of the transition state. During the course of one of our programs several 2,5-dimethyl-6-phenyl-3-cyclohexene-1-methanol isomers were required as key intermediates. Retrosynthetic evaluation of these compounds led us to choose the Diels-Alder reaction for their syntheses. Although the Diels-Alder reaction has been systematically studied for a wide variety of dienes and dienophiles, cinnamates have surprisingly received little attention, especially in reactions with hexadiene derivatives. We are aware of only two papers where cinnamic acids are condensed with *trans,trans*-2,4-hexadiene and in both cases, the cyclohexene ring was subsequently aromatized.^{1,2}



Scheme 1

Our synthesis is based on the reaction of both *trans*- and *cis*-ethyl cinnamate with *trans,trans*-2,4-hexadiene to produce the cyclohexene adduct followed by reduction of the ester to the

desired alcohol (Scheme 1). The stereochemical outcome of the cycloaddition can be predicted in part. It is known that with few exceptions, the relative configuration of the dienophile is retained in the adduct.³ It was expected that the ester group of the cinnamate would control the stereochemistry of the 1,2-substituents of the product relative to the 3 and 6-methyl groups, and therefore **1** should produce *trans*-1,6-analogs whereas **6** should afford the corresponding *cis*-1,6-isomers. If the ester adopts an endo-like position relative to the diene, then product **2** should be the preferred isomer.

Reaction of **1** with *trans,trans*-2,4-hexadiene at 180° produced an inseparable 4:1 mixture of cycloadducts isolated in 82% yield. Reduction of the ester groups with lithium aluminum hydride gave a mixture of alcohols **4** and **5** which were readily separable by column chromatography.

The NMR spectrum of the major isomer was readily analyzed by homonuclear decoupling experiments. Methyl doublets at δ 0.75 and δ 1.15 are assignable to Me_f and Me_e with the associated resonances for H_e and H_f at δ 2.30 and δ 2.45 respectively (see Figure 1). The signal for H_d appears at δ 3.10 as a doublet of doublets with apparent couplings of 12 and 5 Hz, suggesting one axial and one equatorial partner. The resonance for H_g is characteristic of an axial proton with two axial partners (a triplet with two large couplings of 12 Hz). The pseudoaxial relationship of H_e and pseudoequatorial H_f are confirmed by decoupling experiments and the magnitude of their allylic coupling to H_a and H_b. It was observed that J_{AE} is larger than J_{BE} while J_{FA} is smaller than J_{FB}. These results are consistent with structure **4**.

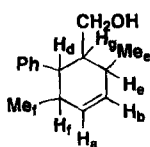
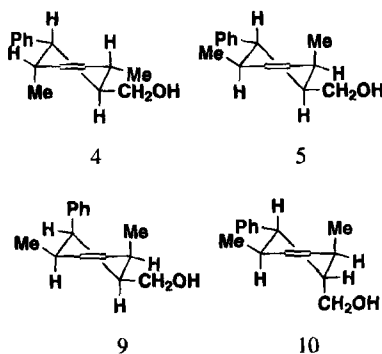


Figure 1

Figure 2. Conformational representations of structures **4**, **5**, **9**, **10**

In the NMR spectrum of the minor isomer, the proton signal for H_g and H_d are observed at δ 2.20 and δ 2.10 with H_d showing two large couplings to H_g and H_f. The axial-like disposition of H_f is further confirmed by its allylic couplings to H_a and H_b. NOE from irradiation of Me_e gives enhancement of signals H_e, H_b, H_d and of the CH₂ protons, which is consistent with structure **5**.

Ethyl *cis*-cinnamate (**6**) was readily prepared by partial catalytic reduction of ethyl phenylpropionate in the presence of Pd/C poisoned with benzaldehyde dimethylthioacetal (PhCH(SMe)₂). No ethyl *trans*-cinnamate was formed as in other methods⁴⁻⁶ and only traces of over reduction to the alkane were detected. Reaction of **6** with *trans,trans*-2,4-hexadiene at 190° produced a 1.2:1 mixture of Diels-Alder adducts (52% yield) along with 12% of unreacted cinnamate. Reduction of the ester

Prep 500 apparatus using 30% MTBE/hexane to elute the products. The less polar product **4** (15.1 g) was isolated as a colorless oil in 60% yield (99.6% pure determined by GC). IR (CHCl₃): 3680, 3490, 1460, 1235, 1080 cm⁻¹. ¹H-NMR (CDCl₃): δ 7.39-7.10 (m, 5H), 5.75 (m, 1H, H_a), 5.51 (d, broad, 1H, H_b), 3.63 (s, broad, 2H, CH₂), 3.10 (dd, 1H, H_d), 2.45 (m, 1H, H_c), 2.30 (m, 1H, H_f), 1.75 (tt, 1H, H_g), 1.15 (d, J=7.5 Hz, 3H, Me_e), 0.98 (s, broad, 1H, OH), 0.75 (d, J=7.5 Hz, 3H, Me_e).

Anal. Calcd for C₁₅H₂₀O: C, 83.28; H, 9.32. Found: C, 83.10; H, 9.30

The more polar product **5** (5.6 g) was isolated as a colorless oil in 22% yield (96.1% pure determined by GC). IR (CHCl₃): 3680, 3470, 1460, 1370, 1230, 1000 cm⁻¹. ¹H-NMR (C₆D₆): δ 7.21-7.05 (m, 3H), 7.00-6.91 (m, 2H), 5.77 (m, 1H, H_b), 5.52 (d, broad, 1H, H_a), 3.11 (d, broad, 2H, CH₂), 2.59 (m, 1H, H_c), 2.28 (m, 1H, H_f), 2.20 (m, 1H, H_g), 2.10 (m, 1H, H_d), 1.10 (d, J=7.5 Hz, 3H, Me_e), 0.75 (d, J=7.5 Hz, 3H, Me_e), 0.68 (s, broad, 1H, OH). *Anal.* Calcd for C₁₅H₂₀O: C, 83.28; H, 9.32. Found: C, 83.59; H, 9.40

Ethyl cis-Cinnamate (6).- A solution of ethyl phenylpropiolate (3.0g, 17.2 mmol) and benzaldehyde dimethylthioacetal⁷ (50 mg, 0.27 mmol) in 40 mL of ethyl acetate was hydrogenated over 5% Pd/C (300 mg) at 1 atm for 48 h. The reaction mixture was filtered through Celite and the solvent evaporated to give 3.1g (100%) of **6** as a colorless oil. ¹H-NMR (CDCl₃): δ 7.64-7.45 (m, 2H), 7.40-7.16 (m, 3H), 6.94 (d, J=12.5 Hz, 1H), 5.94 (d, J=12.5 Hz, 1H), 4.16 (q, 2H), 1.23 (t, 3H).

Reaction of 6 with trans,trans-2,4-Hexadiene.- A mixture of ethyl cis-cinnamate (3.0 g, 17 mmol), trans, trans-2,4-hexadiene (4 g, 49 mmol) and hydroquinone (20 mg) was heated at 190° in a sealed vessel for 4 days. GC analysis of the mixture showed a 1.2:1 ratio of adducts. The mixture was chromatographed on a Waters Prep 500 apparatus using 5% ethyl acetate/hexane to elute 2.3g (52%) of a mixture of **7** and **8**.

(1S,2S,5R,6R)-rel-2,5-Dimethyl-6-phenyl-3-cyclohexene-1-methanol (9) and (1R,2S,5R,6S)-rel-2,5-dimethyl-6-phenyl-3-cyclohexene-1-methanol (10).- To a 1.0N solution of lithium aluminum hydride in tetrahydrofuran (8.0 mL) was added dropwise a solution of **7** and **8** (520 mg, 2 mmol) in 2 mL tetrahydrofuran. The mixture was stirred at room temperature for 4h then saturated Na₂SO₄ solution was added dropwise until a thick precipitate formed. Ether was added and the mixture filtered through Celite. The filtrate was evaporated and the residual oil was chromatographed on a Waters Prep 500 apparatus using 40% MTBE/hexane to elute the products. The less polar product **10** (125 mg) was isolated as an oil in 29% yield (94.2% pure determined by GC). IR (CHCl₃): 3680, 1460, 1375, 1240, 1060, 1020 cm⁻¹. ¹H-NMR (C₆D₆): δ 7.31-7.06 (m, 5H), 5.58 (s, 2H, H_a and H_b), 3.35 (m, 2H, CH₂), 2.83 (dd, 1H, H_d), 2.33 (m, 2H, H_c and H_f), 1.65 (m, 1H, H_g), 1.05 (d, J=7.5 Hz, 3H), 0.90 (d, J=7.5 Hz, 3H), 0.67 (s, broad, 1H, OH).

Anal. Calcd for C₁₅H₂₀O: C, 83.28; H, 9.32. Found: C, 83.40; H, 9.40

The more polar product **9** (145 mg) was isolated as a solid (mp 115-117°) in 33% yield (99.9% pure determined by GC). IR (CHCl₃): 3680 cm⁻¹. ¹H-NMR (C₆D₆): δ 7.49-7.37 (m, 2H), 7.26-7.02 (m, 3H), 5.67 (s, 2H, H_a and H_b), 3.35 (m, 2H, CH₂), 3.05 (t, 1H, H_d), 2.60 (m, 1H, H_f), 2.35 (m, 1H, H_c), 2.18 (m, 1H, H_g), 0.92 (d, J=7.5 Hz, 3H, Me_e), 0.66 (d, J=7.5 Hz, 3H, Me_e), 0.52 (s, broad, 1H, OH).

Anal. Calcd for C₁₅H₂₀O: C, 83.28; H, 9.32. Found: C, 83.30; H, 9.50

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