h and then the solution was concentrated under reduced pressure to a volume of 5 mL. This solution was diluted with 50% EtOAc/hexane and washed with saturated $NaHCO_3$. The aqueous layer was washed with additional EtOAc/hexane and the combined organic extracts were washed with saturated NaCl and dried ($Na_2SO_4$). Drying agent was removed by vacuum filtration, and the solution was concentrated under reduced pressure to afford 260 mg (90%) of **4** as a light yellow oil: IR 3483, 1740, 1665 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.29 (t, 3, $CH_2CH_3$, $J$ = 7.5 Hz), 1.60 (br s, 1, OH), 2.10 (d, 2, $=CCH_3$, $J$ = 1 Hz), 4.16 (br s, 2, $CH_2OH$), 4.17 (q, 2, $CH_2CH_3$, $J$ = 7.5 Hz), 5.99 (m, 1, =CH).

**Ethyl *trans*-3-Formyl-2-butenoate (1).** To an oven-dried, round-bottomed flask equipped with a magnetic stirrer, Ar inlet, and $CaSO_4$ drying tube was added a solution of 195 mg (1.4 mmol) of **4** in 10 mL of $CH_2Cl_2$. The solution was cooled in an ice bath and 587 mg (6.8 mmol) of $MnO_2$ was added. The suspension was stirred for 1 h while being warmed to ambient temperature. The reaction mixture was vacuum filtered through diatomaceous earth and the $CH_2Cl_2$ was removed under reduced pressure at 23 °C to afford 152 mg (88%) of **1** as a light yellow oil. Flash chromatography of this oil (80% $CH_2Cl_2$/hexane) afforded 124 mg (72%) of **1**: TLC (EtOAc/hexane, 1:3) $R_f$ 0.41; IR 1710, 1625 $cm^{-1}$; UV (hexane) $\lambda_{max}$ 228 nm ($\epsilon$ 2250); NMR ($CDCl_3$) $\delta$ 1.34 (t, 3, $CH_2CH_3$, $J$ = 7 Hz), 2.16 (d, 3, $=CCH_3$, $J$ = 1.5 Hz), 4.28 (q, 2, $CH_2CH_3$, $J$ = 7 Hz), 6.49 (d, 1, =CH, $J$ = 1.5 Hz), 9.54 (s, 1, CHO); GC/MS, $m/e$ (relative intensity) $(M)^+$ 142 (2), $(M - CH_3CH_2OH)$ 96 (100).

The 2,4-dinitrophenylhydrazone derivative of **1** was prepared by standard procedures: mp 197–199 °C (lit.[16] mp 199–200 °C); HRMS, $m/e$ required for $C_{13}H_{14}N_4O_6$ 332.0914, observed 322.0923.

**Acknowledgment.** Partial financial support of this work by a Pilot Research Grant from the American Cancer Society, Ohio Division, and a Seed Grant from the Office of Research and Graduate Studies, the Ohio State University; is gratefully acknowledged. We also acknowledge the assistance of The Ohio State University Campus Chemical Instrument Center for assistance in obtaining mass spectra. We also thank Ms. Rose Smith for the preparation of this manuscript.

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## Model Studies for the Synthesis of Trichothecenes. Synthesis of *rac*-Trichodiene and *rac*-Bazzanene

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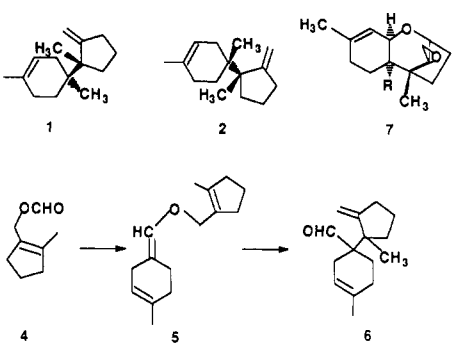
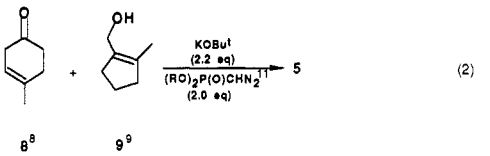
The recent publication by Suda of a novel, albeit stereorandom, approach to the synthesis of *rac*-trichodiene (**1**) and *rac*-bazzanene (**2**)[1] and the difficulties encountered by other workers in repeating the Wittig reaction that constitutes the first step in the sequence (eq 1)[2] prompt the present report of our closely related synthetic approach to these hydrocarbons.

A critical step in the aforementioned synthesis is the Claisen rearrangement of the allyl vinyl ethers **5**, intermediates obtained from the Wittig reaction between **3** and **4** and characterized spectroscopically (eq 1); the resulting




50–50 mixture of the aldehydes **6** was reduced to **1** and **2** by use of the Wolff–Kishner reaction.[1] We have also prepared the ethers **5**,[3] in 50% isolated yield based on ketone **8**, by application of our previously reported methodology that involves generation and trapping of alkylidenecarbenes (eq 2),[4] and have converted them to




**1** and **2**[5] by the same sequence of reactions as that used by Suda.[1] However, the present synthesis of **5** is conceptually significant because its success augurs well for the eventual development of a diastereoselective approach to *rac*-trichodiene (**1**)[6] and of a convergent preparation of its biosynthetic descendants,[7] the trichothecenes **7**.

Prediction of the stereochemical outcome of any synthetic sequence involving formation and subsequent rearrangement of **5** requires knowledge of the conformation preferred for the latter step. As shown in Figure 1, if a chair-like conformation is adopted, it is the *E* isomer of **5** that provides an aldehyde, **6T**, having the stereochemistry appropriate for generation of **1**; should isomerization occur by way of a boat-like conformation, this same isomer leads to the diastereomeric aldehyde **6B** that would serve as a precursor of **2**. The converse is true for (*Z*)-**5**, of course.

That the chair-like geometry is preferred was demonstrated in the following way. Application of the methodology of eq 2 provided a 60:40 mixture of the isomeric ethers **5**, the major component of which was shown to be (*Z*)-**5** by dissection of the $^1H$ NMR spectrum. Most diagnostic for assignment of relative stereochemistry to the isomers were the multiplets centered at $\delta$ 2.54 and 2.79 that are ascribable to the bis-allylic methylene groups at C-2 of the cyclohexene ring; the lower field resonance is assigned to the *Z* isomer by analogy to data drawn from $^1H$ NMR spectra of *acyclic* enol ethers.[12] Mixtures containing

(1) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427.

(2) Prof. D. Cane (Brown University) has informed us that his research group has been unable to repeat the preparation of an allyl vinyl ether from an allyl formate, as reported in ref 1 (personal communication with permission to cite).

(3) The mixture of **5** has a $^1H$ NMR spectrum consonant with that reported by Suda.[1]. Moreover, its $^{13}C$ NMR spectrum and exact mass are consistent with those expected (see Experimental Section).

(4) Gilbert, J. C.; Weerasooriya, U.; Wiechman, B.; Ho, L. *Tetrahedron Lett.* **1980**, *21*, 5003.

(5) Identified by comparison of mass and $^1H$ NMR spectra with those of authentic **1** and **2**; the latter spectra were kindly provided by Prof. S. C. Welch (University of Houston).

(6) Three highly stereoselective syntheses of *rac*-trichodiene (**1**) have been reported: Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077. Schlessinger, R. H.; Schultz, J. A. *Ibid* **1983**, *48*, 407. Harding, K. E.; Clement, K. S. *Ibid* **1984**, *49*, 3871.

(7) Evans, R.; Hanson, J. R. *J. Chem. Soc. Perkin Trans 1* **1976**, 326.

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(9) Prepared in 53% overall yield from 1-acetyl-2-methylcyclopentene[10a] by oxidation with KOCl,[10bc] followed by reduction of the resulting acid with LAH.[10d]

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**Table I. Stereoselectivity for Rearrangement of Ethers 5**

| entry | % *E*-(5) | % (*Z*)-5 | method[a] | yield, % | % 6T[b] | % 6B[b] | method[a] | selectivity[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | 20 | 80 | A | 70[d] | 30 | 70 | C | 83 |
| 2 | 23 | 77 | B | 73[e] | 27 | 73 | D | 93 |
| 3 | 25 | 75 | A | 84[e] | 33 | 67 | D | 84 |
| 4 | 33 | 67 | B | 75[e] | 40 | 60 | C | 82 |
| 5 | 67 | 33 | A | 80[d] | 63 | 37 | D | 88 |

[a] Methods: A, integration of bis-allylic hydrogens vs. either the alkoxy or vinylic hydrogens of the enol moiety (90-MHz $^1$H NMR spectrum); B, integration of vinylic hydrogen of the enol moiety (200-MHz $^1$H NMR spectrum); C, integration of aldehydic hydrogen (90-MHz $^1$H NMR spectrum); D, integration of aldehydic hydrogen (200-MHz $^1$H NMR spectrum). [b] Structural assignments based on subsequent conversion to **1** and **2**; see text. [c] Preference for chair-like conformation calculated as follows: selectivity = (100)|(% **6T** − % (*Z*)-**5**)/(% (*Z*)-**5** − % (*E*)-**5**)|. [d] Based on analysis by $^1$H NMR spectroscopy. [e] Isolated yield.

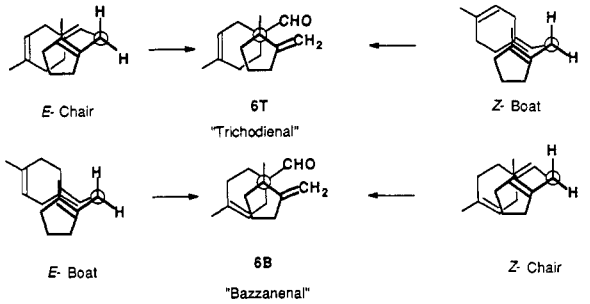



**Figure 1.** Newman projections of conformations for rearrangement of (*E*)-**5** and (*Z*)-**5**.

(*Z*)- and (*E*)-**5** in other proportions were obtained by HPLC of the original mixture.

The results of thermally rearranging each of these mixtures are contained in Table I. In order to assign relative stereochemistries to the aldehydes **6** that were produced, a 33:67 *E*:*Z* mixture of them (entry 3) was reduced (85% yield) to give **1** and **2** in a 1:2 ratio, as shown by analysis of the products by capillary gas chromatography. Consequently, the preferred conformation for the rearrangement of **5** must be *chair-like*, so that this system follows the normal stereochemical course for Claisen rearrangements.[13,14] The data in the table show that the preference is on the order of 85:15; this corresponds to a $\Delta\Delta G^{\ddagger}$ at 150 °C of about 1.8 kcal/mol in favor of the chair-like transition state.

The definition of the conformation for [3,3]-sigmatropic rearrangement of allyl vinyl ethers such as **5** has important ramifications in terms of a diastereoselective synthesis of systems like **1** and **7**. Clearly, the key to success is development of a correspondingly diastereoselective preparation of (*E*)-**5** or its synthetic equivalent. Efforts to accomplish this are presently underway in our laboratories.[15]

## Experimental Section

IR samples were run as liquid films between salt plates; only major absorptions are reported.

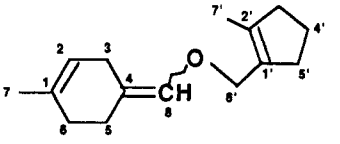
NMR chemical shifts are reported in units of $\delta$ downfield of internal $Me_4Si$. Unless noted otherwise, chloroform-*d* was used as the solvent and as the internal lock for the FT spectra.

HPLC was performed with a Waters Model 6000A instrument equipped with two contiguous 2 ft × $^1/_4$ in. columns packed with LC Porasil (type A) silica gel.

All reagents and solvents were purified according to standard methods.

**(*E*)- and (*Z*)-4-Methyl-1-[[(2-methyl-1-cyclopentenyl)-methoxy]methylene]cyclohex-3-ene (5).** In a 100-mL, round-bottomed flask were placed 0.110 g (1.00 mmol) of 4-methyl-3-cyclohexenone (**8**),[8] 0.400 g (2.00 mmol) of diethyl (diazomethyl)phosphonate,[11] and 1.0 g (9.0 mmol) of 2-methyl-1-cyclopentenemethanol (**9**)[9] at room temperature. To this magnetically stirred solution, kept under an atmosphere of dry nitrogen, was added potassium *tert*-butoxide (0.225 g, 2.10 mmol) in small portions over 0.5 h. After the addition was complete, stirring was continued for 2 h, and then the solution was diluted with an equal volume of pentane. The resulting organic layer was washed with three 25-mL portions of brine, dried ($MgSO_4$), and concentrated to yield crude ethers **5** and unchanged alcohol. The excess alcohol was removed either by distillation at reduced pressure (bp 40 °C (0.1 mmHg)) or by flash chromatography on silica gel with hexanes. Once the alcohol was removed the crude ethers were again subjected to flash chromatography (silica gel/hexanes) to give 0.120 g (50% yield) of (*Z*)-**5** and (*E*)-**5** as a 60:40 mixture that was adjudged to be pure on the basis of $^1$H NMR analysis. Separation of the *Z* isomer was accomplished by HPLC, using either 50% dichloromethane/hexanes or 10% ethyl acetate/hexanes. Recycling was required with both solvent systems to achieve the separation. It was noted that less decomposition occurred with ethyl acetate/hexanes as the eluent, although more recycling was necessary to obtain the same degree of separation.

**Spectral data:** 200-MHz $^1$H NMR ((*Z*)-**5**) $\delta$ 5.88 (br, s, 1 H, enolic vinyl) 5.35 (br s, 1 H, vinyl), 4.23 (br s, 2 H, $ROCH_2R$), 2.78 (m, 2 H, H-2), 2.45–2.25 (m, 4 H, cyclopentyl allylic), 2.10 (m, 2 H, H-6), 2.00 (m, 2 H, H-5), 1.88–1.70 (m, 2 H, cyclopentyl $CH_2$), 1.68 (br s, 3 H, methyl), 1.65 (br s, 3 H, methyl); ((*E*)-**5**) 5.86 (br s, 1 H, enolic vinyl), 5.35 (br s, 1 H, vinyl), 4.23 (br s, 2 H, $ROCH_2R$), 2.53 (m, 2 H, H-6), 2.45–2.25 (m, 6 H, cyclopentyl allylic and H-2), 2.00 (m, 2 H, H-5), 1.88–1.70 (m, 2 H, cyclopentyl $CH_2$), 1.65 (br s, 3 H, methyl), 1.62 (br s, 3 H, methyl); $^{13}$C NMR (peaks denoted by * have been assigned to the *Z* isomer and those by a # to the *E* isomer; the numbering system used is shown on the structure below): 13.9 (C-7′), 21.4 (C-4′), 22.2, 23.7, 25.1, 26.8* (C-3), 29.2 (C-2)#, 30.2, 31.1# (C-3), 31.8* (C-5), 34.6, 35.4, 38.9, 68.0 (C-6′), 113.8* (C-4), 114.3# (C-4), 119.9* (C-2), 122.5# (C-3), 131.9, 133.7* C-1), 134.1# (C-1), 136.9, 138.0# (C-8), 138.1* (C-8); IR 1690 cm$^{-1}$ (s, C=COR); HRMS, calcd for $C_{15}H_{22}O$ *m*/*z* 218.1671, found *m*/*z* 218.1678.




**General Procedure for the Thermolysis of Allyl Vinyl Ethers.** A solution of the allyl vinyl ether (1.00 mmol) in 0.3 g of dry benzene was placed in a base-washed ampule (7 mm o.d. × 5 mm i.d.) and cooled in liquid nitrogen under a blanket of dry

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(14) Substrates that preferentially rearrange by way of boat-like transition states have chair-like conformations that appear to suffer from destabilizing interactions that are not apparent from examination of molecular models of our substrates; e.g., see: Cave, R. J.; Lythgoe, B.; Metcalfe, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1218. Ziegler, F. M.; Thattahill, J. K. *Tetrahedron Lett.* **1982**, *23*, 3581.

(15) The partial support of this research by the Robert A. Welch Foundation, the University Research Institute, and the National Institutes of Health (GM 29972) is gratefully acknowledged.

nitrogen or argon. The sample was then degassed with five freeze–thaw cycles under reduced pressure (ca. 0.05 mmHg) and then sealed while cold. The tube was heated at 170–180 °C for a 2- to 3-h period, allowed to cool to room temperature, and opened. Solvent was removed in vacuo and the residue was purified by flash column chromatography over silica gel.

**(±)-4-Methyl-1-(1-methyl-2-methylenecyclopentyl)-3-cyclohexene-1-carboxaldehyde: Trichodienal (6T) and Bazzanenal (6B).** A 40:60 *E*:*Z* mixture of **5** was thermally rearranged at 180 °C for 2.0 h to give the crude aldehydes **6T** and **6B** in a 40:60 ratio, as determined by analysis of the $^1$H NMR spectrum. Purification over silica gel (10% ethyl acetate/hexanes) afforded a spectroscopically pure mixture of the two aldehydes in 78% yield.

**Spectral data**: 200-MHz $^1$H NMR δ 9.80 (s, 0.6 H, aldehydic), 9.60 (0.4 H, aldehydic), 5.40 (br s, 1 H, H-3), 5.05 (br s, 1 H, *exo*-vinyl), 4.78 (br s, 1 H, *exo*-vinyl), 2.5–1.4 (m, 12 H, H-2, H-5, H-6, cyclopentyl $CH_2$), 1.60 (br s, 3 H, allylic methyl), 1.00 (s, 3 H, methyl); IR 1725 cm$^{-1}$ (s, C=O).

**(±)-1,4-Dimethyl-1-(1-methyl-2-methylenecyclopentyl)-1-cyclohexene: Trichodiene (1) and Bazzanene (2). Method A.** A 20:80 mixture of allyl vinyl ethers (*E*)-**5** and (*Z*)-**5** (70 mg; 0.3 mmol) in 0.5 mL of dry 1-butanol was placed in an base-washed glass ampule (7 mm o.d., 5 mm i.d.), under dry argon at room temperature. To this was added a solution containing anhydrous hydrazine (32 mg, 1.0 mmol) and potassium *tert*-butoxide (80 mg, 0.7 mmol) in 0.5 mL of 1-butanol, to give a homogeneous yellow solution. The sample was then degassed with five successive freeze–thaw cycles and sealed at ca. 0.1 mmHg pressure. The tube was heated in an oil bath at 200–210 °C for 3.5–4.0 h, during which time the reaction mixture became clear. After cooling, the tube was opened and and its contents were diluted with 5 mL of pentane. The separated organic layer was washed 4 times with 5-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo to yield a light yellow oil. Chromatography over 5 g of silica gel (pentane) afforded a fraction containing 50 mg (82%) of a 40:60 mixture of natural products **1** and **2**.[5]

**Spectral data**: 200-MHz $^1$H NMR δ 5.30 (m, 1 H, C=CH), 4.97 (br s, 1 H, exocyclic C=CH), 4.79 (br s, 0.6 H, *exo*-C=CH), 4.74 (br s, 0.4 H, *exo*-C=CH), 1.60 (br s, 3 H, allylic methyls), 2.3–1.2 (m, 12 H, ring protons), 1.05 (s, 1.2 H, $CH_3$), 1.02 (s, 1.8 H, $CH_3$), 0.86 (s, 1.2 H, $CH_3$), 0.84 (s, 1.8 H, $CH_3$); IR 1638 cm$^{-1}$ (m, C=C); MS (70 eV), *m/e* 204 ($M^+$).

**Method B.** Subjection of a 33:67 mixture of aldehydes **6T** and **6B** to the conditions of method A, and on a similar scale, yielded a 33:67 mixture of trichodiene and bazzanene in 80% yield.

## Insect Sex Pheromones. Stereospecific Synthesis of (*E*)-13,13-Dimethyl-11-tetradecen-1-ol Acetate via a Thiophenol-Mediated Olefin Inversion

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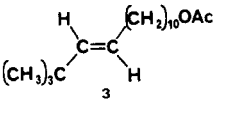
In the course of our study on structure–activity relationships between analogues of the sex pheromone of the European corn borer *Ostrinia nubilalis* (Hübner),[1] the geometrical isomers of 13,13-dimethyl-11-tetradecen-1-ol acetate were required. Coates and Johnson[2] described the synthesis of the cis isomer of an analogous olefin, (2*Z*,6*Z*)-1-(benzyloxy)-3,8,8-trimethyl-2,6-nonadiene, by the Wittig reaction between pivaldehyde and the appropriate phosphorane. They found, however, that even under Schlosser–Wittig conditions,[3] which normally favor formation of *trans*-olefins, in their special case involving a sterically hindered aldehyde, only the cis isomer could be obtained. Coates and Johnson prepared the (2*Z*,6*E*) isomer via a multistage procedure that involved reduction of the *trans*-6,7-enol phosphate with lithium in liquid ammonia as the final olefin-forming step. As an alternative to their approach, we explored the acetylenic route[4] to prepare the two desired compounds.

Alkylation of lithium *tert*-butylacetylide by [(10-bromodecyl)oxy]tetrahydro-2*H*-pyran was carried out in THF/hexamethylphosphorictriamide (HMPT) solvent. Conversion of the crude alkylation product by heating with a 10:1 acetic acid/acetic anhydride mixture gave 13,13-dimethyl-11-tetradecyn-1-ol acetate (**1**). Semihydrogenation of **1** in the presence of $P_2$–nickel[5] yielded (*Z*)-13,13-dimethyl-11-tetradecen-1-ol acetate (**2**).


Two convenient methods are available for the stereospecific trans reduction of isolated triple bonds: reduction with $LiAlH_4$ in refluxing diglyme;[6] reduction with Na in liquid ammonia/THF.[4] However, when **1** was refluxing in diglyme with excess $LiAlH_4$ for 12 h, starting material was recovered quantitatively after reacetylation. Reduction with Na in liquid $NH_3$/THF led only to partial reduction of **1**; ca. 70% of starting material remained after 8 h of contact time with excess Na. GC/MS analysis showed that the product now contained other positional isomers resulting from double-bond migrations. Although a mixture of *trans*-olefinic products could be readily separated by HPLC on an $AgNO_3$-impregnated silica column from acetylenic starting material, this mixture was not amenable to further purification.

As a third alternative for the preparation of the desired trans compound, the equilibration of the corresponding cis isomer in the presence of thiophenol[7] was investigated. At this point, this route looked attractive because separation by HPLC of the expected cis/trans equilibrium mixture would present no problem. When neat **2** was heated with a catalytic amount of thiophenol in a sealed tube to 100 °C,[8] slow isomerization was observed, but equilibrium had not been reached even after 24 h. Increasing the reaction temperature to 140 °C led to a 4:96 cis to trans mixture after 24 h. Refluxing a mixture of **2** and thiophenol in xylene in an inert atmosphere for *1* week led to a crude product that was essentially pure **3**. The




reaction time could be shortened if air was bubbled through the refluxing solution. We supposed that air oxidation must have increased the benzenethiyl radical concentration, leading, in turn, to an increased rate of

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