**Oxidation of 1 with $I_2O_5$ in Ethylene Glycol.** Diphenylacetylene (1.78 g, 10 mmol) and $I_2O_5$ (3.34 g, 10 mmol) were heated in ethylene glycol (70 mL) at 70 °C overnight. After the workup procedure used for the methanol cases, a yellow solid was obtained: 2.05 g; IR ($CHCl_3$) 2950, 1700, 1230, 1110, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.7 (s, 10 H), 7.2–7.5 (m, 20 H). A portion (1.0 g) was crystallized twice from $CHCl_3$ to give white needles: 0.6 g; mp 175–178 °C; IR ($CHCl_3$) 2950, 1230, 1110, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.7 (s, 8 H), 7.2–7.5 (m, 10 H); mass spectrum, *m/e* (relative intensity) 258, 227, 210, 182, 165 149 (100), 105. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C 72.43; H, 6.01. The remainder of the material was subjected to silica gel column chromatography with chloroform as eluant. First fraction: 0.2 g; mp 91–92 °C (benzil). Second fraction: 0.75 g; mp 175–178 °C (diketal). The second fraction had the same IR, NMR, and mass spectral characteristics as those of the material prepared by the reaction of benzil (21 g, 0.1 mol), ethylene glycol (8 mL), and *p*-toluenesulfonic acid (0.5 g) in benzene (150 mL).

**Oxidation of Anisole with $I_2O_5$ in Methanol.** Anisole (1.08 g, 10 mmol) was dissolved in methanol (75 mL) and the solution was refluxed overnight under nitrogen with $I_2O_5$ (3.34 g, 10 mmol). After the aforementioned workup, a red liquid was obtained: 1.3 g; $^1H$ NMR ($CDCl_3$) δ 3.7 (s, 7 H), 3.8 (s, 8 H), 6.65–7.5 (m, 19 H); IR (neat) 1600, 1490, 1470, 1280, 1250, 1030, 820 $cm^{-1}$; mass spectrum, *m/e* (relative intensity) 360 (100), 345 (30), 234 (30), 219 (70), 191 (30), 107 (20), 91 (70).

**Oxidation of 1 with $I_2/I_2O_5$ in Methanol.**[15] Diphenylacetylene (1.78 g, 10 mmol), iodine (10.2 g, 40 mmol), and $I_2O_5$ (1.67 g, 5 mmol) were stirred in methanol (100 mL) for 14 h at room temperature under nitrogen. After the usual workup the residue from evaporation of the $CH_2Cl_2$ was treated with $CCl_4$. Insoluble white crystals of diiodostilbene (125 mg) were collected. The $CCl_4$ was evporated. A portion (1.35 g) of the $CCl_4$-soluble products was chromatographed on silica gel. First fraction: 36 mg; $^1H$ NMR ($CD_2Cl_2$) δ 3.3 (s, 9 H), 7.0 (s, 7 H), 7.3 (s, 9 H). Second fraction: 637 mg; $^1H$ NMR δ 3.3 (s, 19 H), 7.0 (s, 14 H); compound **5**. Third fraction: 193 mg; $^1H$ NMR δ 3.1 (s, 9 H), 3.35 (s, 18 H), 3.65 (s, 6 H), 7.0–8.0 (m, 35 H). Fourth fraction: 401 mg; $^1H$ NMR δ 3.1 (s, 23 H), 7.1–8.1 (m, 34 H); compound **3**.

**Oxidation of 1 with $I_2$–HgO in Methanol.** Diphenylacetylene (1.78 g, 10 mmol) was treated with iodine (10.16 g, 40 mmol) and mercuric oxide (2.16 g, 10 mmol) in methanol under nitrogen for 24 h. After the usual workup, a red oil was obtained: 1.6 g; $^1H$ NMR ($CDCl_3$) δ 3.2 (s, 7 H), 3.4 (s, 1 H), 3.7 (s, 1 H), 7.1–8.2 (m, 20 H); IR (neat) 1735, 1700, 1450, 1230, 1110, 1060 $cm^{-1}$.

**Registry No.** 1, 501-65-5; 2, 134-81-6; 3, 24650-42-8; 4, 93-58-3; 5, 39787-30-9; 6, 25062-95-7; 7, 51552-62-6; $H_2IO_6$, 10450-60-9; $I_2O_5$, 12029-98-0; $I_2$, 7553-56-2; ethylene glycol, 107-21-1; anisole, 100-66-3.

(15) This experiment was performed by M. Cohen, New York University.

# Improved Synthesis of the Perhydroindenone Precursor of Dendrobine

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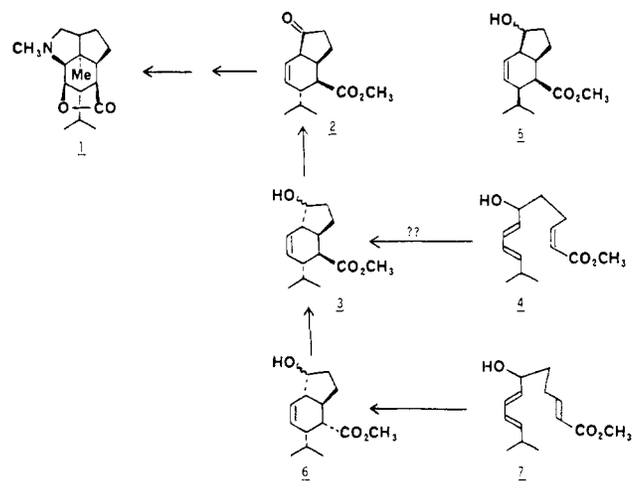
An improved synthesis of the perhydroindenone precursor (**2**) of dendrobine is described. The route requires only eight steps from 4-pentynoyl chloride (**8**) and proceeds in greater than 20% overall yield. The key step of this synthesis is the exo intramolecular Diels–Alder cyclization of (*Z,E,E*)-triene **14**.

We recently described a total synthesis of (±)-dendrobine (**1**) which proceeded via perhydroindenone **2** and alcohol **3**.[1] In considering routes to these intermediates, we recognized that each of the stereocenters in **3** could *formally* be introduced from **4** by an intramolecular Diels–Alder reaction. However, this approach was not pursued because it was assumed that the cyclization **4** → **3**, an exo Diels–Alder reaction, would be disfavored relative to the endo pathway leading to **5**, a useless stereoisomer of **3**. Rather, intermediates **2** and **3** were synthesized from **7** as indicated in Scheme I. During the course of these studies we discovered that the assumption regarding **4** was incorrect,[2] since alcohols **3** are, in fact, the major products of the Diels–Alder reaction of **4**. Subsequently, we have found that the unexpected behavior of **4** is general for trienes of this type.[3] We report herein on an improved synthesis of **2** by a route which utilizes the exo cycloaddition reaction of **14** as the key step.

The new route to **2** is outlined in Scheme II. The known acid chloride **8**[4] was transformed via the imidazolide **9**[5] (2.0 equiv of imidazole, THF, 98%; mp 85–87 °C)[6] into phosphorane **10** (mp 141–144 °C; 2.0 equiv of $(C_6H_5)P{=}CH_2$, $C_6H_6$)[7] by standard procedures in 80% overall yield. Condensation of **10** with 4-methylpent-2(*E*)-enal[8] in re-

Scheme I

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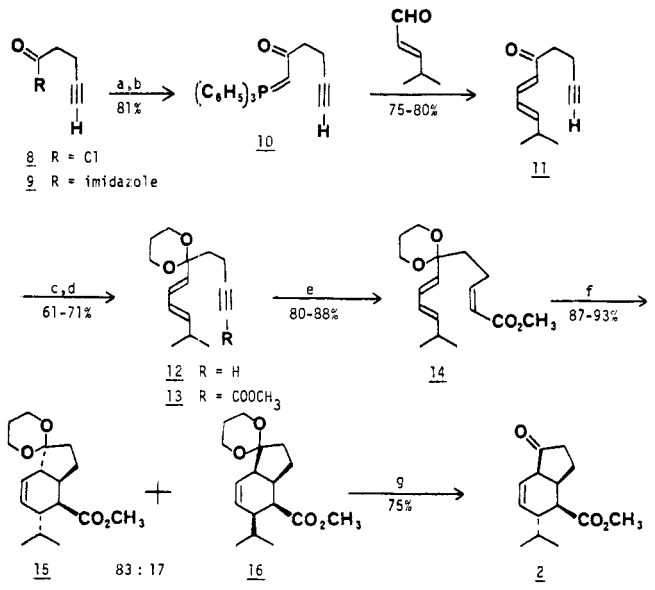
0022-3263/80/1945-4283$01.00/0 

Scheme II[a]




[a] (a) Imidazole, THF, 98%; (b) $(C_6H_5)_3P{=}CH_2$, $C_6H_6$, 82%; (c) 2-methoxy-1,3-dioxane, $HOCH_2CH_2CH_2OH$, *p*-TsOH, 68–75%; (d) *n*-$C_4H_9Li$, THF, −78 °C, then $CH_3OCOCl$, −78 → +23 °C, 90–95%; (e) $H_2$, 5% Pd/$CaCO_3$, 80–88%; (f) 180 °C, 0.5 h, then 1 N NaOH, $CH_3OH$, 23 °C, 3 h, 87–93%; (g) 1 N HCl, DME, 23 °C, 12 h, 75%.

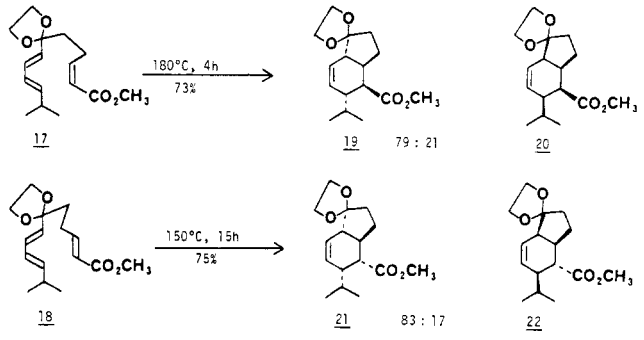
fluxing benzene afforded ketone **11** in 75–80% yield. This intermediate has been synthesized previously by a somewhat longer sequence.[9] Treatment of **11** with 2-methoxy-1,3-dioxane,[10] propylene glycol, and *p*-TsOH afforded 68–75% of **12**, carbomethoxylation (*n*-$C_4H_9Li$, THF, −78 °C followed by $CH_3OCOCl$, −78 → +23 °C) of which afforded 90–95% of **13**. Finally, Lindlar hydrogenation[11] of **13** ($H_2$, 10% w/w of 5% Pd/$CaCO_3$, lead poisoned) afforded 80–88% of **14**, the substrate for the Diels–Alder reaction.

Cyclization of **14** (toluene, sealed tube, 180 °C, 0.5 h) followed by mild alkaline hydrolysis (1 N NaOH, $CH_3OH$, 23 °C, 3 h) to remove residual uncyclized triene afforded 87–93% of a 83:17 mixture of **15** and **16**. The major product was assigned structure **15** on the basis of spectroscopic evidence and by eventual conversion to **2**. In particular, the $^1H$ NMR signal for the C4 H of **15** ($\delta$ 2.77) appears as a doublet ($J$ = 4.9 Hz) which is characteristic of trans-fused perhydroindene Diels–Alder adducts having an axial carbomethoxyl group flanked by a pseudoaxial alkyl group at C5.[1-3] In addition, the IR spectrum contains a weak C=C stretching vibration centered at 1645 $cm^{-1}$ which is also characteristic of a trans-fused perhydroindene cycloadduct. In fact, we have found that IR spectroscopy is most useful in assigning ring-fusion stereochemistry to cycloadducts of this type since, without exception, the C=C stretch of trans-fused isomers occurs at 1640–1645 $cm^{-1}$, whereas this vibration for cis-fused stereoisomers, if observable, occurs at 1650–1655 $cm^{-1}$.[3] The $^1H$ NMR signal for the C4 H ($\delta$ 2.93) of the minor cycloadduct **16** appears as a triplet ($J$ = 5 Hz). The multiplicity and coupling constants of this resonance are typical of cis-fused cycloadducts having an axial carbomethoxyl group flanked by a pseudoequatorial isopropyl group at C5.[1-3]

The mixture of **15** and **16** obtained in this manner proved to be difficult to separate and was therefore used in the next step without separation. Thus, hydrolysis (1 N HCl, DME, 23 °C, 8 h) of this mixture followed by chromatographic purification afforded **2** directly in 75% yield (65–70% from **14**). The trans-fused ketone corresponding to **15** was not detected in the hydrolysis mixture, which is not surprising since we have previously observed that this isomer readily epimerizes to **2**.[1]

This synthesis of **2** is shorter and more efficient than the original route. Whereas the original method required ten steps and proceeded in 11–12% overall yield starting from methyl 4-(diethylphosphono)crotonate,[1] the present route requires but eight steps and proceeds in greater than 20% overall yield from **8**.

In connection with these studies we have also examined the Diels–Alder reactions of **17** and **18**. As would be




expected on the basis of our previous studies,[2,3] the major product in each case possesses a trans ring fusion, and the product selectivity again seems to be independent of dienophile stereochemistry.[12] Unsurprisingly, the spectroscopic properties of **19** [NMR $\delta$ 2.81 (d, $J$ = 5.3 Hz, C4 H); IR 1645 $cm^{-1}$] and **20** [NMR $\delta$ 2.97 (t, $J$ = 5.1 Hz, C4 H)] are very similar to the data reported for **15** and **16**. The spectroscopic data for **21** [NMR $\delta$ 2.75 (dd, $J$ = 10.5, 7.2 Hz, C4 H); IR 1640 $cm^{-1}$] leaves little doubt about the stereochemistry of this compound, since the coupling constants involving the C4 H are characteristic of trans-fused perhydroindene cycloadducts having an equatorial carbomethoxyl group flanked by an axial isopropyl group at C5.[1-3] In principle, Diels–Alder adduct **19** might also serve as a precursor to perhydroindenone **2**. However, attempts to achieve this transformation have not been successful, as a number of products are obtained when **19** is subjected to acid hydrolysis conditions.

## Experimental Section

$^1H$ NMR spectra were measured at 60 MHz on Perkin-Elmer R-24B and Varian T-60 instruments, at 250 MHz on a Bruker 250 instrument, and at 270 MHz on a Bruker 270 instrument located at the NMR Facility, Francis Bitter National Magnet Laboratory. Chemical shifts are reported in $\delta$ units relative to internal $Me_4Si$. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotometer and were calibrated with the 1601-$cm^{-1}$ absorbtion of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High-resolution mass spectra were provided by the Facility supported by NIH Grant RR0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Divison of Research Resources, and were obtained on a CEC 21-110B high-resolution mass spectrometer equipped with an IBM 1800 computer system to process data recorded on photographic plates. Elemental analyses were performed by Robertson Laboratories. Melting points were recorded on a Fisher-Johns hot-stage melting point apparatus and are uncorrected.

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(12) Control experiments were performed to establish that each of the cyclizations reported in the text is a kinetically controlled process.

All reactions were conducted in oven-dried (120 °C) or flame-dried glassware under atomospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from Na–benzophenone ketyl; $CH_2Cl_2$ and $Me_2SO$ were distilled from $CaH_2$; benzene was distilled from $LiAlH_4$; toluene was distilled from sodium metal. Preparative thin-layer chromatography (TLC) was performed by using 20 × 20 cm plates coated with 0.5- and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chromatography was performed using activity I Woelm silica gel. All chromatography solvents were distilled prior to use.

***N*-(Pent-4-ynoyl)imidazole (9).**[5] To a solution of 2.33 g of **8**[4] (20.0 mmol) in 21 mL of THF was added 2.72 g of imidazole (40.0 mmol). The resulting mixture was stirred at 23 °C for 30 min, and then all solids were removed by filtration with ether. The filtrate was concentrated in vacuo, giving 2.92 g of pure imidazolide **9** (98%): mp 85–87 °C (THF); NMR ($Me_2SO$-$d_6$, 60 MHz) δ 8.3 (br s, 1 H), 7.5 (br s, 1 H), 6.9 (br s, 1 H), 3.1 (t, $J$ = 7 Hz, 2 H, $CH_2CO$), 2.7 (t, $J$ = 2 Hz, 1 H, C≡CH), 2.3 (m, 2 H); IR ($CH_2Cl_2$) 3300, 3160, 3140, 2930, 2130, 1740, 1530, 1475, 1390 $cm^{-1}$; mass spectrum, $m/e$ 148 (parent ion). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.77; H, 5.45; N, 18.79.

**[(Pent-4-ynoyl)methylidene]triphenylphosphorane (10).** Methyltriphenylphosphonium bromide (6.21 g, 17.4 mmol) was suspended in 385 mL of benzene at 23 °C. To this suspension was added 11.7 mL of 1.5 M phenyllithium in benzene–ether (7:3, 17.6 mmol), and the resulting mixture was stirred vigorously overnight. A solution of 1.20 g (8.11 mmol) of **9** in 50 mL of benzene was added dropwise. After the mixture was stirred for 1 h at 23 °C, the solids were removed by filtration, and the filtrate was washed with 50 mL of half-saturated aqueous $NaHCO_3$. The aqueous phase was washed with ether (3 × 20 mL), and then the combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to give 3.54 g of crude, crystalline **10**. Recrystallization of this material from EtOAc–hexane gave 2.18 g (75%) of pure **10**, mp 134–139 °C. A second crop afforded an additional 0.36 g of less pure material, the purity of which was estimated to be 60% by condensation with 4-methylpent-2(*E*)-enal which afforded 48% of **11** (with pure **10** the yield of **11** is 75–80%). The second crop therefore contained 0.22 g (7%) of **10**. The analytical sample was recrystallized three times from EtOAc–hexane: mp 141–144 °C; NMR ($CDCl_3$, 60 MHz) δ 7.20–7.90 (m, 15 H), 2.55 (m, 4 H), 1.90 (m, 1 H); IR ($CH_2Cl_2$) 3300, 3060, 3040, 2960, 2920, 2115, 1530 $cm^{-1}$; mass spectrum, $m/e$ 356 (parent ion). Anal. Calcd for $C_{24}H_{21}PO$: C, 80.88; H, 5.94. Found: C, 80.63; H, 6.06.

**10-Methylundeca-6(*E*),8(*E*)-dien-1-yn-5-one (11).** A solution of 712 mg (2.00 mmol) of recrystallized **10** in 7 mL of benzene was treated with 235 mg (2.4 mmol) of 4-methylpent-2(*E*)-enal.[8] This mixture was refluxed overnight, and then all volatile components were removed in vacuo. Chromatography of the residue over 10 g of silica gel using 10% ether–hexane as eluant afforded 266 mg of pure **11** (75%): NMR ($CCl_4$, 60 MHz) δ 7.25 (m, 1 H), 6.18 (s, 2 H), 6.00 (d, $J$ = 15 Hz, 1 H), 2.75 (m, 2 H), 2.35 (m, 2 H), 1.80 (t, $J$ = 2 Hz, 1 H), 1.05 (d, $J$ = 7 Hz, 6 H); IR (neat) 3305, 2970, 2120, 1690, 1665, 1635, 1595 $cm^{-1}$; mass spectrum, $m/e$ 176 (parent ion); high-resolution mass spectrum, calcd for $C_{12}H_{16}O$ $m/e$ 176.12011, found $m/e$ 176.12063.

**10-Methyl-5-oxoundeca-6(*E*),8(*E*)-dien-1-yne Propylene Ketal (12).** 2-Methoxy-1,3-dioxane was prepared as follows.[10] A mixture of 14 mL (125 mmol) of triethyl orthoformate, 10 mL (138 mmol) of 1,3-propanediol, and a small crystal of *p*-TsOH was stirred at room temperature. MeOH was removed by distillation at reduced pressure, and the residual, crude, mixed ortho ester was used without further purification.

Ketone **11** (380 mg, 2.16 mmol) was combined with 1.78 g (23.4 mmol) of 1,3-propanediol and 0.92 g (7.8 mmol) of crude 2-methoxy-1,3-dioxane in 4 mL of THF containing a small crystal of *p*-TsOH at 23 °C. The reaction was monitored by analytical TLC [7:1 hexane–ether: $R_f$(**12**), 0.4, $R_f$(**11**) 0.3]. When complete, the reaction was quenched with half-saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with hexane (4×). Then the combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to give the crude product. This material was purified by preparative thin-layer chromatography (PTLC) on two 2-mm silica gel plates (7:1 hexane–ether), giving 336 mg (68%) of pure **12**:[13] NMR ($CDCl_3$, 60 MHz) δ 5.2–6.4 (m, 4 H), 3.8 (m, 4 H), 2.2 (m, 3 H), 1.75 (m, 4 H), 1.35 (m, 1 H), 1.0 (d, $J$ = 7 Hz, 6 H); IR (neat) 3310, 2935, 2870, 2125, 1655 $cm^{-1}$; mass spectrum, $m/e$ 234 (parent ion); high-resolution mass spectrum, calcd for $C_{15}H_{22}O_2$ $m/e$ 234.1620, found $m/e$ 234.1643.

**Methyl 11-Methyl-6-oxododeca-7(*E*),9(*E*)-dien-2-ynoate Propylene Ketal (13).** Ketal **12** (325 mg, 1.39 mmol) was dissolved in 12 mL of THF and cooled to −78 °C. To this solution was added 0.90 mL of 2.4 M *n*-butyllithium in hexane (2.11 mmol). After 15 min at −78 °C, 300 mg (0.250 mL, 3.17 mmol) of methyl chloroformate was added, and the reaction was then allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ was added, and this two-phase mixture was stirred for 20 min. This mixture was extracted with ether (3×), and the combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to give the crude product. This material was purified by PTLC (one 2-mm silica gel plate, 5:1 hexane–ether), giving 394 mg (97%) of pure **13**:[13] NMR ($CCl_4$, 60 MHz) δ 5.20–6.55 (m, 4 H), 3.8 (m, 4 H), 3.65 (s, 3 H), 2.35 (m, 3 H), 1.80 (m, 3 H), 1.35 (m, 1 H), 1.05 (d, $J$ = 7 Hz, 6 H); IR (neat) 2965, 2875, 2245, 1720, 1655, 1620 $cm^{-1}$; mass spectrum, $m/e$ 292 (parent ion); high-resolution mass spectrum, calcd for $C_{17}H_{24}O_4$ $m/e$ 292.167 46, found $m/e$ 292.168 51.

**Methyl 11-Methyl-6-oxododeca-2(*Z*),7(*E*),9(*E*)-trienoate Propylene Ketal (14).** A solution of 212 mg (0.726 mmol) of **13** in 4 mL of toluene was hydrogenated over 20 mg of Lindlar catalyst (5% Pd/$CaCO_3$, lead poisoned). The progress of the reaction was monitored by $H_2$ uptake and by TLC (1% EtOAc–$CH_2Cl_2$, two developments: $R_f$(**14**) 0.60, $R_f$(**13**) 0.75). When **13** could no longer be detected by analytical TLC (UV analysis), the catalyst was removed by filtration, and toluene was removed in vacuo. Chromatography of the product on a 2-mm silica gel plate (1% EtOAc–$CH_2Cl_2$, two developments) afforded 17 mg (8%) of recovered **13** and 171 mg (80%, 87% based on unrecovered **13**) of triene **14**:[13] NMR ($CDCl_3$, 250 MHz) δ 6.27 (m, 2 H), 6.07 (dd, $J$ = 15.0, 10.4 Hz, 1 H), 5.73 (m, 2 H: $H_{10}$ superimposed on $H_2$, $J_{2,3}$ = 11.5 Hz, $J_{9,10}$ = 15 Hz, $J_{10,11}$ = 7 Hz), 5.49 (d, $J_{7,8}$ = 15.4 Hz, $H_7$), 3.94 (dt, $J$ = 2.5, 11.9 Hz, 2 H), 3.80 (ddd, 11.9, 4.9, 2.5 Hz, 2 H), 3.69 (s, 3 H), 2.74 (q, $J$ = 7.6 Hz, 2 H, $H_4$), 2.35 (m, 1 H, $H_{11}$), 2.02 (m, 1 H), 1.75 (m, 2 H), 1.29 (m, 1 H), 1.03 (d, $J$ = 6.7 Hz, 6 H); IR (neat) 2965, 2875, 1725, 1645 $cm^{-1}$; mass spectrum, $m/e$ 294 (parent ion); high-resolution mass spectrum, calcd for $C_{17}H_{26}O_4$ $m/e$ 294.183 11, found $m/e$ 294.183 05. Anal. Calcd: C, 69.36; H, 8.90. Found: C, 69.90; H, 9.03.

**Methyl 5α-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroinden-1-one-4β-carboxylate (2).** A solution of 95 mg (0.32 mmol) of triene **14** in 4 mL of toluene was transferred to a resealable Carius tube. 2,6-Di-*tert*-butyl-4-methylphenol (4 mg, 0.02 mmol) was added, and the resulting mixture was degassed with a stream of argon. The sealed tube was heated at 180 °C for 30 min in an oil bath, and then all volatile components were removed in vacuo. The residue was dissolved in 4.5 mL of a 4:1 $CH_3OH$–1 N NaOH solution. This mixture was stirred for 3 h at room temperature. It was then diluted with saturated aqueous $NaHCO_3$ and was extracted with ether (3×). The combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to give 93 mg (93%) of a 83:17 mixture of **15** and **16** (GC analysis; 6-ft, 10% SE-30 on Chromosorb G column, 150 °C). The spectroscopic data for **15** and **16** in this mixture are in excellent agreement with those obtained for **19** and **20** (vide infra). Data for **15**: NMR ($CDCl_3$, 250 MHz) δ 6.02 (br d, $J$ = 10.4 Hz, 1 H), 5.68 (dt, $J$ = 10.4, 3 Hz, 1 H), 3.91 (m, 4 H), 3.66 (s, 3 H), 2.77 (d, $J$ = 4.9 Hz, $H_4$), 0.95 (d, $J$ = 6.7 Hz, 3 H), 0.92 (d, $J$ = 6.7 Hz, 3 H); IR (neat) 3030, 2960, 2870, 1730, 1645 $cm^{-1}$; mass spectrum, $m/e$ 294 (parent ion). Data for **16**: NMR ($CDCl_3$, 250 MHz) δ 5.97 (ddd, $J$ = 10.6, 3.7, 2.5 Hz 1H), 5.82 (br d, $J$ = 10.6 Hz, 1 H), 3.91 (m, 4 H), 3.62 (s, 3 H), 2.93 (t, $J$ = 5 Hz, $H_4$), 0.98 (d, $J$ = 7 Hz, 3 H), 0.89 (d, $J$ = 7 Hz, 3 H).

A solution of 93 mg (0.316 mmol) of the mixture of **15** and **16** in 10 mL of DME, 2.2 mL of distilled $H_2O$, and 1.0 mL of 1 N HCl was stirred for 8 h at room temperature. The reaction was then diluted with saturated aqueous $NaHCO_3$ and was extracted

(13) It is not possible to effectively purify **12–14**, **17**, **23**, or **24** by distillation (Kugelrohr) since these compounds readily undergo intramolecular Diels–Alder reactions.

with hexane (4×). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated to give crude **2**. This material was purified by chromatography on a 0.5-mm silica gel plate developed with 1:1 ether–hexane, giving 53 mg (75% from **15**–**16**; 70% from **14**) from the major band. This material was recrystallized from hexane. After one recrystallization, **2** had a melting point of 63–66 °C; the analytical sample previously described had a melting point of 62–67 °C after one recrystallization and 69–71 °C after three recrystallizations.[1] The NMR, IR, and mass spectra of **2** so obtained were in complete agreement with the data previously reported.

**Synthesis and Diels–Alder Reaction of 17. (a) 10-Methyl-5-oxoundeca-6(*E*),8(*E*)-dien-1-yne Ethylene Ketal (23).** A solution of 560 mg (3.18 mmol) of **11**, 1.33 g (12.8 mmol) of 2-methoxy-1,3-dioxolane,[10] 2.39 g (38.5 mmol) of ethylene glycol, and one small crystal of *p*-TsOH in 10 mL of dry THF was stirred at 23 °C. The progress of the reaction was monitored by analytical TLC (silica gel, 10% ether–hexane: $R_f$ (**11**) 0.40, $R_f$ (**23**) 0.70). When complete (48 h in this case), the reaction was quenched with saturated aqueous $NaHCO_3$ and was extracted with hexane (3×). The combined extracts were dried ($Na_2SO_4$), filtered, and evaporated to give 1.08 g of crude product. This material was purified by PTLC (two 2-mm silica gel plates, 7:1 hexane–ether), giving 585 mg (84%) of ethylene ketal **23**:[13] NMR ($CCl_4$, 60 MHz) δ 5.15–6.45 (m, 4 H), 3.80 (br s, 4 H), 1.85–2.40 (m, 5 H), 1.80 (t, $J$ = 1 Hz, 1 H), 1.00 (d, $J$ = 7 Hz, 6 H); IR (neat) 3300, 2970, 2120, 1655 $cm^{-1}$; low-resolution mass spectrum shows no parent ion; high-resolution mass spectrum, calcd for $C_{14}H_{20}O_2$ $m/e$ 220.146 33, found $m/e$ 220.145 22.

**(b) Methyl 11-Methyl-6-oxododeca-7(*E*),9(*E*)-dien-2-ynoate Ethylene Ketal (24).** A solution of 305 mg (1.39 mmol) of **23** in 10 mL of THF at −78 °C was carbomethoxylated by using 0.90 mL of 2.45 M *n*-butyllithium in hexane (2.10 mmol) and 265 mg (2.80 mmol) of methyl chloroformate as described for **13**. The crude product was purified by PTLC (two 2-mm silica gel plates, 6:1 hexane–ether), giving analytically pure **24**:[13] 363 mg (94%); NMR ($CCl_4$, 60 MHz) δ 5.15–6.50 (m, 4 H), 3.85 (br s, 4 H), 3.65 (s, 3 H), 2.40 (m, 3 H), 1.95 (m, 2 H), 1.00 (d, $J$ = 7 Hz, 6 H); IR (neat) 2975, 2250, 1715, 1660 $cm^{-1}$; mass spectrum, $m/e$ 278 (parent ion). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.02; H, 7.84.

**(c) Methyl 11-Methyl-6-oxododeca-2(*Z*),7(*E*),9(*E*)-trienoate Ethylene Ketal (17).** Acetylene **24** (109 mg, 0.39 mmol) was hydrogenated in 2 mL of toluene in the presence of 12 mg of Lindlar catalyst (5% Pd/$CaCO_3$, lead poisoned). The progress of the reaction was monitored by $H_2$ uptake and by TLC (3% EtOAc–$CH_2Cl_2$; $R_f$(**24**) 0.70, $R_f$(**17**) 0.60). The reaction was stopped when **24** could no longer be detected by TLC (UV analysis). The crude product (107 mg) obtained by filtration of the catalyst and evaporation of all volatile components was chromatographed (one 0.5-mm silica gel plate, 1% EtOAc–$CH_2Cl_2$) to give pure **17**:[13] 96 mg (87%); NMR ($CDCl_3$, 250 MHz) δ 6.29 (m, 2 H, $H_3$, superimposed on another 1-H signal), 5.99 (dd, $J$ = 15.3, 11.0 Hz, 1 H), 5.75 (br d, $J$ = 11.3 Hz, $H_2$), 5.71 (dd, $J$ = 15.3, 6.7 Hz, $H_{10}$), 5.47 (d, $J$ = 15.3 Hz, $H_7$), 3.92 (m, 4 H), 3.70 (s, 3 H), 2.77 (br q, $J$ = 7 Hz, 2 H, $H_4$), 2.33 (m, 1 H, $H_{11}$), 1.86 (t, $J$ = 7 Hz, 2 H, $H_5$), 1.01 (d, $J$ = 6.7 Hz, 6 H); IR (neat) 2975, 1725, 1645 $cm^{-1}$; mass spectrum, $m/e$ 280 (parent ion). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.37; H, 8.53.

**(d) Methyl 5α-(2-Propyl)-2,3,3aα,4,5,7aβ-hexahydroinden-1-one-4β-carboxylate Ethylene Ketal (19) and Methyl 5β-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroinden-1-one-4β-carboxylate Ethylene Ketal (20).** A solution of triene **17** (308 mg, 1.10 mmol) in 10 mL of toluene in a resealable Carius tube was degassed with a stream of $N_2$. The tube was then sealed and heated at 180 °C for 4 h in an oil bath. The volatile components were removed in vacuo to give the crude product. GC analysis (10-ft, SE-30 on Chromosorb G column, 170 °C) of this material indicated the presence of ~10% of uncyclized triene and two new compounds with $R_f$ 41 min (**19**, 79%) and 54 min (**20**, 21%). These isomers were separated by PTLC (three 0.5-mm silica gel plates, 10% $Et_2O$–hexane, three developments) to give 180 mg (58%) of **19** and 45 mg (15%) of **20**.

Data for **19**: NMR ($CDCl_3$, 270 MHz) δ 5.92 (br d, $J$ = 10 Hz, 1 H), 5.68 (dt, $J$ = 10, 3 Hz, 1 H), 3.95 (m, 4 H), 3.68 (s, 3 H), 2.81 (d, $J$ = 5.3 Hz, $H_4$), 2.47 (br d, $J$ = 12.7 Hz, 1 H), 2.31 (m, 1 H), 0.99 (d, $J$ = 7 Hz, 3 H), 0.95 (d, $J$ = 7 Hz, 3 H); IR (neat) 3040, 2975, 2880, 1735, 1645 $cm^{-1}$; mass spectrum, $m/e$ 280 (parent ion). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.77.

Data for **20**: NMR ($CDCl_3$, 270 MHz) δ 5.94 (m, $J$ = 10 Hz, 1 H), 5.77 (m, $J$ = 10 Hz, 1 H), 3.93 (m, 4 H), 3.66 (s, 3 H), 2.97 (t, $J$ = 5.1 Hz, $H_4$), 2.73 (m, 1 H), 2.60 (m, 1 H), 1.00 (d, $J$ = 7 Hz, 3 H), 0.90 (d, $J$ = 7 Hz, 3 H); IR (neat) 3040, 2960, 2880, 1735 $cm^{-1}$; mass spectrum, $m/e$ 280 (parent ion); high-resolution mass spectrum, calcd for $C_{16}H_{24}O_4$ $m/e$ 280.167 46, found $m/e$ 280.166 78.

**Synthesis and Diels–Alder Reaction of 18. (a) Methyl 11-Methyl-6-oxododeca-2(*E*),7(*E*),9(*E*)-trienoate (25).** Trifluoroacetic anhydride (306 mg, 1.47 mmol) in 0.5 mL of dry $CH_2Cl_2$ was added dropwise to a solution of 153 mg (1.96 mmol) of $Me_2SO$ in 2 mL of $CH_2Cl_2$ at −78 °C.[14] Ten minutes later, a solution of 232 mg (0.98 mmol) of methyl 6-hydroxy-11-methyldodeca-2(*E*),7(*E*),9(*E*)-trienoate[1] in 1.3 mL of $CH_2Cl_2$ was added. This mixture was stirred for 40 min at −78 °C before 0.4 mL (2.88 mmol) of $Et_3N$ was added. The reaction mixture was warmed to room temperature and then was diluted with saturated $NaHCO_3$. The aqueous phase was separated and was extracted with ether (2×). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated in vacuo, giving the crude product, which was purified by preparative TLC (one 2-mm silica gel plate, 7:1 hexane–ether) to give the trienone **25**: 158 mg (68%); NMR ($CCl_4$, 60 MHz) δ 6.75–7.45 (m, 2 H), 5.65–6.45 (m, 4 H), 3.65 (s, 3 H), 2.05–3.00 (m, 5 H), 1.05 (d, $J$ = 7 Hz, 6 H); IR (neat) 2975, 1730, 1690, 1660, 1640, 1600 $cm^{-1}$; the low-resolution mass spectrum shows no parent ion.

**(b) Methyl 11-Methyl-6-oxododeca-2(*E*),7(*E*),9(*E*)-trienoate Ethylene Ketal (18).** Without further purification ketone **25** (131 mg, 0.55 mmol) was ketalized with 187 mg (1.8 mmol) of 2-methoxy-1,3-dioxolane, 320 mg (5.16 mmol) of ethylene glycol, and one crystal of *p*-TsOH according to the procedure described for **25**. Chromatography of the crude product (one 2-mm silica gel plate, 4:1 hexane–ether) gave 118 mg (76%) of pure **18**: NMR ($CCl_4$, 60 MHz) δ 6.95 (dt, $J$ = 16, 6 Hz, $H_3$), 5.2–6.4 (m, 5 H), 3.82 (br s, 4 H), 3.65 (s, 3 H), 2.25 (m, 3 H), 1.80 (m, 2 H), 1.02 (d, $J$ = 7 Hz, 6 H); IR (neat) 2965, 1725, 1660 $cm^{-1}$; mass spectrum $m/e$ 280 (parent ion); high-resolution mass spectrum, calcd for $C_{16}H_{24}O_4$ $m/e$ 280.197 46, found $m/e$ 280.165 40.

**(c) Methyl 5α-(2-Propyl)-2,3,3aα,4,5,7aβ-hexahydroinden-1-one-4α-carboxylate Ethylene Ketal (21) and Methyl 5β-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroinden-1-one-4α-carboxylate Ethylene Ketal (22).** A solution of 37 mg of **18** dissolved in 5 mL of toluene was transferred to a resealable Carius tube and was throughly degassed with a stream of argon. The tube was sealed and then was heated at 150 °C for 15 h in an oil bath. Toluene was then removed in vacuo. The resulting crude product was treated with NaOH in aqueous $CH_3OH$ at 23 °C to remove residual uncyclized triene. A standard workup of the resulting mixture afforded 28 mg (75%) of a mixture of **21** and **22** (83:17 at determined by GC analysis: 10-ft, 4% SE-30 on Chromosorb G column, 170 °C). This mixture could not be separated by silica gel chromatography. However, a chromatographed sample was crystallized from hexane to give pure **21**: mp 58.5–61.0 °C; NMR ($CDCl_3$, 250 MHz) δ 5.92 (br d, $J$ = 10.4 Hz, 1 H), 5.68 (ddd, $J$ = 10.4, 3.2, 2.2 Hz, 1 H), 3.96 (m, 4 H), 3.69 (s, 3 H), 2.75 (dd, $J$ = 10.5, 7.2 Hz, $H_4$), 2.64 (m, 1 H), 0.98 (d, $J$ = 7 Hz, 3 H), 0.89 (d, $J$ = 7 Hz, 3 H); IR ($CH_2Cl_2$) 3030, 2960, 2880, 1735, 1640 $cm^{-1}$; mass spectrum, $m/e$ 280 (parent ion). Anal. Calcd for $C_{16}H_{24}O_4$: $m/e$ 280.167 46. Found: $m/e$ 280.169 77.

Isomer **22** was characterized only as a mixture with **21**. The characteristic NMR signals for **22** are as follows: 5.71 (s, 2 H), 0.79 (d, $J$ = 7 Hz, 3 H). The signals for $OCH_2CH_2O$, $OCH_3$, and the second isopropyl $CH_3$ group are coincident with those of **21**.

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**Registry No.** 2, 74763-43-2; 7, 71516-83-1; 8, 55183-44-3; 9, 37794-60-8; 10, 74763-44-3; 11, 74763-45-4; 12, 74763-46-5; 13, 74763-47-6; 14, 74763-48-7; 15, 74763-49-8; 16, 74806-92-1; 17, 74763-50-1; 18, 74763-51-2; 19, 74763-52-3; 20, 74806-93-2; 21, 74806-94-3; 22, 74806-95-4; 23, 74763-53-4; 24, 74763-54-5; 25, 74763-55-6; imidazole, 288-32-4; methyltriphenylphosphonium bromide, 1779-49-3; 4-methylpent-2(*E*)-enal, 24502-08-7; 2-methoxy-1,3-dioxane, 17230-31-8; 1,3-propanediol, 504-63-2; methyl chloroformate, 79-22-1; ethylene glycol, 107-21-1.

# Regio- and Stereoselectivity in the Ene Reaction of *N*-Phenyl-1,2,4-triazoline-3,5-dione with α,β-Unsaturated Carbonyl Substrates

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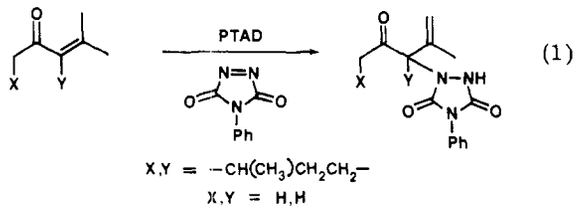
*N*-Phenyltriazoline-3,5-dione reacts with α,β-unsaturated ketones, esters, and lactones **1a–l** to give ene adducts **2a–l**. The reactions usually proceed in good yield with high regioselectivity and, where possible, high stereoselectivity. Ene substrates capable of adopting an s-cis conformation show much greater reactivity. A variety of mechanistic interpretations is considered.

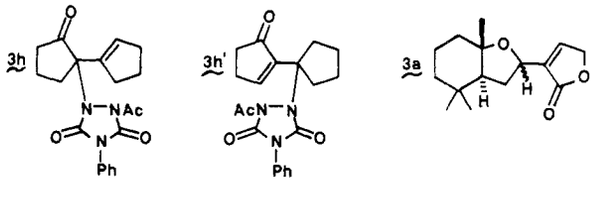
The ene reaction between an olefin bearing an allylic hydrogen atom (ene) and a multiple π bond (enophile) is a well-documented[2a] and powerful[2b,c] transformation. In the vast majority of these reactions the olefinic ene partner is an electron-rich double bond. In the course of another synthetic study we encountered a need to allylically functionalize compound **1a** and observed its efficient transformation into **2a** (see entry 1, Table I) upon exposure to *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD). This result was somewhat surprising in view of the reported[3] mode of reaction of PTAD with pulegone and mesityl oxide (eq 1), since each of these substrates gave rise to β,γ-unsaturated carbonyl products whereas **1a** led specifically to the allylically transposed α,β-unsaturated lactone **2a**. We therefore investigated the reaction of PTAD with a variety of α,β-unsaturated carbonyl substrates in an attempt to define the structural parameters responsible for these differences in reactivity. In contrast to the voluminous literature on singlet oxygen ene selectivity with unsymmetrical electron-rich olefins,[4] a recent communication by Magnus and co-workers[5a] and reports by Butler et al.[5b] appear to be the only reports of similar studies with PTAD as the enophile. Herein we report the results of our study of the reaction between electron-deficient olefins (i.e., carbonyl-substituted olefins) and PTAD.



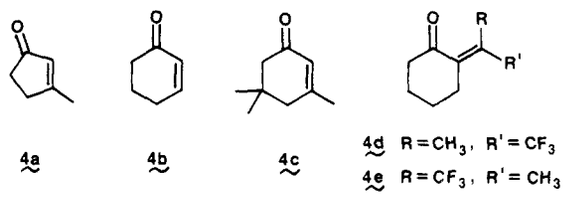

(1)

## Results

In Table I are listed the α,β-unsaturated carbonyl ene substrates **1a–l** which were allowed to react with PTAD (1.0 equiv) at room temperature in methylene chloride ($CH_2Cl_2$) or deuteriochloroform ($CDCl_3$). The substrates were converted with high regioselectivity (with the exception of **1h**) and, where detectable (entries 12, 13), high stereoselectivity to the ene adducts **2a–l** in good yields. While some of these adducts were crystalline, others were amorphous solids or oils, and all behaved poorly when subjected to silica gel chromatography. Thus, it was in general difficult to assay for minor regio- and stereoisomeric products beyond the limits of $^1H$ NMR analysis of the crude reaction mixtures (5–10% detection limits, depending upon product structure). Late in the study it was discovered that the ene adducts **2** could be acetylated at the free NH group. The crude products **2h** and **2h′** were derivatized in this manner, and the resulting acetamides **3h** and **3h′** could be readily separated chromatographically. In a similar attempt to acetylate and separate the epimeric ene adducts **2a**, we observed a facile base-induced ring closure to the epimeric tetrahydrofurans **3a**. Further synthetic aspects of this cyclization will be discussed elsewhere.




Enones **4a–e** did not react with PTAD at room temperature in $CDCl_3$ even after several days. Product ene adducts containing both a β,γ-enone moiety and an α-hydrogen atom (i.e., **2b** and **2c**) underwent partial isom-

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