Competing Diels–Alder intramolecular pathways from cross-conjugated trienes: Fused hydrindenones (bicyclo[4.3.0]nonenones) vs. bridged-ring (bicyclo[3.3.1]nonenones) adducts from a diene-transmissive precursor[1]

Matthew D. Clay, Ditte Riber, and Alex G. Fallis

Abstract: D-Isoascorbic acid was converted to the tetraenone **12** to examine its behaviour in the intramolecular Diels–Alder reaction with pendant dienes in a diene-transmissive environment. These studies were directed toward the synthesis of the hydrindenone nucleus via a tether-controlled Diels–Alder reaction. It was anticipated that this would lead to a diene-transmissive strategy for steroids such as Desogestrel®. In contrast to our previous studies with decalins, the dominant isomer (150 °C) was the bicyclo[3.3.1]nonadieneone adduct **23**, and none of fused adduct **27** was detected. These products were accompanied by two minor hydrindenone adducts **24** and **25**. The isomer ratio was dependent on the temperature of the reaction.

Key words: Diels–Alder, hydrindane, pentadienylation, intramolecular cycloaddition, bicyclo[3.3.1]nonenone.

Résumé : L'acide D-isoascorbique a été transformé en tétraénone **12** dans le but d'étudier son comportement dans la réaction intramoléculaire de Diels–Alder avec des dièns pendants, dans un environnement permettant une transmission. Ces études ont été dirigées vers la synthèse du noyau hydrindénone via une réaction de Diels–Alder contrôlée par une laisse. Il était prévu que cette méthode permettrait de développer une stratégie diénique permettant une transmission pour réaliser la synthèse de stéroïdes tel le Desogestrel®. Par opposition aux études antérieures réalisées dans ce laboratoire avec des décalines, l'isomère dominant (150 °C) est l'adduit bicyclo[3.3.1]nonadiénone **23** et on n'a pas détecté la présence du produit condensé **27**. Ces produits étaient accompagnés de deux adduits hydrindénones mineurs, **24** et **25**. Le rapport des isomères varie avec la température de la réaction.

Mots clés : Diels–Alder, hydrindane, pentadiénylation, cycloaddition intramoléculaire, bicyclo[3.3.1]nonénone.

[Traduit par la Rédaction]

Introduction

Despite decades of research, the total synthesis of steroid nuclei by improved strategies continues to receive considerable attention. A short synthesis of unnatural steroids, such as the oral contraceptive Desogestrel®, has proved particularly challenging (1).

Previously we reported the enantioselective synthesis of *cis*-decalins via intramolecular Diels–Alder reactions (2). These strategies employed either planar or isopropylidene tether control groups to bias the stereochemistry of the adducts. We discovered that *cis*-acetonides are preferred compared with *trans*-acetonides. The cycloadditions directed by *cis*-acetonides (**1**) occurred under milder conditions and allowed for the introduction of an inside methyl group into the decalin adducts (Scheme 1). Because of the unfavourable *trans*-geometry of the diene induced by this substituent, its introduction is often a challenge in related intermolecular cycloadditions.

We have also extended this tether control group protocol to the stereoselective construction of highly oxygenated nor-steroid and nor-triterpenoid skeletons via a diene-transmissive Diels–Alder strategy (3). A key step in our approach was the selective indium-mediated γ-pentadienylation of the appro-

Received 20 September 2004. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 14 June 2005.

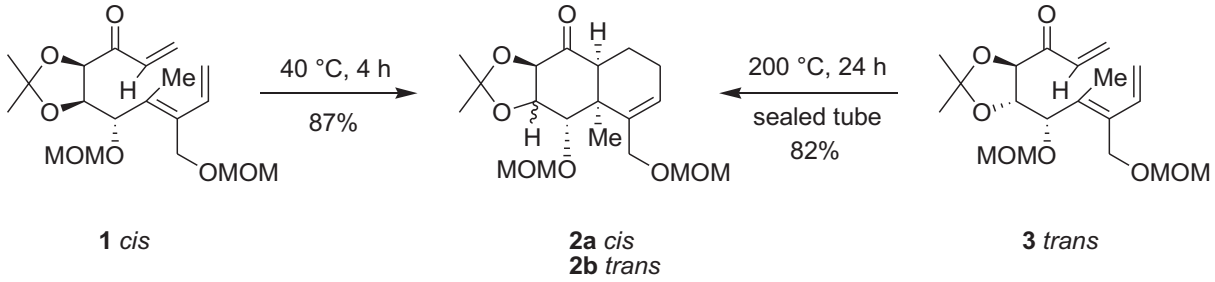
This paper is dedicated to Professor Howard Alper. Presented with respect and gratitude for his contributions to organometallic chemistry and to our friendship.

M.D. Clay, D. Riber,[2] and A.G. Fallis.[3] Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, ON K1N 6N5, Canada.

[1]This article is part of a Special Issue dedicated to Professor Howard Alper.
[2]Present address: Department of Chemistry, University of Aarhus, DK-8000, Aarhus, Denmark.
[3]Corresponding author (e-mail: afallis@science.uottawa.ca).

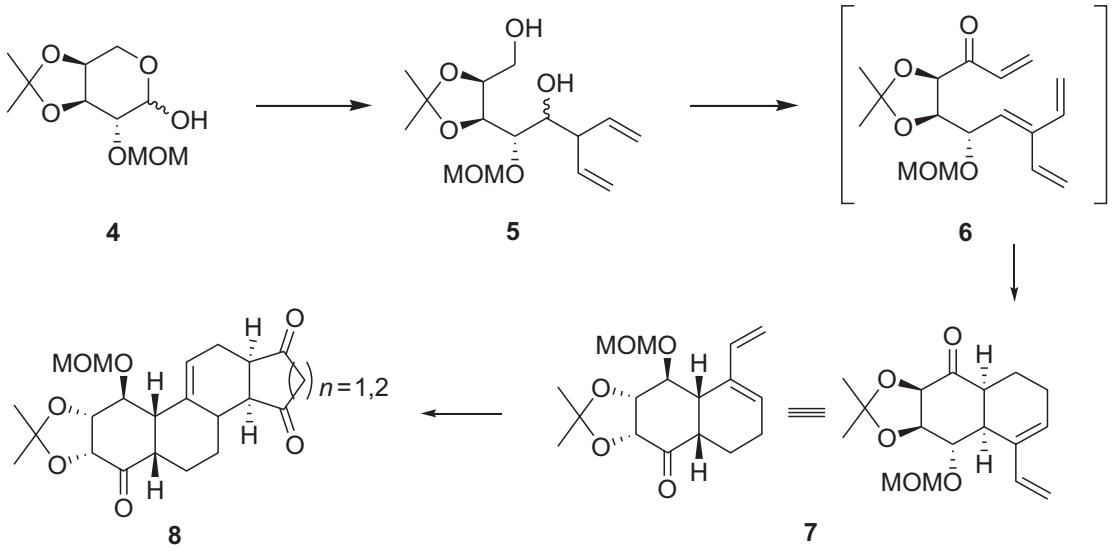
 doi: 10.1139/V05-055

Scheme 1. Cycloadditions controlled by *cis*- and *trans*-acetonides.



1 *cis* **2a** *cis* **2b** *trans* **3** *trans*

Scheme 2. A diene-transmissive Diels–Alder approach to steroids.



4 **5** **6** **7** **8**

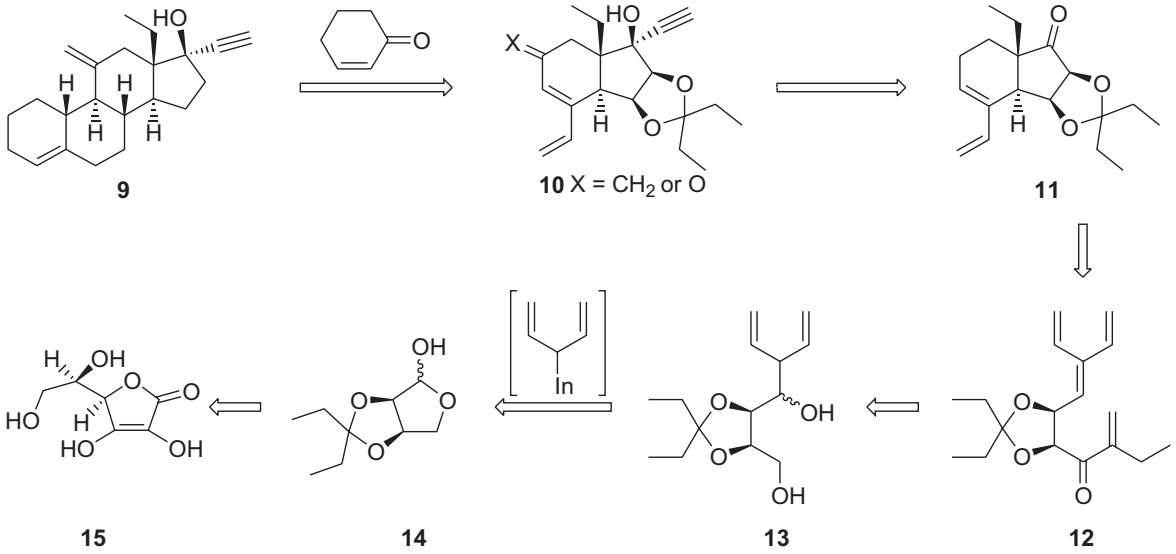
priate aldehyde-hemiacetal **4** derived from L-arabinose. Elimination of water from the product **5**, as illustrated in Scheme 2, afforded the cross-conjugated triene **6**. Sequential cycloaddition reactions rapidly produced the tetracyclic nor-steroid or nor-terpenoid core structures **8** (4).

The versatility of this protocol prompted us to investigate the reverse synthetic strategy for steroids in which the hydrindane portion would be constructed first by a related tether-controlled cycloaddition reaction, followed by a second intermolecular cyclization. The challenge of efficiently and stereoselectively synthesizing the *trans*-fused hydrindane system of steroids is well recognized. Previous successful solutions have been based on an intramolecular ester enolate alkylation (5) or on the Lewis acid assisted cyclization of a suitably substituted dienone (6). Strategies involving an intramolecular Diels–Alder cyclization as the key step have also been employed (7).

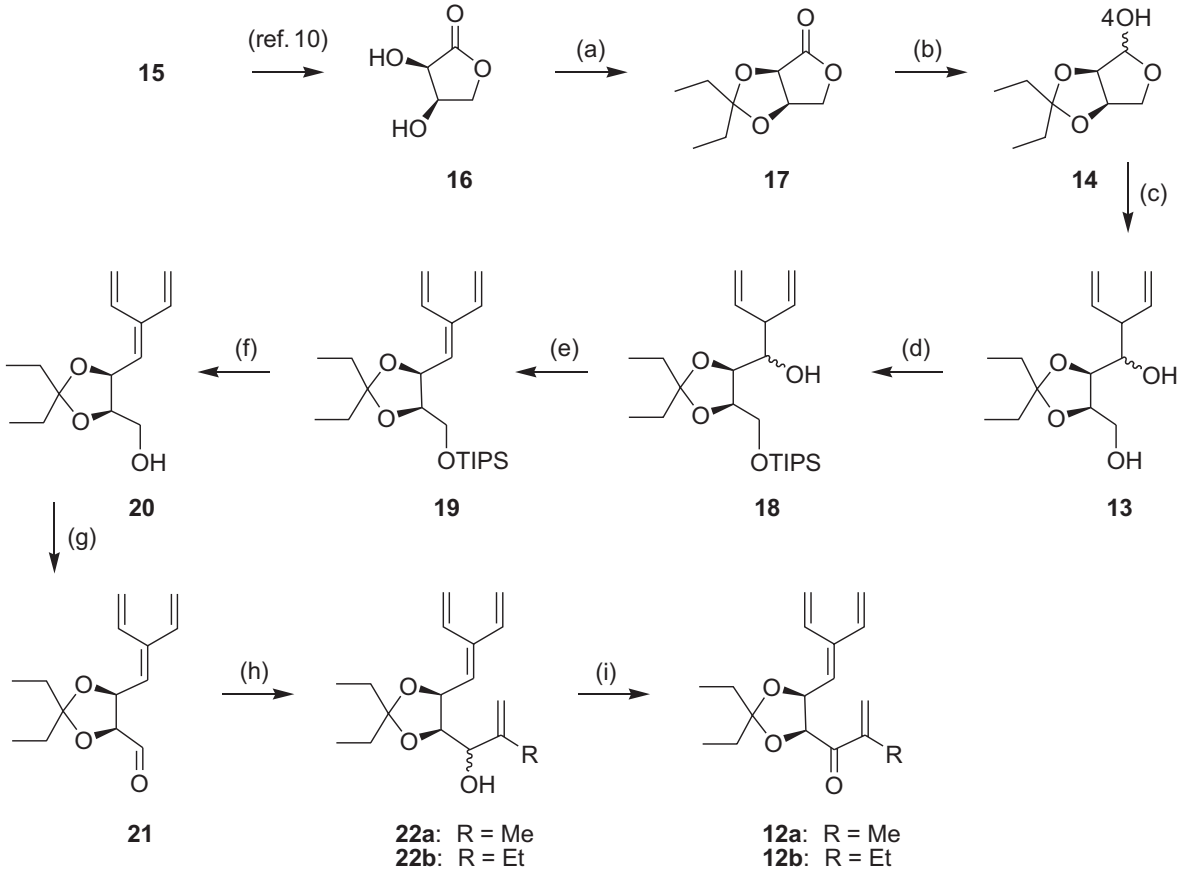
To explore the feasibility of our protocol for the construction of the *trans*-fused hydrindane ring system of steroids, a widely prescribed oral contraceptive, Desogestrel® (**9**), was selected as a commercially important and challenging target. The initial industrial synthesis of Desogestrel® required 24 steps from diosgenin, the cost of which was partially offset by the potent activity of the drug (0.150 mg per pill) (8). The ethyl group at C13 of Desogestrel® is responsible for a 50-fold enhancement in activity compared with the methyl analogue. Corey et al. (1*a*) have demonstrated that this modest structural change presents a significant complication in its synthesis. In his initial synthesis, Corey surmounted this challenge by starting with the ethyl substituted Wieland–Miescher ketone (1*a*). A more recent solution employs an oxazaborolidinium-catalyzed Diels–Alder reaction as a key step (1*b*).

Our strategy to Desogestrel® envisaged sequential Diels–Alder cycloadditions in which the CD ring system was initially constructed via a tether-controlled intramolecular Diels–Alder reaction, followed by an intermolecular cycloaddition to provide the AB rings, as outlined retrosynthetically in Scheme 3. The AB rings of Desogestrel® (**9**) should arise from a Diels–Alder reaction of **10** (exocyclic alkene or ketone) with a suitable cyclohexanone derivative using Northrup and MacMillan's imine-catalyzed protocol (9). The hydrindane portion **11** could be generated via a tether-controlled intramolecular Diels–Alder reaction of triene **12**. An unknown variable in this approach was whether the hydrindane portion could be generated in acceptable yield and with the desired stereoselectivity, especially in view of the large number of unsaturated centers in the tetraenone. An earlier model study using an isopropylidene acetal gave poor selectivity in the Diels–Alder reaction, so we chose to protect the diol of **14** as an isopentylidene acetal. It was anticipated that the additional steric bulk of the acetal would help to differentiate the competing Diels–Alder transition states and would improve the selectivity of the initial cycloaddition. The Diels–Alder precursor **12** can be synthesized from **13**, a product arising from an indium-mediated penta-

Scheme 3. Retrosynthetic route to Desogestrel®.



Scheme 4. Synthesis of Diels–Alder precursors **12a** and **12b**.



dienylation of lactol **14**. This enantiomerically pure lactol can be easily prepared from D-isoascorbic acid (**15**).

Results and discussion

Our synthesis commenced with the known oxidative degradation of D-isoascorbic acid to generate the enantiopure *cis*-diol **16** (Scheme 4) (10). Acetalization of **16** with 3-pentanone and a catalytic amount of *p*-toluenesulfonic acid using a Dean–Stark apparatus provided *cis*-isopentylidene acetal **17** in 92% yield after distillation. Reduction of the lactone moiety with diisobutylaluminum hydride gave lactol **14** in 87% yield as a 5:1 mixture of diastereomers, epimeric at C4. Indium-mediated pentadienylation onto the aldehyde

Table 1. Summary of Diels–Alder reactions.

Entry	Conditions	Results[a]
1	Et_2AlCl, CH_2Cl_2, –78 °C (2 h) (R = Me)	Starting material
2	Et_2AlCl, CH_2Cl_2, –78 °C (30 min) to 21 °C (4 h) (R = Me)	Starting material
3	Et_2AlCl, CH_2Cl_2, –78 °C (30 min) to 42 °C (4 h) (R = Me)	Partial decomposition
4	BF_3OEt_2, CH_2Cl_2, –78 °C (4 h) (R = Me)	Starting material
5	BF_3OEt_2, CH_2Cl_2, –78 °C (30 min) to 0 °C (1 min) (R = Me)	Complete decomposition
6	HN(*i*-Pr)$_2$, $HClO_4$, H_2O, 0 °C (16 h) (R = Et)	Starting material
7	HN(*i*-Pr)$_2$, $HClO_4$, H_2O, rt (24 h) (R = Et)	Starting material
8	HN(*i*-Pr)$_2$, $HClO_4$, EtOH, 0 °C (6 h) to rt (16 h) (R = Et)	Starting material
9	HN(*i*-Pr)$_2$, $HClO_4$, EtOH, 0 °C (5 min) to 65 °C (6 h) (R = Et)	Starting material
10	*p*-TsOH, $HO(CH_2)_2OH$, PhH, 80 °C (20 h) (R = Et)	3 isomers (23:21:56)[b]
11	Toluene, 75 °C (6 days) (R = Me)	3 isomers (28:24:48)[b]
12	Toluene, 150 °C, microwave (3 h) (R = Me)	3 isomers (41:20:39)[b]
13	Toluene, 150 °C, microwave (3 h) (R = Et)	3 isomers (53:17:30)[b]

[a]Ratio determined by NMR integration.
[b]Ratio of **23**:**24**:**25**.

of the open-chain form of the lactol provided diol **13** in 82% yield as a variable mixture of diastereomers. This was inconsequential as this secondary alcohol stereocenter was removed later in the synthesis. Selective protection of the primary alcohol as a triisopropylsilyl ether provided **18** in 93% yield (as a mixture of diastereomers).

Mitsunobu-type dehydration of **18** with three equivalents each of triphenylphosphine and diethyl azodicarboxylate generated triene **19**. Interestingly, the minor isomer of **18** was resistant to dehydration. Whereas reaction of the major isomer (of the mixture) was complete within one day, dehydration of the minor isomer required three days, and often additional reagents (PPh_3 and DEAD) were required. This is likely because of steric hindrance about the reaction center caused by the isopentylidene acetal and the bulky triisopropylsilyl protecting group. Experimentally, triene **19** was isolated in 44% yield, and subsequent desilylation with tetrabutylammonium fluoride provided **20** in 82% yield. The low yield of the dehydration step was attributed to the instability of **19**, which readily decomposed during column chromatography or upon storage in a refrigerator for short periods. Thus a one-pot reaction sequence, in which **18** was first dehydrated and then desilylated to **20** without isolation of intermediate **19**, was investigated. We were gratified to achieve a higher yield of crude **20** from the one-pot procedure (~71%, compared with 36% over the two separate steps). However, **20** could not be easily separated from several impurities generated during the dehydration phase. Thus the preferred experimental method to ensure purity was the original two-step sequence.

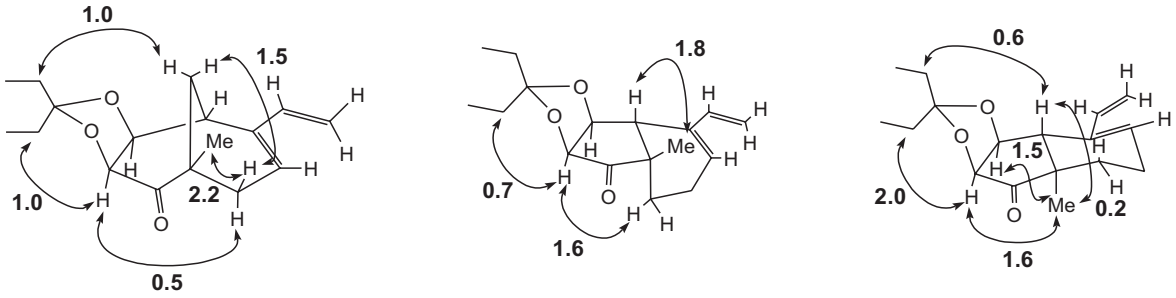
Oxidation of the alcohol of trienol **20** also proved challenging. Oxidation occurred under a variety of conditions (e.g., Collins, Corey–Schmidt, IBX, Dess–Martin, Swern), but the product aldehyde slowly decomposed under the reaction conditions. In accord with earlier observations (11), a substantial rate enhancement occurred when water was added to the Dess–Martin oxidation of **20**. This technique pushed the oxidation to completion before noticeable decomposition of the product aldehyde had occurred and provided stable aldehyde **21** in an isolated yield of 74%. Addition of *iso*-propenyllithium or *sec*-butenyllithium (generated from the corresponding bromides via lithium–halogen exchange) to the aldehyde provided allyl alcohols **22a** and **22b**, respectively. It was subsequently discovered that addition of the Grignard reagent to the aldehyde was more efficient on larger scales and afforded **22a** and **22b** in 58% and 53% yields, respectively. Oxidation of both compounds was accomplished using the Dess–Martin periodinane–water combination (described above) and provided Diels–Alder precursors **12a** and **12b** in 78% and 72% yield, respectively.

We initially attempted the Diels–Alder reaction on the simpler model system **12a** (rather than the ethyl analogue **12b**). However, once this material was consumed, subsequent reactions were conducted using **12b**. The details of these Diels–Alder studies are presented in Table 1. It was initially believed that a Lewis acid mediated cycloaddition at low temperature would provide the best selectivity. Therefore, the cycloaddition was attempted with either diethylaluminum chloride or boron trifluoride etherate as Lewis acid catalysts. However, neither gave any trace of cycloaddition products at low temperatures, and only decomposition was observed at higher temperatures (entries 1–5). In both cases, the decomposition products were not the free diol from Lewis acid assisted cleavage of the isopentylidene acetal. Apparently the increased bulk created by Lewis acid association with the carbonyl inhibits the beneficial effect anticipated from the electronic activation.

An attempt to induce the cycloaddition using a variation of MacMillan's imine-catalyzed procedure was also examined (9). Diisopropylamine was employed as the amine component, in place of the more complex amine used by MacMillan. Unfortunately, despite several attempts, no reaction or decomposition occurred, even in the presence of perchloric acid and refluxing ethanol (entries 6–9).

We next attempted the cycloaddition under thermal conditions. Heating tetraene **12a** in the microwave at 150 °C for 3 h gave a mixture of Diels–Alder adducts in 78% yield. The individual isomers were separated by preparative HPLC, and their structures and relative stereochemistry were determined by NOESY and COSY NMR experiments. The significant

Fig. 1. Significant nOe interactions in Diels–Alder adducts **23**, **24**, and **25**.



23 **24** **25**

nOe interactions are illustrated in Fig. 1. We were intrigued to find that the major isomer was the unexpected bicyclo[3.3.1]nonadieneone **23** rather than one of the anticipated hydrindenone isomers.

The highest ratio of the bicyclo[3.3.1]nonenone isomer **23** was obtained with the ethyl substrate **12b** (53:17:30, **23**:**24**:**25**) upon heating in a microwave oven at 150 °C for 3 h in toluene (entry 13). In contrast, under identical microwave conditions, the methyl substrate **12a** afforded only a slight excess of **23** (41:20:39) (entry 12). The ratio changed to favor formation of hydrindenone **25** (28:24:48) when the temperature was lowered to 75 °C. The reaction required 6 days at this temperature for completion (entry 11). In an attempt to change the electronic environment in the precursor **12b**, acetalization of the ketone of **12b** was attempted using ethylene glycol and catalytic *p*-toluenesulfonic acid in refluxing benzene (80 °C) for 20 h (entry 10). To our surprise, the acetal did not form; rather, **12b** underwent the Diels–Alder reaction to generate **25** as the major isomer in a ratio of 23:21:56 (**23**:**24**:**25**). This ratio was similar to the thermal reaction in toluene at 75 °C. The substantially shorter reaction time (20 h vs. 6 days) indicated the rate influence from ketone protonation by the *p*-toluenesulfonic acid.

Examination of the transition states in Fig. 2 suggests that formation of the desired *trans*-isomer **27** was disfavored by steric repulsion between the R group of the dienophile and the "extra" vinyl group of the diene as illustrated in **26**. This hypothesis was supported by the fact that this Diels–Alder precursor can rotate to avoid this interaction (**28**) and preferentially generate the bicyclic isomer **23**, with lesser amounts of **24** and **25**. It is also interesting that the *cis*-hydrindenone **24**, from transition state **30**, was formed in approximately the same quantity under all conditions. It was anticipated that the steric repulsion between the acetal ethyl group and the R group of the dienophile would disfavor this adduct formation. This is partly why the large isopentylidene acetal was chosen instead of the smaller isopropenyl acetal used in model studies.

General experimental

All non-aqueous reactions were performed under a positive pressure of dry nitrogen in flame-dried glassware using dry solvents. Tetrahydrofuran and diethyl ether were distilled from sodium–benzophenone. Dichloromethane, toluene, triethylamine, and methyl vinyl ketone were distilled from calcium hydride. Standard inert atmosphere techniques were employed in handling air- and moisture-sensitive reagents. *n*-BuLi solutions in hexanes from Aldrich Chemical Company (Oakville, Ont.) were titrated prior to use against diphenylacetic acid and used directly. Starting materials were purchased from Aldrich Chemical Company (Oakville, Ont.) and used without further purification unless otherwise stated.

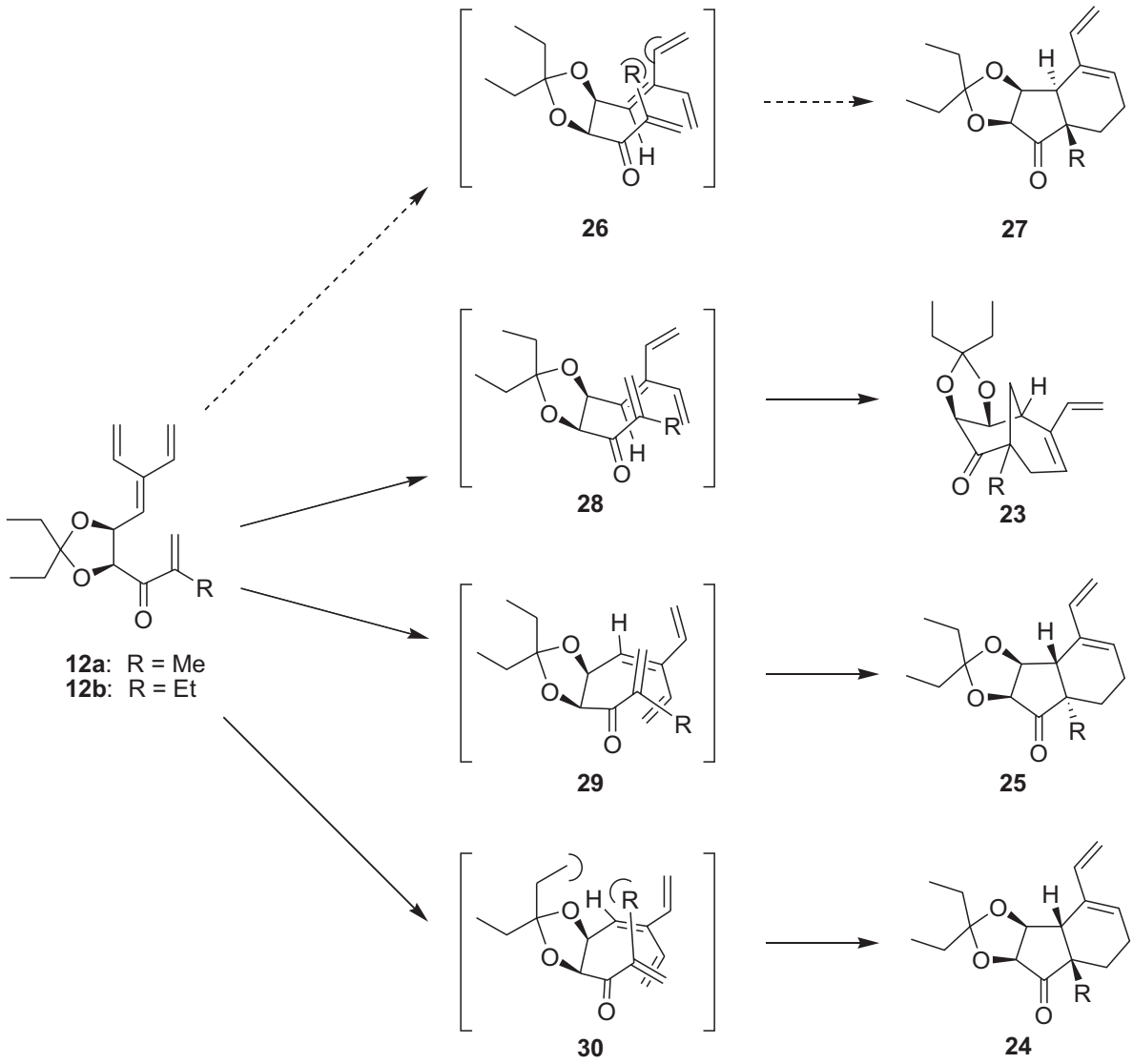
Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254} (E. Merck, Darmstad, Germany). TLC spots were developed by heating the plate after treatment with a 5% solution of ammonium molybdate in 10% aqueous sulphuric acid or a solution of $KMnO_4$ in aqueous potassium hydroxide. Room temperature corresponds to 21 °C. Anhydrous magnesium sulfate ($MgSO_4$) was used to dry solutions in organic solvents. Excess solvents were removed (concentrated) in vacuo at pressures obtained by a water or air aspirator connected to a Büchi rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with E. Merck Silica Gel 60 (230–400 mesh). Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30–60 °C.

Melting points were determined with a Thomas Hoover Unit melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat thin films or as a solution of the sample in $CDCl_3$ or $CHCl_3$ in a sodium chloride solution cell. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FT-IR). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were run on a Brucker AMX500 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. ^{1}H NMR data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet), coupling constants (Hz), and integration). Low-resolution mass spectroscopy (MS), using electron impact (EI), was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV. High-resolution mass spectroscopy (HR-MS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam energy of 70 eV. The purity of all title compounds was judged to be >95% as determined by a combination of ^{1}H NMR and ^{13}C NMR analyses.

3,4-Dihydroxy-dihydro-furan-2-one (16)

The title compound was prepared according to the literature procedure (10). mp 103–104 °C (lit. (10) value mp 97.5–99.5 °C). IR (neat, cm^{-1}) ν: 3421, 3281, 2989, 2922, 2867, 1773, 1154, 1105, 1031, 970. ^{1}H NMR (500 MHz,

Fig. 2. Transition states leading to various adducts.



D_2O) δ: 4.77 (d, *J* = 4.9 Hz, 1H), 4.65 (dd, *J* = 4.9, 3.0 Hz, 1H), 4.59 (dd, *J* = 10.8, 3.0 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ: 178.2 (C), 72.5 (CH_2), 69.2 (CH), 68.4 (CH). EI-MS *m/z* (%): 118 ([M]$^+$, 3), 73 (26), 60 (91), 56 (100), 43 (56). HR-MS calcd. for $C_4H_6O_4$ ([M]$^+$): 118.0242; found: 118.0268.

2,2-Diethyl-dihydro-furo[3,4-d][1,3]dioxol-4-one (17)

Diol **16** (14.00 g, 0.1186 mol), 3-pentanone (125 mL, 1.186 mol), and *p*-toluenesulfonic acid (2.0 g, catalytic) were dissolved in benzene (150 mL) and refluxed overnight using a Dean–Stark apparatus. The solution was then cooled to room temperature, and the majority of the solvent and excess 3-pentanone were removed by rotary evaporation at a bath temperature of ~50 °C. The remaining brown-coloured oil was distilled under aspirator pressure using a propane burner. The title compound collected as a pale brown oil (20.38 g, 92%) over a fluctuating (the aspirator pressure varied during the distillation) temperature range of 160–200 °C. IR (neat, cm^{-1}) ν: 2976, 2946, 2880, 1785, 1465, 1183, 1107, 1069, 921. ^{1}H NMR (500 MHz, C_6D_6) δ: 4.17–4.19 (m, 1H), 4.02–4.05 (m, 1H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.54–3.58 (m, 1H), 1.41 (q, *J* = 7.5 Hz, 2H), 1.56 (q, *J* = 7.5 Hz, 2H), 0.75 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.0 (C), 117.7 (C), 75.6 (CH), 74.7 (CH), 70.3 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 7.9 (CH_3), 7.0 (CH_3). EI-MS *m/z* (%): 157 ([M$^+$ – C_2H_5], 45), 57 (100), 29 (85). HR-MS calcd. for $C_7H_{11}O_4$ ([M$^+$ – C_2H_5]): 157.0501; found: 157.0492.

2,2-Diethyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-ol (14)

Lactone **17** (19.0 g, 0.102 mol) was dissolved in CH_2Cl_2 (285 mL) and cooled to –78 °C. A 1.5 mol/L solution of DIBAL-H in THF (81.6 mL, 0.122 mol) was added dropwise over a period of 15 min, after which the solution was stirred for 5 h at –78 °C. The reaction was quenched at –78 °C with MeOH (16.0 mL) and brine (8.0 mL) and allowed to warm to room temperature. Ether (420 mL) and $MgSO_4$ (121 g) were then added under vigorous stirring, and stirring was continued overnight. The mixture was filtered (suction), and the filter cake was washed generously with ether (~1.0 L) in several portions until the presence of prod-

uct was no longer detected in the filtrate (use of a soxlet extractor to extract the product from the filter cake was also effective). The solvent was removed under reduced pressure to yield a colorless oil identified as a 5:1 mixture of diastereomers of the title compound (16.72 g, 87%). Major diastereomer: IR (neat, cm^{-1}) ν: 3425, 2975, 2943, 2883, 1464, 1102, 1075, 929. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.38 (s, 1H), 4.79 (dd, *J* = 6.0, 3.3 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 1H), 4.03–3.92 (m, 2H), 3.18 (1H, bs), 1.65 (q, *J* = 7.5 Hz, 2H), 1.54 (q, *J* = 7.5 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 116.5 (C), 101.9 (CH), 85.3 (CH), 80.2 (CH), 72.1 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 8.3 (CH_3), 7.3 (CH_3). EI-MS *m/z* (%): 159 ([$M^+ - C_2H_5$], 64), 85 (17), 57 (100), 29 (37). HR-MS calcd. for $C_7H_{11}O_4$ ([$M^+ - C_2H_5$]): 159.0657; found: 159.0659.

1-(2,2-Diethyl-5-hydroxymethyl-[1,3]dioxolan-4-yl)-2-vinyl-but-3-en-1-ol (13)

Lactol **14** (5.00 g, 26.56 mmol) was dissolved in DMF (15 mL); the solution was cooled to 0 °C, and 5-bromo-1,3-pentadiene (15.62 g, 106.3 mmol) was added. Indium powder (100 mesh, 6.10 g, 53.13 mmol) was added to the vigorously stirred solution in small portions over a period of 55 min. The dark green mixture was then warmed to room temperature and stirred overnight. The reaction was poured into a vigorously stirred solution of ether (1000 mL) and water (3.2 mL) and stirred for a further 10 min. The mixture was then dried, filtered, and concentrated. Column chromatography (4:1, petroleum ether – ethyl acetate) yielded the title compound as a waxy solid mixture of diastereomers (5.55 g, 82%). Major diastereomer: mp 42.5–44.0 °C. IR (neat, cm^{-1}) ν: 3323, 3245, 2940, 2916, 2880, 1459, 1173, 1081, 920. ^1H NMR (500 MHz, C_6D_6) δ: 6.05–6.14 (m, 2H), 5.06–5.26 (m, 4H), 4.15–4.23 (m, 2H), 3.92 (m, 1H), 3.69–3.74 (m, 1H), 3.56–3.60 (m, 1H), 3.33–3.37 (m, 2H), 2.73 (bs, 1H), 1.57 (q, *J* = 7.5 Hz, 2H), 1.51 (q, *J* = 7.5 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 139.6 (CH), 136.1 (CH), 118.4 (CH_2), 116.4 (CH_2), 112.4 (C), 78.0 (CH), 77.7 (CH), 72.7 (CH), 61.9 (CH_2), 51.4 (CH), 30.5 (CH_2), 29.4 (CH_2), 9.2 (CH_3), 8.4 (CH_3). EI-MS *m/z* (%): 227 ([$M^+ - C_2H_5$], 38), 209 (0.2), 159 (11), 87 (100), 57 (87). HR-MS calcd. for $C_{12}H_{19}O_4$ ([$M^+ - C_2H_5$]): 227.1284; found: 227.1283.

1-(2,2-Diethyl-5-triisopropylsilanyloxymethyl-[1,3]dioxolan-4-yl)-2-vinyl-but-3-en-1-ol (18)

Diol **13** (19.01 g, 74.2 mmol) was dissolved in a mixture of DMF (65 mL) and THF (200 mL) and cooled to 0 °C. Imidazole (10.12 g, 148.5 mmol) and triisopropylsilyl chloride (23.83 mL, 111.4 mmol) were added sequentially, and the solution was stirred overnight. Water was then added, and the mixture was extracted with ether. The ether extracts were washed once with saturated NH_4Cl, dried, filtered, and concentrated. Column chromatography (50:1, petroleum ether – ethyl acetate) yielded the title compound as a colorless oil (28.62 g, 93%). Major diastereomer: IR (neat, cm^{-1}) ν: 3467, 2965, 2940, 2867, 1638. ^1H NMR (500 MHz, C_6D_6) δ: 6.31–6.41 (m, 2H), 5.12–5.32 (m, 4H), 4.37–4.41 (m, 1H), 4.29–4.33 (m, 1H), 4.19 (ddd, *J* = 5.5, 2.5, 0.5 Hz, 1H), 4.00 (t, *J* = 10.2 Hz, 1H), 3.96 (dd, *J* = 3.3, 1.3 Hz, 1H), 3.73 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.46 (t, *J* = 7.8 Hz, 1H), 1.64 (dq, *J* = 7.5, 1.5 Hz, 2H), 1.58 (q, *J* = 7.5 Hz, 2H), 0.92–1.00 (m, 21H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 140.5 (CH), 137.2 (CH), 117.6 (CH_2), 115.6 (CH_2), 112.5 (C), 78.6 (CH), 77.9 (CH), 72.8 (CH), 63.6 (CH), 51.9 (CH), 30.7 (CH_2), 29.4 (CH_2), 18.2_9 (CH_3), 18.2_8 (CH_3), 12.7 (CH), 12.4 (CH), 9.3 (CH_3), 8.5 (CH_3). EI-MS *m/z* (%): 383 ([$M^+ - C_2H_5$], 8), 187 (53), 131 (56), 67 (100). HR-MS calcd. for $C_{21}H_{39}O_4Si$ ([$M^+ - C_2H_5$]): 383.2618; found: 383.2628.

[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-ylmethoxy]-triisopropyl-silane (19)

Alcohol **18** (21.99 g, 53.3 mmol) was dissolved in benzene (1.20 L) and cooled to 0 °C, and PPh_3 (41.92 g, 159.8 mmol) and DEAD (25.16 mL, 159.8 mmol) were successively added. The solution was refluxed for two days and the majority of the solvent was removed in vacuo to yield a red oil. A slurry of silica gel (30:1, petroleum ether – ethyl acetate) was then added, and the mixture was quickly filtered through a thin (~7 cm) plug of silica gel to remove the majority of reaction byproducts. The silica gel plug was washed (30:1, petroleum ether – ethyl acetate) until no additional product was detected in the filtrate. The washes were combined and concentrated, and petroleum ether was added, and the triphenylphosphine oxide precipitate was filtered off and discarded. Column chromatography (100:1, petroleum ether – ethyl acetate) yielded the title compound as a colorless oil (9.36 g, 44%). Owing to the instability of the product in common NMR solvents, clean NMR spectra could not be obtained. IR (neat, cm^{-1}) ν: 3089, 2867, 2943, 2867, 1464, 1129, 1087, 939, 883. EI-MS *m/z* (%): 394 ([M]$^+$, 19), 265 (100), 108 (84). HR-MS calcd. for $C_{23}H_{42}O_3Si$ ([M]$^+$): 394.2903; found: 394.2925

[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-methanol (20)

Triene **19** (13.71 g, 34.7 mmol) was dissolved in THF (300 mL), cooled to 0 °C, and a 1.0 mol/L solution of TBAF in THF (41.7 mL, 41.7 mmol) was added dropwise over a period of 2 min. The reaction was stirred at 0 °C for 1 h. Water was added, and the reaction was extracted with ether, dried, filtered, and concentrated. Column chromatography (9:1, petroleum ether – ethyl acetate) yielded the title compound as a clear oil (6.79 g, 82%). IR (neat, cm^{-1}) ν: 3431, 3090, 2975, 2941, 2882, 1604, 1173, 1077, 1041, 927. ^1H NMR (500 MHz, C_6D_6) δ: 6.27 (dd, *J* = 17.4, 10.7 Hz, 1H), 6.23 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.25 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 5.02 (m, 1H), 4.96 (d, *J* = 10.7 Hz, 1H), 4.13 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.47–3.57 (m, 2H), 2.16 (bs, 1H), 1.70 (q, *J* = 7.5 Hz, 2H), 1.58 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 141.2 (C), 138.1 (CH), 132.2 (CH), 128.0 (CH), 119.8 (CH_2), 116.4 (CH_2), 113.1 (C), 79.9 (CH), 74.5 (CH), 62.8 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 9.3 (CH_3), 8.5 (CH_3). EI-MS *m/z* (%): 238 ([M]$^+$, 4), 135 (38), 108 (38), 91 (78), 57 (100), 29 (88). HR-MS calcd. for $C_{14}H_{22}O_3$ ([M]$^+$): 238.1569; found: 238.1551.

2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolane-4-carbaldehyde (21)

Triene-ol **20** (1.50 g, 6.29 mmol) was dissolved in CH_2Cl_2 (60 mL), and Dess–Martin reagent (5.45 g, 13.2 mmol) was added. The solution was stirred for 30 min at room temperature, and then water (0.113 mL, 6.29 mmol) was added. A white precipitate formed within a few minutes. After a further 15 min of stirring the reaction was quenched with a 1:1 mixture of 2 mol/L $Na_2S_2O_3$ and sat. $NaHCO_3$, and the reaction was extracted with CH_2Cl_2. The combined organics were dried, filtered, and concentrated. Column chromatography (12:1, petroleum ether – ethyl acetate) yielded the title compound as a clear oil (1.11 g, 74%). IR (neat, cm^{-1}) ν: 3093, 2976, 2942, 2884, 2812, 1736, 1464, 1172, 1075, 924. ^1H NMR (500 MHz, C_6D_6) δ: 9.45 (d, J = 3.5 Hz, 1H), 6.17 (dd, J = 17.4, 10.7 Hz, 1H), 6.16 (dd, J = 17.6, 11.2 Hz, 1H), 5.51 (d, J = 9.0 Hz, 1H), 5.22 (dd, J = 17.6, 1.9 Hz, 1H), 5.20 (dd, J = 17.4, 0.9 Hz, 1H), 5.12 (dd, J = 11.2, 1.7 Hz, 1H), 5.10 (t, J = 8.5 Hz, 1H), 4.94 (dd, J = 10.7, 0.9 Hz, 1H), 4.08 (dd, J = 8.0, 3.5 Hz, 1H), 1.75 (q, J = 7.5 Hz, 2H), 1.48 (q, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 199.5 (C), 142.7 (C), 137.7 (CH), 132.0 (CH), 125.7 (CH), 120.6 (CH_2), 117.2 (CH_2), 115.7 (C), 83.5 (CH), 76.2 (CH), 30.2 (CH_2), 29.5 (CH_2), 9.1 (CH_3), 8.5 (CH_3). EI-MS *m/z* (%): 207 ([$M^+ - C_2H_5$], 11), 133 (31), 99 (100), 57 (95), 29 (53). HR-MS calcd. for $C_{12}H_{15}O_3$ ([$M^+ - C_2H_5$]): 207.1021; found: 207.1016.

1-[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-2-methyl-prop-2-en-1-ol (22a)

2-Bromopropene (1.00 mL, 11.26 mmol) was dissolved in THF (10 mL) and added dropwise to a flask containing freshly washed (sequentially with 10% HCl, water, and acetone) and dried magnesium turnings (0.27 g, 11.26 mmol) in THF (10 mL). A small chip of iodine was added to initiate the Grignard reaction. When the Grignard had fully formed (as indicated by the complete consumption of Mg), 1.1 equiv. of it (13.3 mL, 7.49 mmol) was added dropwise to a solution of aldehyde **21** (1.61 g, 6.83 mmol) in THF (90 mL). The resultant pale yellow solution was stirred for 45 min. The reaction was quenched with saturated NH_4Cl, extracted with ether, dried, filtered, and concentrated. Column chromatography (30:1, petroleum ether – ethyl acetate) yielded the title compound as a waxy solid mixture of two diastereomers (1.10 g, 58%). IR (neat, both diastereomers, cm^{-1}) ν: 3422, 3089, 2973, 2941, 1648, 1460, 1172, 1073. Major diastereomer: ^1H NMR (500 MHz, C_6D_6) δ: 6.36 (dd, J = 17.3, 10.7 Hz, 1H), 6.29 (dd, J = 17.6, 11.2 Hz, 1H), 6.13 (d, J = 9.1 Hz, 1H), 5.34 (dd, J = 17.3, 1.5 Hz, 1H), 5.21 (dd, J = 17.7, 1.8 Hz, 1H), 5.14 (ddd, J = 11.2, 1.9, 0.7 Hz, 1H), 5.09 (dd, J = 9.1, 7.3 Hz, 1H), 5.01 (dd, J = 10.7, 1.5 Hz, 1H), 5.01 (quintet, J = 0.9 Hz, 1H), 4.87 (t, J = 1.5 Hz, 1H), 4.10 (dd, J = 7.9, 3.1 Hz, 1H), 2.58 (d, J = 6.9 Hz, 1H), 1.74 (q, J = 7.5 Hz, 2H), 1.73 (s, 3H), 1.58 (q, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H), (OH not detected). ^{13}C NMR (125 MHz, C_6D_6) δ: 146.0 (C), 141.0 (C), 138.2 (CH), 132.4 (CH), 129.1 (CH), 119.5 (CH_2), 116.5 (CH_2), 113.2 (CH_2), 112.9 (C), 80.5 (CH), 75.0 (CH), 74.1 (CH), 30.0 (CH_2), 28.8 (CH_2), 19.2 (CH_3), 9.3 (CH_3), 8.6 (CH_3). EI-MS (both diastereomers) *m/z* (%): 278 ([$M]^+$, 0.1), 249 (5), 121 (52), 105 (85), 91 (65), 57 (100), 29 (63). HR-MS calcd. for $C_{15}H_{21}O_3$ ([$M^+ - C_2H_5$]): 249.1491; found: 249.1488.

1-[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-2-methyl-propenone (12a)

Allyl alcohol **22a** (1.10 g, 3.96 mmol) was dissolved in CH_2Cl_2 (60 mL), and Dess–Martin reagent (3.35 g, 8.12 mmol) was added. The solution was stirred for 30 min at room temperature, and then water (0.071 mL, 3.96 mmol) was added. A white precipitate formed within a few minutes. After a further 15 min of stirring the reaction was quenched with a solution of 2 mol/L $Na_2S_2O_3$ and saturated $NaHCO_3$ (1:1), and the reaction was extracted with CH_2Cl_2. The solution was dried, filtered, and concentrated. Column chromatography (30:1, petroleum ether – ethyl acetate) yielded the title compound as a clear oil (0.85 g, 78%). IR (neat, cm^{-1}) ν: 3091, 2974, 2942, 2883, 1693, 1463, 1173, 1071, 1056, 930. ^1H NMR (500 MHz, C_6D_6) δ: 6.20 (dd, J = 17.6, 11.2 Hz, 1H), 6.12 (dd, J = 17.3, 10.7 Hz, 1H), 5.58 (d, J = 9.7 Hz, 1H), 5.33 (s, 1H), 5.10–5.23 (m, 6H), 4.88 (d, J = 10.7 Hz, 1H), 2.01 (qd, J = 7.5, 2.4 Hz, 2H), 1.69 (t, J = 0.6 Hz, 3H), 1.65 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 196.5 (C), 144.9 (C), 141.3 (C), 137.7 (CH), 132.0 (CH), 127.8 (CH), 124.5 (CH_2), 119.8 (CH_2), 117.0 (CH_2), 115.3 (C), 80.3 (CH), 75.0 (CH), 30.5 (CH_2), 29.6 (CH_2), 18.3 (CH_3), 9.3 (CH_3), 8.9 (CH_3). EI-MS *m/z* (%): 276 ([$M]^+$, 0.2), 247 (11), 139 (50), 69 (100), 57 (44), 41 (58), 29 (33). HR-MS calcd. for $C_{15}H_{19}O_3$ ([$M^+ - C_2H_5$]): 247.1334; found: 247.1334.

1-[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-2-ethyl-prop-2-en-1-ol (22b)

The title compound was prepared by a method analogous to that used to prepare the methyl analogue (**22a**), except that *iso*-butenylmagnesium bromide was used as the Grignard reagent. (53% yield). IR (neat, both diastereomers, cm^{-1}) ν: 3475, 3089, 2971, 2940, 2882, 1463, 1172, 1074, 1056, 928. Major diastereomer: ^1H NMR (500 MHz, C_6D_6) δ: 6.33 (ddd, J = 17.3, 10.7, 0.6 Hz, 1H), 6.26 (dd, J = 17.5, 11.2 Hz, 1H), 6.10 (d, J = 9.1 Hz, 1H), 5.32 (dd, J = 17.4, 1.5 Hz, 1H), 5.19 (dd, J = 17.3, 1.9 Hz, 1H), 5.05–5.13 (m, 3H), 4.98 (dd, J = 10.7, 1.5 Hz, 1H), 4.89 (m, 1H), 4.21 (dd, J = 7.3, 3.9 Hz, 1H), 4.10–4.13 (m, 1H), 2.08–2.16 (m, 1H), 1.93–2.01 (m, 1H), 1.72 (q, J = 7.5 Hz, 2H), 1.57 (q, J = 7.5 Hz, 2H), 0.97 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H) (OH not detected). ^{13}C NMR (125 MHz, C_6D_6) δ: 151.2 (C), 140.9 (C), 138.2 (CH), 132.4 (CH), 129.2 (CH), 119.4 (CH_2), 116.4 (CH_2), 112.9 (CH_2), 110.9 (C), 80.6 (CH), 75.0 (CH), 73.7 (CH), 30.1 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 12.7 (CH_3), 9.3 (CH_3), 8.6 (CH_3). EI-MS (both diastereomers) *m/z* (%): 263 ([$M^+ - C_2H_5$], 3), 149 (34), 121 (54), 105 (74), 91 (61), 57 (100), 29 (79). HR-MS calcd. for $C_{16}H_{23}O_3$ ([$M^+ - C_2H_5$]): 263.1647; found: 263.1664.

1-[2,2-Diethyl-5-(2-vinyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-2-ethyl-propenone (12b)

The title compound was prepared by a method analogous to that used to prepare the methyl analogue (**12a**) (72%

yield). IR (neat, cm^{-1}) ν: 3091, 2973, 2940, 2882, 1692, 1463, 1173, 1078, 930. ^{1}H NMR (500 MHz, C_6D_6) δ: 6.20 (dd, *J* = 17.6, 11.2 Hz, 1H), 6.12 (ddd, *J* = 17.4, 10.7, 0.6 Hz, 1H), 5.59 (d, *J* = 9.6 Hz, 1H), 5.40 (s, 1H), 5.10–5.25 (m, 6H), 4.88 (dd, *J* = 10.6, 1.5 Hz, 1H), 2.19 (qq, *J* = 7.5, 0.8 Hz, 2H), 2.01 (dq, *J* = 7.5, 2.4 Hz, 2H), 1.65 (dq, *J* = 7.5, 1.1 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 196.2 (C), 150.5 (C), 141.2 (C), 137.8 (CH), 132.1 (CH), 127.9 (CH), 123.2 (CH_2), 119.9 (CH_2), 116.9 (CH_2), 115.2 (C), 80.2 (CH), 75.1 (CH), 30.5 (CH_2), 29.7 (CH_2), 24.9 (CH_2), 13.0 (CH_3), 9.3 (CH_3), 8.9 (CH_3). EI-MS *m/z* (%): 290 ([M]$^+$, 0.1), 261 (6), 153 (28), 83 (100), 55 (73), 29 (62). HR-MS calcd. for $C_{16}H_{21}O_3$ ([$M^+ - C_2H_5$]): 261.1491; found: 261.1508.

Diels–Alder adducts 23, 24, 25

Diels–Alder precursor **12a** (0.051 g, 0.185 mmol) was dissolved in toluene (20 mL), and the solution was purged with argon for 20 min. The solution was then placed in the microwave oven (program: 300 W power, ramp temperature to 150 °C in 15 min, then hold at 150 °C for 3 h). After allowing the reaction to cool to rt, the toluene was removed under reduced pressure. Column chromatography (20:1, petroleum ether – ethyl acetate) afforded a 41:20:39 mixture of Diels–Alder adducts (0.039 g, 78%) (Table 1, entry 12). A pure sample of each isomer was obtained by exhaustive preparative HPLC (2% hexanes in ethyl acetate; Waters Nova-Pak 19 × 300 mm silica (6 μm) column).

(1R,2S,6S,8R)-4,4-Diethyl-8-methyl-11-vinyl-3,5-dioxa-tricyclo[6.3.1.0^{2,6}]dodec-10-en-7-one (23)

T_r = 64.5 min. ^{1}H NMR (500 MHz, C_6D_6) δ: 6.08 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.26 (dd, *J* = 4.3, 4.3 Hz, 1H), 5.16 (d, *J* = 17.7 Hz, 1H), 4.87 (d, *J* = 10.9 Hz, 1H), 4.49 (dt, *J* = 6.3, 2.2 Hz, 1H), 3.95 (d, *J* = 6.3 Hz, 1H), 3.00 (d, *J* = 2.2 Hz, 1H), 2.37 (dt, *J* = 13.2, 1.9 Hz, 1H), 1.96 (dd, *J* = 19.6, 4.6 Hz, 1H), 1.71 (q, *J* = 7.6 Hz, 2H), 1.65 (dd, *J* = 19.6, 1.1 Hz, 1H), 1.50 (qd, *J* = 7.6, 2.4 Hz, 1H), 1.22 (ddd, *J* = 13.2, 3.6, 1.8 Hz, 1H), 1.10 (s, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ: 210.8 (C), 137.6 (CH), 136.9 (C), 130.2 (CH), 114.5 (C), 111.3 (CH_2), 78.8 (CH), 77.4 (CH), 43.1 (C), 38.2 (CH_2), 32.6 (CH), 30.7 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 25.0 (CH_3), 8.7 (CH_3), 8.6 (CH_3). EI-MS *m/z* (%): 276 ([M]$^+$, 1), 247 (77), 191 (19), 145 (38), 119 (54), 105 (27), 91 (15), 57 (100). HR-MS calcd. for $C_{15}H_{19}O_3$ ([$M^+ - C_2H_5$]): 247.1334; found: 247.1314.

(3aS,3bR,7aS,8aS)-2,2-Diethyl-7a-methyl-4-vinyl-7,7a-dihydro-3aH-indeno[2,1-d][1,3]dioxol-8(3bH,6H,8aH)-one (24)

T_r = 70.0 min. ^{1}H NMR (500 MHz, C_6D_6) δ: 6.26 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.66 (d, *J* = 17.7 Hz, 1H), 5.49 (t, *J* = 4.3 Hz, 1H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.29 (dd, *J* = 6.9, 2.8 Hz, 1H), 4.23 (dd, *J* = 6.9, 0.5 Hz, 1H), 2.80 (br s, 1H), 1.65 (q, *J* = 7.5 Hz, 2H), 1.70–1.53 (m, 2H), 1.47 (q, *J* = 7.5 Hz, 2H), 1.22 (ddd, *J* = 13.0, 8.4, 5.5 Hz, 1H), 1.10 (s, 3H), 0.97–0.93 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 215.6 (C), 138.7 (CH), 136.0 (C), 130.0 (CH), 116.8 (C), 112.8 (CH_2), 80.7 (CH), 79.7 (CH), 48.7 (C), 46.6 (CH), 30.0 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 22.0 (CH_2), 22.0 (CH_3), 8.6 (CH_3), 8.2 (CH_3). EI-MS *m/z* (%): 276 ([M]$^+$, 2), 247 (44), 191 (8), 162 (12), 145 (34), 119 (100), 105 (24), 57 (50), 43 (32). HR-MS calcd. for $C_{17}H_{24}O_3$ ([M]$^+$): 276.1725; found: 276.1748.

(3aS,3bR,7aR,8aS)-2,2-Diethyl-7a-methyl-4-vinyl-7,7a-dihydro-3aH-indeno[2,1-d][1,3]dioxol-8(3bH,6H,8aH)-one (25)

T_r = 72.0 min. ^{1}H NMR (500 MHz, C_6D_6) δ: 6.37 (ddd, *J* = 17.8, 11.5, 0.8 Hz, 1H), 5.93 (d, *J* = 17.8 Hz, 1H), 5.39 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 11.5 Hz, 1H), 4.59 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 4.49 (d, *J* = 7.6 Hz, 1H), 2.67 (br dd, *J* = 8.3, 2.9 Hz, 1H), 1.84–1.74 (m, 2H), 1.63 (qd, *J* = 7.6, 2.9 Hz, 2H), 1.60–1.57 (m, 1H), 1.51–1.45 (m, 1H), 1.46 (q, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.81 (t, *J* = 7.6 Hz, 3H), 0.58 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ: 208.6 (C), 137.5 (CH), 135.4 (C), 127.9 (CH), 118.5 (C), 113.6 (CH_2), 79.9 (CH), 77.4 (CH), 51.8 (C), 50.8 (CH), 29.5 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 23.4 (CH_2), 15.3 (CH_3), 8.7 (CH_3), 7.8 (CH_3). EI-MS *m/z* (%): 276 ([M]$^+$, 0.1), 247 (38), 181 (30), 145 (16), 119 (46), 99 (14), 43 (100). HR-MS calcd. for $C_{15}H_{19}O_3$ ([$M^+ - C_2H_5$]): 247.1334; found: 247.1342.

Conclusions

Twenty years ago we commented that the then-current literature indicated that, for the synthesis of bicycle[4.3.0]nonenones from intramolecular Diels–Alder reactions, the following applied: "The ring fusion is determined by a complex interplay of conformational, steric, and electronic effects that may vary independently" (12). Clearly this still applies! We have discovered that, contrary to our expectations based on studies in the decalin series, these relatively flat tetraenes follow a novel pathway in which the *trans*-adduct bicycle[4.3.0]nonenone was not generated but instead the bicyclo[3.3.1]nonenone skeleton was formed preferentially at 150 °C in toluene in a microwave oven. At lower temperatures, the fused-ring hydrindenone products dominated, but the bridged-ring product was still produced. Indeed, once we understand more about nuances that control these competing reactions it may be possible to direct the product to either the fused- or bridged-ring pathway from related tetraenes. A contributing factor to begin to achieve this control is to examine the size and nature of the R group. Unfortunately, the adduct mixture from the synthesis made further study impractical, despite the attraction of generating the steroid framework from a second cycloaddition. Possibly future investigations, with simpler and (or) sterically more demanding dienophile–diene combinations, may permit the stereoselective synthesis of functionalized hydrindanes in this manner.

Acknowledgements

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research. M. Clay thanks NSERC, the Ontario Graduate Scholarship Program, and the University of Ottawa for Graduate Scholarships. D. Riber thanks the University of Aarhus for a visiting fellowship. Preliminary experiments by A. Melekhov and S. Graham are also acknowledged. We

thank K. Fagnou for use of his chiral columns and the referees for their suggestions.

References

1. (*a*) E.J. Corey and A.X. Huang. J. Am. Chem. Soc. **121**, 710 (1999); (*b*) Q.-Y. Hu, P.D. Rege, and E.J. Corey. J. Am. Chem. Soc. **126**, 5984 (2004).
2. (*a*) C. Martin, N. Macintosh, N. Lamb, and A.G. Fallis. Org. Lett. **3**, 1021 (2001); (*b*) A. Melekhov, P. Forgione, S. Legoupy, and A.G. Fallis. Org. Lett. **2**, 2793 (2000); T. Wong, P.D. Wilson, S. Woo, and A.G. Fallis. Tetrahedron Lett. **38**, 7045 (1997).
3. S. Woo, S. Legoupy, S. Parra, and A.G. Fallis. Org. Lett. **1**, 1013 (1999).
4. S. Woo, N. Squires, and A.G. Fallis. Org. Lett. **1**, 573 (1999).
5. D. Kim and Y.K. Lee. Tetrahedron Lett. **32**, 6885 (1991).
6. B.B. Snider and T.C. Kirk. J. Am. Chem. Soc. **105**, 2364 (1983).
7. (*a*) S.A. Bal and P. Helquist. Tetrahedron Lett. **22**, 3933 (1981); (*b*) M.E. Jung and K.M. Halweg. Tetrahedron Lett. **22**, 3929 (1981); (*c*) J. Shiina and S. Nishiyama. Tetrahedron, **59**, 6039 (2003).
8. J. Endrikat, M. Cronin, C. Gerlinger, A. Ruebig, W. Schmidt, and B. Dusterberg. Contraception, **64**, 201 (2001).
9. A.B. Northrup and D.W.C. MacMillan. J. Am. Chem. Soc. **124**, 2458 (2002).
10. N. Cohen, B.L. Banner, A.J. Laurenzano, and L. Carozza. Org. Synth. **63**, 127 (1984).
11. S.D. Meyer and S.L. Schreiber. J. Org. Chem. **59**, 7549 (1994).
12. A.G. Fallis. Can. J. Chem. **62**, 183 (1984).