Cation Radical Diels-Alder Cycloadditions in Organic Synthesis: A Formal Total Synthesis of (-)-β-Selinene

Bijan Harirchian and Nathan L. Bauld*

Contribution from the Department of Chemistry, The University of Texas, Austin, Texas 78712.
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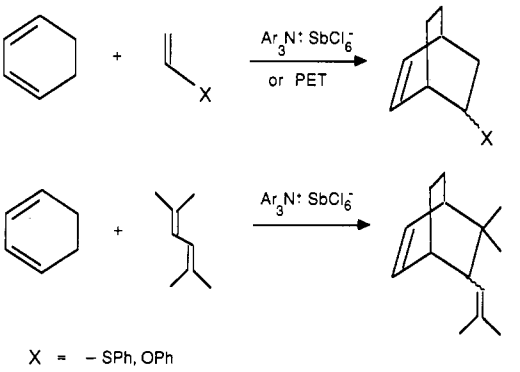
Abstract: The site-specific, regiospecific, and Diels-Alder periselective hole-catalyzed addition of phenyl vinyl sulfide to (*S*)-(-)-1-ethenyl-4-isopropenylcyclohexene is shown to provide a very direct route to the sesquiterpenoid natural product (-)-β-selinene. The present synthesis of β-selinene represents the first such natural product synthesis to exploit the hole-catalyzed Diels-Alder reaction.

The cycloaddition of cation radicals to neutral substrates has emerged as one of the most facile carbon-carbon bond-forming reactions available, rivaling even carbene/olefin cycloadditions with respect to the minuteness (0-2 kcal/mol) of the typical activation energy.[1-3] This extraordinary reactivity notwithstanding, cation radical/neutral cycloadditions are often efficient, stereospecific, and highly stereoselective.[1-5] The synthetic utility of the cation radical Diels-Alder (DA) reaction has been emphasized in this laboratory and priority given to mapping the scope and selectivity profile of the reaction. These studies envision unique synthetic niches for the cation radical DA in the specific realms of cycloadditions to electron-rich dienophiles[7] and sterically hindered dienophiles[1] (Scheme I), reaction categories in which the uncatalyzed (or even the Lewis acid catalyzed) DA is notoriously deficient. The effectiveness of the new methodology is, of course, best displayed in the context of illustrative natural product synthesis. The present formal total synthesis of the sesquiterpene natural product (-)-β-selinene is the first such natural product synthesis to exploit the cation radical DA reaction.

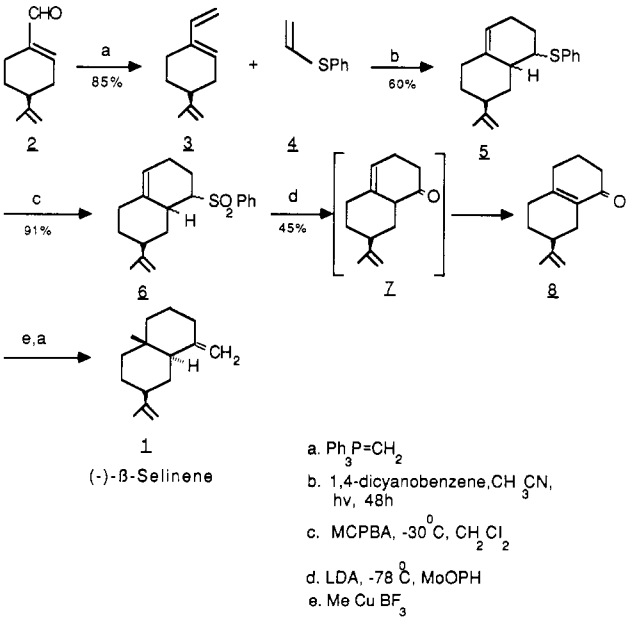
Scheme I



Results and Discussion

(-)-β-Selinene (**1**), a sesquiterpene of the eudesmane family, has been isolated from ginseng,[8] celery seed,[9] oak moss,[10] and Japanese hops.[11] Two elegant, yet rather lengthy (9-10 steps), syntheses had been recorded some time ago,[12,13] but Cohen's recent synthesis, which is based upon an oxyanion assisted vinylcyclobutane (VCB) rearrangement strategy, is unusually compact.[15] The present synthesis (Scheme II) is conceptually even more direct in implementing a cation radical DA strategy to construct the octalin ring, although the overall yield appears to be somewhat less than in the Cohen synthesis. Both syntheses commence with the commercially available (-)-perillaldehyde (**2**) as one key precursor. As the reaction partner for **2**, the present synthesis uses phenyl vinyl sulfide (PVS, **4**), which is also commercially

Scheme II. Synthesis of (-)-β-Selinene via the Hole-Catalyzed Diels-Alder Reaction



available, whereas the Cohen route requires 1-lithio-1-methoxycyclopropane, obtained in a three-step sequence from cyclopropyl phenyl sulfide. The present synthesis converges with the Cohen route at ketone **8**.

The key step in the present synthesis of β-selinene is the cation radical DA cycloaddition of PVS (**4**) to triene **3**, which is obtained efficiently from **2** via a Wittig reaction. Previous research had established the DA (as opposed to cyclobutane) periselectivity of cation radical cycloadditions of electron-rich alkenes (e.g., PVS and phenyl vinyl ether) to a rigidly s-cis diene (1,3-cyclohexadiene),[7] but cycloadditions to predominantly s-trans dienes (e.g., (*E*,*E*)-2,4-hexadiene) were found to exhibit cyclobutane (CB) periselectivity.[15] Conformationally flexible dienes with substantial

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s-cis populations (e.g., 1,1′-dicyclopentenyl) are observed to yield CB/DA mixtures.[16] The 1-vinylcyclohexene framework of **3** appears to belong to the latter category; thus it was expected that a mixture of CB and DA adducts would result. Nevertheless, an extremely facile cation radical VCB rearrangement recently developed in this laboratory was potentially available to convert this mixture to DA adducts.[16,17] In a surprising and mildly fortuitous turn of events, the cycloaddition actually afforded predominantly (≥90%), and perhaps only, DA cycloadducts. Evidence to be presented (vide infra) suggests that the DA periselectivity is real and not merely the apparent result of cyclobutanation followed by rapid VCB rearrangement.

A distinctive feature of the typical cation radical DA reaction is its exceptionally high regiospecificity, and the present reaction is no exception to that generalization.[5,6] The specific orientation favored was anticipated primarily on the basis of other studies on the DA cycloaddition of **3** and *trans*-anethole.[18] This regiochemical mode is considered to be controlled by steric effects in the transition state of the highly nonsynchronous reaction path, especially since neither FMO considerations nor consideration of the more stable diradicaloid (more properly cation radicaloid) structure appear to clearly distinguish the two regiochemical modes.[6]

Endo/exo diastereoselectivity in the cation radical DA, though capable of attaining high levels in certain systems, typically is rather variable. Thus, endo selectivity in the PVS addition to 1,3-cyclohexadiene is 15:1,[7] but in the DA component of the addition of PVS to 1,1′-dicyclopentenyl the endo/exo ratio is only 2.6:1. Diastereofacial selectivity in the cation radical DA has not been studied extensively, but facial selection is actually quite high in the cyclobutanation of **3** by *N*-methyl-*N*-vinylacetamide (MVA).[16,19] In any event, the cycloaddition of **3** with PVS yields three diastereoisomers in the ratio 1.9:1.3:1, thus indicating that neither endo/exo nor diastereofacial selectivity is highly developed in this reaction system. This lack of stereoselectivity, fortunately, is not problematic in the present synthesis since both new stereogenic centers involved are absent in ketone **8**.

A final and extremely critical selectivity element is implicit in the cation radical DA addition of Scheme II, viz., site selectivity. This latter element is highlighted by an attempt to effect thermal DA cycloaddition of phenyl vinyl sulfone, an electron-deficient dienophile, to **3**. Unlike the cation radical DA reaction of **3** with **4**, the thermal reaction of **3** with the sulfone does not proceed under mild conditions but rather requires refluxing in xylene for several days. More critically, the adducts (produced in 42% yield) consist of eleven isomers formed in comparable amounts, the predominant reaction mode involving the isopropenyl double bond, presumably in an ene type reaction. *Thus the kinetic impetus and the selectivity of the cation radical DA, which are its most* fundamental *distinctives, are capable of providing major synthetic advantages over thermal DA reactions even where the latter involve electron-deficient dienophiles.*

Conversion of the DA adducts to the corresponding sulfones is efficient, but the oxidation by MoOPH (molybdenum pentoxide/pyridine/HMPA complex) is only modestly so. The two unconjugated enones (1.3:1 ratio) produced in the latter oxidation confirm the lack of diastereofacial selectivity, and their conversion on alumina to a single conjugated enone **8** confirms the regiospecificity.

The use of an electron-rich dienophile having a sulfur substituent as the donor group (e.g., phenylthio), as opposed to one having an oxygen or nitrogen-linked donor group, is strongly preferred, in the present context, for several reasons. Vinyl ethers and *N*-vinylamides are quite reactive as partners for diene cation radical cycloadditions, but both, and particularly the *N*-vinylamides, have a far more pronounced CB periselectivity than PVS.[16,19] Thus the reaction of MVA with **3** yields only the (syn and anti) CB adducts corresponding to selection of the exocyclic double bond.[18] Although the regioselectivity of this CB reaction is the proper one to furnish the desired DA adduct substitution pattern after VCB rearrangement, the latter rearrangement cannot be induced by a purely cation radical mechanism. Hydrolysis of the amide, followed by an anion assisted (KH/THF) VCB rearrangement does produce the desired DA adducts efficiently,[19] but subsequent oxidation of the secondary amine function to a carbonyl group has not proved straightforward. The addition of **3** to vinyl ethers (ethyl vinyl ether or, preferably, β-chloroethyl vinyl ether or *tert*-butyldimethylsilyl vinyl ether) is capable of generating CB adduct alcohols (after deprotection) which are efficiently rearranged and oxidized, but these cycloadditions, unfortunately, produce ca. 15% of the CB adducts corresponding to reaction at the endocyclic double bond. Subsequent to VCB rearrangement, these isomers produce the wrong DA regioisomers.

DA Periselectivity. As noted previously, the predominant DA periselectivity observed in the cation radical cycloaddition of **3** to PVS is somewhat surprising. It has previously been established that PVS tends to be less CB periselective than vinyl ethers and *N*-vinylamides and that high s-cis conformational populations tend to favor DA periselection.[16] Consequently, the obtention of substantial amounts of DA adducts is expected, but the strong preponderance of these adducts over CB adducts is indeed somewhat unexpected. To establish that initially formed CB adducts were not being rearranged to DA adducts under the reaction conditions, several control reactions were carried out.[17] First, the product distribution in the photosensitized electron transfer (PET) initiated reaction was monitored by GC/MS at times as early as they could be detected (a few minutes, corresponding to much less than 1% conversion to cycloadducts). The same three diastereoisomers were present in the same ratio at early times as after long reaction times and no new cycloadducts were observed. Secondly, the corresponding aminium salt initiated reaction was carried out at −30 °C using tris(4-bromophenyl)-aminium hexachloroantimonate/dichloromethane. The reaction was monitored at 1, 3, 4, and 10 s, then every 10 s for 3 min, and then at 5 and 10 min. The same three cycloadduct diastereomers were found from each aliquot and always in the same ratios, which are also those found in the PET reaction. These experiments strongly implicate a direct cation radical DA reaction mechanism. Besides the effect of sulfur and of s-cis conformational content, one additional factor could possibly join in accounting for the unusually strong DA periselectivity. It has been argued that, assuming the cation radical Diels–Alder reaction is indeed concerted, the [4 + 1] DA cycloaddition (the dienophile is the cation radical) should be at least somewhat favored over a [3 + 2] DA (the diene is the cation radical) or the [2 + 1] (CB cycloaddition) since the first is formally allowed and the latter two formally forbidden.[1,3,19] Since PVS is considerably more oxidizable ($E_{1/2}$ = 1.42 V vs SCE) than **3** (1.52 V),[16] the cation radical π complex of PVS and **3**, which should precede cycloaddition, must have cation radical character predominantly on the PVS moiety. The DA cycloaddition would thus be of the basic [4 + 1] type. In the addition of PVS to 1,1′-dicyclopentenyl ($E_{1/2}$ = 1.36), which yields a 2:1 CB/DA product ratio, the cycloaddition should be somewhat more analogous to a [3 + 2] DA cycloaddition. It must be stressed that these arguments could be valid even if the reaction, mechanistically, occurs via diene cation radicals and neutral PVS, since rapid electron transfer to PVS could then occur within the π complex. Indeed, evidence has been presented that diene cation radicals are primarily involved in the cycloadditions of dienes with electron-rich alkenes.[19]

Experimental Section

Analysis. Proton magnetic resonance (PMR) and carbon magnetic resonance (CMR) spectra were recorded on Varian EM-390 or FT-80A spectrometers for routine spectra. High field and COSY (2D NMR) spectra were recorded on a General Electric QE-300 or GN-500 spectrometer.

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Low resolution mass spectra (LRMS) were obtained on a DuPont 21-471 mass spectrometer. High resolution mass spectra (HRMS) were recorded from a DuPont (CEC) 21-110B mass spectrometer.

Infrared spectra (IR) were recorded on a Perkin Elmer 1320 spectrophotometer.

Reagents. Methylene chloride and HPLC grade acetonitrile were distilled from phosphorus pentoxide prior to use. Both dry solvents were stored over molecular sieves. Where possible, freshly distilled acetonitrile was used, since water is a strong inhibitor of the PET reaction.

Dicyanobenzene was recrystallized from benzene prior to use. The PET reactions were run in a dry, inert (nitrogen) atmosphere to exclude moisture.

(*S*)-(−)-Ethenyl-4-isopropenylcyclohexene (3). Methyltriphenylphosphonium iodide[20] (0.11 mol, 46.35 g) was stirred in dry THF (260 mL) and cooled to −78 °C under dry nitrogen atmosphere. *n*-Butyllithium (0.09 mol, 34.6 mL of 2.6 M solution in hexane) was added in a dropwise fashion. Upon formation of the ylide, the mixture turned yellow. It was allowed to warm to −5 °C before addition of (−)-perillaldehyde (**2**, 0.085 mol, 12.75 g) in dry THF (20 mL). The reaction mixture was allowed to stir at room temperature for 8 h. The orange red solution was then quenched with water (200 mL) and taken up in diethyl ether (3 × 100 mL). The organic layer was washed several times with water, dried over anhydrous magnesium sulfate, evaporated, and distilled to give a colorless oil[21] in 85% (10.5 g) yield: bp 81–84 °C (10.5 Torr); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.3 (m, 1 H), 5.75 (br s, 1 H), 5.1 (d, 1 H, *J* = 18 Hz), 4.9 (d, 1 H, 10 Hz), 4.7 (s, 2 H), 1.8 (m, 7 H), 1.70 (s, 3 H); ^{13}C NMR $CDCl_3$, 90 MHz) δ 20.78, 24.28, 27.36, 27.40, 31.26, 41.26, 108.78, 110.04, 129.03, 129.08, 139.71; IR (neat) 2810–3100, 1640, 1370, 890 cm^{-1}; exact mass calculated for $C_{11}H_{16}$: 148.125194; found 148.125009.

4(*R*,*S*)-(Phenylthio)-6(*S*)-isopropenyl-1(9)-octalin (5) via Photoinduced Electron-Transfer Reaction (PET). A solution of freshly distilled phenyl vinyl sulfide (**4**) (0.01 mol, 1.36 g), 1-ethenyl-4-isopropenylcyclohexene (**3**) (0.02 mol, 2.96 g), and 1,4-dicyanobenzene (0.002 mol, 0.256 g) in carefully dried acetonitrile (see solvent section, 10 mL) was placed in a 100-mL Pyrex test tube, sealed with rubber septum, which was then wrapped with aluminum foil, degassed with dry nitrogen, placed in a cool water bath against the outside of the cooling jacket of a medium pressure mercury vapor lamp and irradiated 48 h. The solvent was then removed from the colorless solution by vacuum distillation, and the precipitated dicyanobenzene removed by filtration. Chromatography on silica gel (hexane/diethyl ether, 9:1) gave the Diels–Alder cycloadducts in 60% isolated yield (1.68 g) in the ratios 1.9:1.3:1, plus the unreacted starting materials (triene 3 and phenyl vinyl sulfide (**4**), a total recovery of 1.0 g). High field ^{1}H NMR and GCMS studies showed the cycloadducts to be mainly Diels–Alder adducts (>90%), and no clear evidence was obtained for any significant amount of cyclobutane formation: IR (CCl_4) 3090, 2930, 1635 (w), 1430, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5 H), 5.5 and 5.4 (s, 1 H), 4.70 (brs, 2 H), 3.63 (m, 1 H), 2.3–1.2 (m, 12 H), 1.73 (s, 3 H); mass spectrum *m*/*e* (relative intensity) 284 (7), 205 (12), 175 (12), 1509 (3), 148 (10), 136 (100), 131 (54), 123 (63), 105 (33), 91 (88), 79 (44), 67 (32), 55 (35), 45 (30), 41 (71); exact mass calculated for $C_{19}H_{24}S$: 284.15987; found 284.16005.

Preparation of 5 via Aminium Salt Initiated Reaction at 0 and −30 °C. Phenyl vinyl sulfide (**4**, 0.665 mmol, 90 mg) and 1-ethenyl-4-isopropenylcyclohexene (**3**, 0.670 mmol, 99 mg) were dissolved in dry CH_2Cl_2 (3.0 mL), and the mixture was cooled to −30 °C using a $CaCl_2/H_2O$/dry ice (30.0 g/100 g) solution. Tris(*p*-bromophenyl)-aminium hexachloroantimonate (109 mg, 0.133 mmol) was added under dry nitrogen. The reaction was monitored for 10 min collecting aliquots after 1, 3, 5, and 10 s, every 10 s for 3 min, and then at 5 and 10 min and quenched with sodium methoxide/methanol solution. GCMS and capillary GC(FI) studies showed the formation of the Diels–Alder cycloadducts *5* after 3 s of reaction time. The product distribution obtained after reaction times of 3, 5, 10, and 20 s are exactly the same as those obtained after longer reaction times (as long as 10 min). The above reaction was also repeated at 0 °C and identical results were obtained. These results are also consistent with those obtained for the PET reaction.

4(*R*,*S*)-(Phenylsulfonyl)-6(*S*)-isopropenyl-1(9)-octalin (6). The sulfide **5** (0.0061 mol, 1.73 g) was dissolved in dry CH_2Cl_2 (5.0 mL) and cooled to −30 °C, and *m*-chloroperbenzoic acid (80%, 2.63 g, 0.0152 mol) in dry CH_2Cl_2 (30 mL) was added dropwise. After 30 min the reaction was quenched with saturated aqueous $NaHCO_3$ (200 mL). The crude product was extracted with diethyl ether (3 × 100 mL), washed with water (5 × 100 mL), and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography over silica gel (50% diethyl ether in hexanes) afforded the sulfone (**6**) (1.75 g, 91%): IR ($CHCl_3$) 3100, 2900, 1610, 1425, 1350, 1270, 1120, 1050, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDcl_3$) δ 7.95–7.70 (m, 2 H), 7.62–7.41 (m, 3 H), 5.30 and 4.98 (s, 1 H), 4.70 (brs, 2 H), 3.20–2.78 (m, 1 H), 2.65–1.10 (m, 12 H), 1.70 (s, 3 H); mass spectrum *m*/*e* (relative intensity) 316 (2), 174 (100), 159 (27), 143 (5), 131 (58), 119 (23), 105 (21), 91 (90), 83 (62), 77 (73), 67 (44), 55 (48), and 40 (83); exact mass calculated for $C_{19}H_{24}SO_2$ 316.14970, found 316.15000.

Preparation of Oxodiperoxymolybdenum–(Pyridine)–(Hexamethyl Phosphoric Triamide) (MoOPH).[22,23] Molybdenum trioxide (30 g, 0.2 mol) was mixed with 30% H_2O_2 (150 mL) and stirred with a paddle stirrer at an external temperature of 40 °C. As soon as the internal temperature reached 35 °C, the external heating was removed, and the reaction temperature was maintained between 35 and 40 °C by occasional cooling with a water bath. After the initial exothermic period, the mixture was heated at 40 °C for a total of 3.5 h with stirring. After cooling the mixture to 20 °C, the reaction mixture was filtered, and the solution was cooled to 10 °C. Hexamethylphosphoric triamide (37.5 g) was added with stirring, and the crystalline precipitate was collected. Recrystallization from methanol (40 °C maximum) gave $MoO_5 \cdot H_2O \cdot$ HMPA as yellow needles (50 g, 66%). This complex was dried in a vacuum desiccator (0.1 mmHg, over P_2O_5, 48 h). The resulting $MoO_5 \cdot$HMPA complex (36.0 g, 103.8 mmol) in dry THF (80 mL) was stirred at 20 °C, while dry pyridine (8.22 g, 103.8 mmol) was added dropwise. The yellow crystalline precipitate was washed with dry THF (20 mL) and anhydrous diethyl ether (200 mL) and dried under vacuum to afford MoOPH (40 g, 90%). This was placed in a dark bottle and kept in a desiccator over drierite in a refrigerator.

3,4,5,6,7,8-Hexahydro-7-(2-propenyl)-1(2*H*)-naphthalenone (8). Diisopropylamine (2.11 g, 0.0209 mol) and *n*-BuLi (8.33 mL, 0.0209 mol, 2.5 M in hexanes) were mixed at −78 °C for 30 min. The resulting LDA solution was added to a solution of the sulfone **6** (1.10 g, 0.00348 mol) in dry THF (100 mL) at −78 °C within 30 s. After stirring the mixture for 3 min at −78 °C, MoOPH (4.53 g, 0.0104 mol) in dry THF (85.0 mL) was added by using a double-ended needle. The resulting dark red solution was stirred for 1 min at −78 °C and was quenched by saturated aqueous sodium sulfite (42 mL). The reaction mixture was then washed with water (460 mL) and extracted with diethyl ether (3 × 125 mL). The combined extracts were washed with HCl (0.6 N, 450 mL), water (3 × 150 mL), and brine (500 mL) and dried over $MgSO_4$. The solvent was removed, and the resulting unconjugated ketones **7** (1.3:1 ratio) were chromatographed on a column of basic, activity grade 3 alumina (3% ethyl acetate in hexane) to obtain the pure conjugated ketone **8** (45%, 298 mg): IR ($CHCl_3$) 2950, 1665, 1640, 1450, 1390, 1260, 1100, 900 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 and 4.74 (s, 2 H, C=CH_2), 2.65–1.10 (m, 13 H, alicyclic), 1.75 (s, 3 H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.81, 22.40, 26.86, 27.47, 31.07, 32.22, 37.82, 40.73, 109.01, 131.86, 149.10, 156.41, 199.01; mass spectrum: *m*/*e* (relative intensity) 190 (23), 175 (32), 161 (15), 157 (8), 149 (100), 148 (70), 134 (22), 119 (28), 105 (26), 91 (57), 79 (38), 68 (24), 55 (25), 40 (57); exact mass calcd for $C_{13}H_{18}O$ 190.13577, found 190.13614.

Thermal Diels–Alder Reaction of Phenyl Vinyl Sulfone with 1-Ethenyl-4-isopropenylcyclohexene (3). A mixture of phenyl vinyl sulfone (0.0071 mol, 1.20 g) and 1-ethenyl-4-isopropenylcyclohexene (0.0071 mol, 1.06 g) in dry xylene (10.0 mL) was refluxed for 6 days under dry nitrogen. Evaporation of the solvent under vacuum and chromatography of the crude product on silica gel (50% diethyl ether in hexanes) afforded a number of cross adducts (800 mg, 42%). GCMS and capillary GC(FI) studies showed the presence of at least 11 cycloadducts between the diene and dienophile. Mass spectra of all these isomers showed parent ions of 316 and 174. ^{1}H NMR indicated the presence of a mixture of cyclobutanes and Diels–Alder cross adducts, but the major isomers are believed to be the cross adducts between the sulfone and the terminal carbon–carbon double bond of the isopropenyl group of the triene, since the propenyl methylene absorptions are strongly attenuated and the protons of the conjugated diene moiety are present.

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Registry No. 1, 473-12-1; **2**, 18031-40-8; **3**, 118575-87-4; **4**, 1822-73-7; **5**, 118575-88-5; **6**, 118575-89-6; *cis*-**7**, 118628-32-3; *trans*-**7**, 118628-33-4; **8**, 84099-54-7.

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