= 7.6 Hz), 86.3, 73.7, 67.8, 41.8; ^{19}F NMR (282 MHz, D_2O) 116.7 (dd, $J_{P,F}$ = 89.1 Hz, $J_{P,F}$ = 73.3 Hz); ^{31}P NMR (121 MHz, D_2O) 3.86 (dt, $J_{P,P}$ = 51.9 Hz, $J_{P,F}$ = 73.3 Hz), 0.70 (dt, $J_{P,P}$ = 51.9 Hz, $J_{P,F}$ = 89.1 Hz).

Acknowledgment. We thank Kay Stremler for preparing the difluoromethanediphosphonate analogues. Financial support was provided by the National Institutes of Health, Grants GM-25521 and GM-32490. Mass spectrometry is supported by National Science Foundation (Grants CHE-8100424 and CHE-8310031) and the University of Utah Instrument Funds Committee. The 300-MHz NMR spectrometer utilized in this study was acquired with National Science Foundation and National Institutes of Health instrumentation grants.

Registry No. 1 (*S* diastereomer), 107201-92-3; 1 (*R* diastereomer), 107269-58-9; 2, 24380-35-6; 3 (*S* diastereomer), 107201-93-4; 3 (*S* diastereomer), 107201-99-0; 4 (*S* diastereomer), 107201-94-5; 4 (*R* diastereomer), 107202-00-6; 5, 50615-57-1; 6, 7253-19-2; 7 (*S* diastereomer), 107222-38-8; 7 (*R* diastereomer), 107202-01-7; 8 (*S* diastereomer), 107201-95-6; 8 (*R* diastereomer), 107202-02-8; 9, 39947-33-6; 10, 107201-96-7; 13, 6698-29-9; 14, 76947-02-9; 15, 93978-76-8; 16, 107202-03-9; 17, 93978-77-9; 18, 58-98-0; 19, 63-38-7; 20, 491-97-4; 21, 146-91-8; 22, 36373-38-3; 23, 58-64-0; 24, 3768-14-7; 25, 107201-97-8; 26, 56-65-5; 27, 107201-98-9; 2′,3′-*O*-isopropylidene-5′-*O*-tosyladenosine, 5605-63-0; 5′-*O*-tosyladenosine, 5135-30-8; uridine, 58-96-8; cytidine, 65-46-3; 2′-(*S*)-2′,3′-*O*-(methoxymethylidene)cytidine, 107297-06-3; 3′-*O*-(*tert*-butyldimethylsilyl)thymidine, 40733-27-5; guanosine, 118-00-3; 3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine, 51549-31-6; 2′(*R*)-2′,3′-*O*-(methoxymethylidene)cytidine, 107297-07-4.

Scope and Limitations of the Cuprate–Acetylene–Vinyltriphenylphosphonium Bromide–Aldehyde Reaction: Synthesis of (6*Z*,9*Z*)-Heneicosadiene

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Syntheses of (6*Z*,9*Z*)-heneicosadiene, a component of the sex attractant secretion of the female arctiid moth (*Uthetheisa ornatrix*), and of triene **6**, a useful precursor for the synthesis of (8*S*)-HETE, are described using a one-pot four-component (cuprate–acetylene–vinyltriphenylphosphonium bromide–aldehyde) reaction. The use of 1-iodo-1-alkenes as an alternative to Normant's alkenylcuprate methodology is demonstrated.

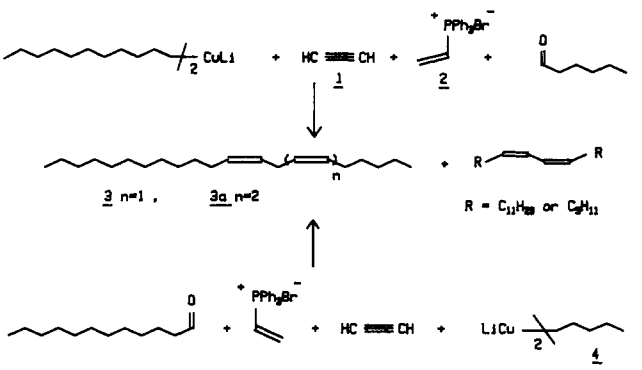
We recently described a general synthesis of 1,5-dialkylpenta-1(*Z*),4(*Z*)-dienes[1] using a one-pot four-component (cuprate–acetylene–vinyltriphenylphosphonium bromide–aldehyde) reaction. This procedure has now been applied to the syntheses of (6*Z*,9*Z*)-heneicosadiene (**3**), a component isolated from the sex attractant secretion of the female arctiid moth (*Uthetheisa ornatrix*) recently synthesized by Meinwald et al.[2] and of triene **6**, a useful precursor for the synthesis of (8*S*)-HETE.[4]

Results and Discussion

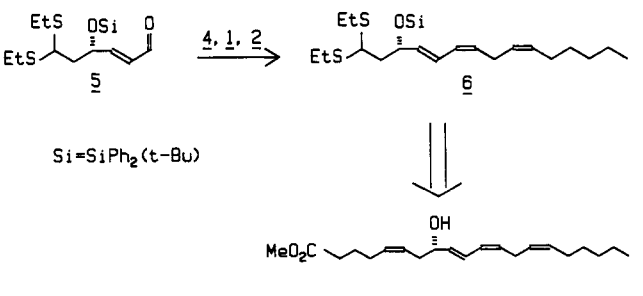
In our approach to the synthesis of (6*Z*,9*Z*)-heneicosadiene (**3**), we could envision starting from 1-undecylcuprate or 1-pentylcuprate as illustrated in Scheme I. When acetylene was introduced into a solution of 1-undecylcuprate[3] and the corresponding 1-tridecenylcuprate treated with vinyltriphenylphosphonium bromide, HMPA, and hexanal, a mixture of (6*Z*,9*Z*)-heneicosadiene (**3**), the diacetylene addition product (6*Z*,9*Z*,11*Z*)-tricosatriene, 1-tridecene, and the alkenyl cross-coupling product ($C_{11}H_{23}CH{=}CH)_2$ were obtained.

Since separation of these hydrocarbons was troublesome, the same sequence was repeated using pentylcuprate **4**.[3] The difficult part in the process was control of the amount of acetylene which added, and on a 1-mmol scale, the desired diene **3** was contaminated with 20–25% of **3a** where two molecules of acetylene had reacted with the pentylcuprate. Kugelrohr distillation gave a 40% yield of **3**, contaminated with 10% of **3a**, as determined by GC/

Scheme I



Scheme II



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(3) 1-Undecylcuprate or 1-Pentylcuprate were prepared by treating the appropriate 1-bromo derivative, in THF, with *tert*-butyllithium (2 equiv) at −78 °C for 20 min followed by the addition of CuBr/SMe_2 (0.5 equiv) and stirring at −50 °C for 1 h.

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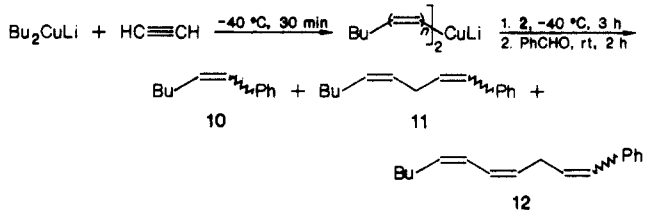
Table I. Study on the Addition of Acetylene to Butylcuprate in the Four-Component Vinyltriphenylphosphonium Bromide Reaction



entry	acetylene introduction: temp, °C (amt, equiv)	product ratio 10/11/12[a]
1[b]	−55 (1)	<2/69/29
2	−40 (1)	<2/74/24
3	−40 (0.5)	24/70/6
4	−78 (1)	30/66/4
5[c]		0/100/0

[a] Ratio determined by GC/MS. [b] Alkenylcuprate formed according to Normant's method.[5] [c] See Scheme III for the preparation of the alkenylcuprate.

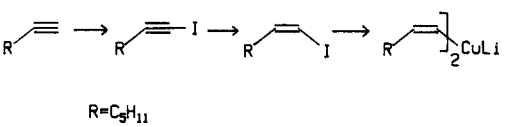
MS. The ^{13}C NMR spectrum of this material indicated a 9*Z*/9*E* ratio of approximately 86/14, whereas its EI MS was superimposable on that of the naturally occurring (6*Z*,9*Z*)-heneicosadiene (**3**).[2]

To apply our methodology to the field of eicosanoids, pentylcuprate **4** was treated sequentially with acetylene (**1**), vinyltriphenylphosphonium bromide (**2**), and HMPA and the resulting copper ylide added to aldehyde **5**.[4] A mixture of triene **6** and a compound in which two acetylene units had been incorporated was isolated in 74% yield (52% and 22%, respectively). Triene **6** has been used as an intermediate in the synthesis of (8*S*)-HETE.[4]

From these results it is apparent that the four-component reaction, although versatile, is plagued by control of the amount of acetylene being incorporated. This was a suprising result since there have been several articles and reviews published concerning alkenylcuprates that fail to mention this particular problem.[5] An extensive search of the literature however yielded one report in which Normant mentions that certain alkenylcuprates may react with acetylene to yield the corresponding (*Z*,*Z*)-dienyl cuprates in varying amounts.[6] This being the case, we decided to examine the incorporation of acetylene by butylcuprate under various conditions. The results are summarized in Table I.

It was found that when acetylene was added to the butylcuprate under Normant's exact conditions (entry 1) or at −40 °C (entry 2), the reaction mixture was always contaminated with aproximately 24–29% of a compound where two acetylene units had been incorporated. When acetylene was introduced at −78 °C, the major contaminant (30%) was now a compound in which no acetylene had been incorporated (entry 4). It is interesting to note that when half the required amount of acetylene was introduced there was still approximately 6% of the double acetylene incorporation adduct being formed (entry 3). These results indicate that Normant's methodology is of limited use in our vinyltriphenylphosphonium bromide reaction due to the lack of selectivity with which the acetylene is incorporated. A different approach toward the synthesis of these alkenylcuprates was therefore required to make our methodology a viable one.

Scheme III



This has been realized by Silverstein et al.[7] whose synthesis of lithium di-(*Z*)-1-heptenylcuprate is outlined in Scheme III. Metalation of 1-heptyne by treatment with *n*-BuLi followed by iodination of the 1-lithio-1-heptyne yields 1-iodo-1-heptyne. This is transformed to (*Z*)-1-iodo-1-heptene by addition of dicyclohexylborane or reduction with diimide.[8] Treatment of this derivative with *n*-BuLi (1 equiv) or *tert*-butyllithium (2 equiv) produces (*Z*)-1-lithio-1-heptene, which upon addition to an ether or THF suspension of CuI yields the lithium di-(*Z*)-1-heptenylcuprate. Starting from 1-hexyne this approach has been successfully applied to preparing the model compound **11** (Table I, entry 5).

The use of the methodology outlined by Silverstein et al. in conjunction with our vinyltriphenylphosphonium bromide reaction therefore constitutes a general approach for the rapid preparation of 1,5-disubstituted (1*Z*,4*Z*)-pentadienes.

Experimental Section

The ^1H NMR (200 MHz) and ^{13}C NMR (300 MHz) were recorded on a Varian XL-200 or XL-300 spectrometer using tetramethylsilane as internal standard, in deuteriochloroform as solvent. Gas chromatographic analysis utilized a Hewlett-Packard 5890 operated with a fused silica capillary column (25 m × 0.2 mm) and a flame ionization detector. Mass spectra were recorded on a MP 5884A or LKB 9000 mass spectrometer.

General Procedure for the Cuprate–Acetylene–Vinyltriphenylphosphonium Bromide–Aldehyde Reaction. Synthesis of (6*Z*,9*Z*)-Heneicosadiene (3). A solution of commercially available 1-bromopentane (0.5 mL, 4 mmol) in dry THF (20 mL) was treated with 1.6 M *tert*-butyllithium (5.0 mL, 8 mmol) at −78 °C for 20 min and the resulting pentyl lithium reacted with $CuBr/SMe_2$[9] (421 mg, 2.05 mmol) at −50 °C for 1 h. Acetylene (96 mL, 4 mmol), cleared from acetone through two dry ice traps and measured in a water gasometer, was bubbled in at −50 °C and the mixture stirred for 45 min followed by the addition of vinyltriphenylphosphonium bromide (774 mg, 2.1 mmol) and hexamethylphosphoric triamide (0.87 mL, 5 mmol). After 20 h[10] at −50 °C, dodecanal (184 mg, 1 mmol) was added and stirring continued at room temperature for 3 h. Hexanes (100 mL) was added, and the mixture was poured into aqueous saturated NH_4Cl (50 mL) and filtered over Celite. The aqueous phase was further extracted with hexanes (2 × 50 mL), the combined hexanes extracts were washed with saturated NH_4Cl (2 × 30 mL) and brine (2 × 30 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. (6*Z*,9*Z*)-Heneicosadiene (**3**), isolated in 40% yield (contaminated with 10% of **3a**) by Kugelrohr distillation, was found to have a 9*Z*/9*E* ratio of approximately 86/14 as determined by ^{13}C NMR: ^1H NMR ($CDCl_3$) δ 0.89 (m, 6 H), 1.26 (m, 24 H), 2.04 (m, 4 H, C(5) H, C(11) H), 2.77 (m, 2 H, C(8) H), 5.35 (m, 4 H, C(6) H, C(7) H, C(9) H, C(10) H); ^{13}C NMR δ 130.46 (C (9*E*)), 130.18 (C (9*Z*)), 128.26 (C (10*E*)), 127.93 (C (10*Z*)); EI MS, molecular ion (M^+) at *m*/*z* 292, corresponding to the molecular formula $C_{21}H_{40}$. It showed other ions at *m*/*z*

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(9) Copper iodide (Aldrich, gold label 99.999%) could be used with identical results.

(10) Reaction times of 9 h gave similar results.

(relative intensity) that were superimposable on that of the naturally occurring compound.[2]

Preparation of (6*Z*,9*Z*,11*E*)-15,15-Bis(ethylthio)-13(*S*)-[(*tert*-butyldiphenylsilyl)oxy]pentadecatriene (6). The ylide was prepared in a manner similar to that used for the synthesis of (6*Z*,9*Z*)-heneicosadiene (3) with the exception that 3.5 equiv of the cuprate reagent and 3 equiv of vinyltriphenylphosphonium bromide were used. Aldehyde 5 was added to the ylide at −50 °C and the reaction brought to −20 °C over 1.5 h followed by stirring at room temperature for 3 h. The mixture was diluted with ether (70 mL), quenched with aqueous saturated NH_4Cl (40 mL), and filtered over Celite and the aqueous layer extracted with ether (2 × 70 mL). The combined ether extracts were washed with brine (3 × 30 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by column chromatography (1% ethyl acetate in petroleum ether) gave a mixture of triene 6 and a compound in which two acetylene units had been incorporated in 74% yield (52% and 22% yields, respectively): ^1H NMR ($CDCl_3$) δ 0.89 (m, 9 H), 1.05 (s, 9 H), 1.12–1.38 (m, 6 H), 2.0 (m, 2 H, CH_2CH=), 2.48 (m, 2 H, CH_2CHOSi), 2.72 (m, 2 H, =$CHCH_2CH$=), 3.78 (dd, 1 H, J_1 = J_2 = 7 Hz, $CH(SEt)_2$), 4.5 (m, 1 H, $CHOSi$), 5.19–5.44 (m, 3 H, CH=$CHCH_2CH$=), 5.56 (dd, 1 H, J ≐ 14.7 Hz, J = 7.7 Hz, CH=$CHCHOSi$), 5.80 (dd, 1 H, J_1 = J_2 = 10.7 Hz, =$CHCH$=CHCHOSi), 6.10 (dd, 1 H, J_1 = 14.7 Hz, J_2 = 10.7 Hz, CH=CHCHOSi), 7.25–7.68 (m, 10 H); LRMS (70 eV) *m/z* (relative intensity) 523 ($M^+ - t$-Bu, 9), 457 ($M^+ - C_9H_{15}$, 83), 199 ($HOSiPH_2$, 72), 135 ($CH(SEt)_2$, 100).

Preparation of 1-Phenyl-1,4-nonadiene (11). To a solution of (*Z*)-1-iodo-1-hexene (140 mg, 0.67 mmol) in dry THF (10 mL), under a nitrogen atmosphere at −78 °C, was added 1.6 M *tert*-butyllithium (0.83 mL, 1.34 mmol) dropwise. After 15 min, CuI (64 mg, 0.335 mmol) was added, the reaction mixture stirred at −40 °C for 1 h followed by the addition of vinyltriphenylphosphonium bromide (124 mg, 0.335 mmol) and HMPA (0.15 mL), and stirring continued at −40 °C for 18 h. Benzaldehyde (18 mg, 0.17 mmol) was introduced and the solution stirred at room temperature for 2 h. The mixture was diluted with hexanes (50 mL), quenched with aqueous saturated NH_4Cl (40 mL), and filtered over Celite and the aqueous layer extracted with hexanes (2 × 50 mL). The combined hexanes extracts were washed with saturated NH_4Cl (2 × 30 mL) and brine (2 × 30 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by flash chromatography (hexanes/ether = 100/1) gave 1-phenyl-1,4-nonadiene as a mixture of its *Z*/*E* isomers (87/13) in 50% yield. No traces of 10 or 12 could be detected by GC/MS. (1*Z*,4*Z*)-1-Phenylnonadiene: ^1H NMR ($CDCl_3$) δ 0.88 (m, 3 H, CH_3), 1.32 (m, 4 H), 2.0–2.1 (m, 2 H, C(6) H), 2.95–3.1 (m, 2 H, C(3) H), 5.43 (m, 2 H, C(4) H, C(5) H), 5.66 (ABX, 1 H, J_{AB} = 11.8 Hz, J_{AX} = 7.4 Hz, C(2) H), 6.43 (ABX, 1 H, J_{AB} = 11.8 Hz, J_{BX} = 1 Hz, C(1) H), 7.29 (s, 5 H); LRMS (70 eV) *m/z* (relative intensity) 200 (M^+, 12), 143 ($M^+ - C_4H_9$, 46), 129 ($M^+ - C_5H_{11}$, 87), 91 ($C_7H_7^+$, 100), 90 ($C_7H_6^+$, 70). (1*E*,4*Z*)-1-Phenylnonadiene: ^1H NMR ($CDCl_3$) δ 0.88 (m, 3 H, CH_3), 1.32 (m, 4 H), 2–2.1 (m, 2 H, C(6) H), 2.9–3.1 (m, 2 H, C(3) H), 5.4 (m, 2 H, C(4) H, C(5) H), 6.25 (ABX, 1 H, J_{AB} = 16 Hz, J_{AX} = 6 Hz, C(2) H), 6.5 (ABX, 1 H, J_{BA} = 16 Hz, J_{BX} = 1 Hz, C(1) H), 7.3 (s, 5 H); LRMS (70 eV) *m/z* (relative intensity) 200 (M^+, 27), 143 ($M^+ - C_4H_9$, 30), 129 ($M^+ - C_5H_{11}$, 72), 91 ($C_7H_7^+$, 69), 90 ($C_7H_6^+$, 100).

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Cyclization of Polyenes. 46.[1] Synthesis of (±)-Asperdiol, an Anticancer Cembrenoid[2]

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On the basis of retrosynthetic perspective (Scheme I), the asperdiol skeleton (I = 24) and its geometrical isomer (II = 25) were constructed from *cis*- and *trans*-isopropenyl alcohols 3a and 3b. I (24) was converted into (±)-asperdiol 1 by the sequential reactions of bromo etherification to 33 followed by epoxidation and then reductive regeneration of the double bond.

Asperdiol (1) was discovered by Weinheimer and his co-workers in 1977 from Caribbean gorgonians of the *Eunicea* genus with the aid of in vitro P-388 lymphocytic leukemia (PS) and KB (cytotoxicity) bioassay.[3] Its structure including absolute configuration was revealed unequivocally as a highly oxygenated cembrenoid by X-ray crystallographic analysis.

The antitumor activity coupled with its conspicuous structural feature has elicited considerable interest in synthetic approaches to this novel macrocylcic natural product.[4]

In connection with our longstanding interest in the synthetic study of cembrenoids,[5] we focused our synthetic attention on asperdiol (1). We delineate here the details of our work starting from isopropenyl alcohols **3a** and **3b**, readily available from our common cembrenoid intermediate chloro ketone **2**.[6] The purpose of our synthetic study

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