ture was heated at reflux overnight. The reaction mixture was washed with 10 mL of water and solvent removed by distillation. The residue was distilled to give 4.1 g (44%) of product, bp 115 °C (9 mm). This material was purified by preparative GLC on a 9 ft × ¼ in. column packed with 20% SE-30 on 60/80 Chromosorb W before use. This material showed a rotation of $[\alpha]^{20}_{313}$ −6.3 ± 0.2 (c 0.0285, absolute ethanol). A solution of 2 g of this pyrrolidinone in 300 mL of 2-propanol was irradiated until 50% of the starting material was consumed (GLC). Solvent was removed by distillation and unreacted starting material purified by preparative GLC. This material showed a rotation $[\alpha]^{20}_{313}$ −6.3 (0.0286, absolute ethanol).

Quantum Yields. Samples consisted of the pyrrolidinone (2 M) in 2-propanol or 2-methyl-2-propanol containing either nonane or decane internal standards. All pyrrolidinones were purified by preparative GLC. Samples were placed in 1.0 × 16 cm quartz tubes, subjected to three freeze–pump–thaw cycles to remove dissolved gases, and sealed at 10^{-6} torr. Samples were irradiated, in triplicate, in a merry-go-round apparatus surrounded by a bank of ten GE 15-T8 germicidal lamps whose principal emission is at 254 nm. The formation of pentenal from cyclopentanone was used as actinometer.[5] Since the pyrroles produced in these reactions have molar absorptivities approximately 100 times larger than those of the pyrrolidinones at the irradiating wavelength (254 nm), conversions were held to below 1% to prevent product competition for the light. Samples were analyzed by GLC on either of the following columns: 20% SE-30 on 100/120 Chromosorb WHP, 6 ft × ¼ in.; 3% OV-17 on 100/120 Chromosorb WHP, 6 ft × ⅛ in. Quantum yield data are presented in Table III.

Acknowledgment. We are indebted to the Center of Materials Research of the University of Maryland for partial support of this work.

Registry No.—**1a,** 932-07-0; **1b,** 68036-46-4; **1d,** 3470-98-2; methylamine, 74-89-5; 2-pyrrolidinone, 616-45-5; 1-bromo-2-methylbutane, 10422-35-2; 1-(2-methylbutyl)-2-pyrrolidinone, 58244-31-8; 1-methylazetidine, 4923-79-9; γ-butyrolactone-5,5-d_2, 68036-47-5; succinic anhydride, 108-30-5.

References and Notes

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Selective Codimerization of Acetylenes and Allyl Halides Catalyzed by Palladium Complexes

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The reaction of various acetylenes and allyl halides with palladium complexes selectively gives substituted 1,4-diene codimers. The $PdX_2(PhCN)_2$ complex is the most active catalyst. In contrast to substituted acetylenes, the reaction of acetylene itself and allyl halides gives a 1-halogeno-1,3,6-heptatriene cotrimer besides codimers. The catalytic reaction proceeds via Pd–halogen bond recycle; initially acetylene inserts into a Pd–halogen bond and subsequently allyl halide inserts into a Pd–vinyl bond, followed by the β-halogen elimination to give a codimer. The successive insertions of acetylene and allyl halide into the Pd–vinyl bond give a cotrimer. This codimerization provides a very convenient synthetic method for halogeno-substituted mono- and/or diolefins.

Homooligomerization of acetylenes or olefins using transition metal catalysts has been extensively studied.[1] However, only a few examples are known of cooligomerization of acetylenes and monoolefins[2–6] probably because of the difficulty caused by the large difference in coordination ability between acetylenes and olefins to metal center; acetylenes are much more reactive to metals than olefins are, which results in exclusive polymerization of the acetylenes. Concerning palladium catalysts, only two examples have been reported. One is a linear cotrimerization of diphenylacetylene and olefins,[5] and the other is a cyclic cotrimerization of dimethoxycarbonylacetylenes and norbornene.[6] The diphenylacetylene and dimethoxycarbonylacetylene used above have a relatively lower reactivity to palladium when compared with common acetylenic compounds. Therefore, in order to accomplish the cooligomerization of acetylenes and olefins, it is very important to select suitable acetylenic or olefinic compounds with similar orders of coordination ability to a metal, or to devise reaction conditions in which extensive acetylene polymerization is prevented. We have found that the selective codi-

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Table I. Codimerization of Substituted Acetylenes and Allyl Halides[a]

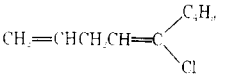
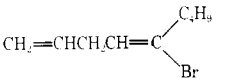
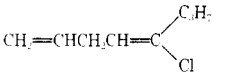
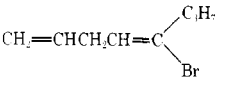
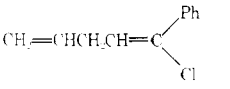
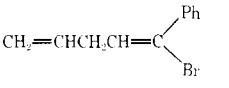
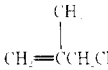
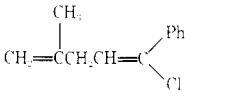
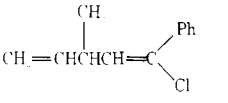
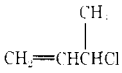
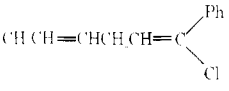
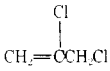
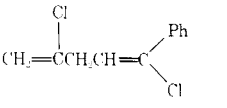
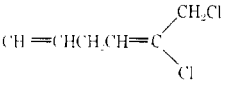
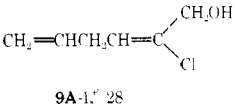
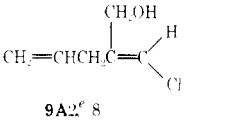
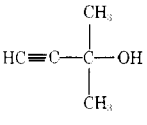
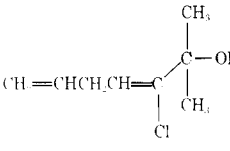
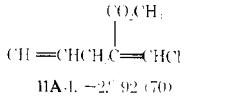
acetylene	registry no.	allyl halide	registry no.	catalyst[b]	registry no.	product, yield,[c] % (isolated yield)	registry no.	bp, °C (mmHg)
$HC{\equiv}CC_4H_9$	693-02-7	$CH_2{=}CHCH_2Cl$	107-05-1	A	14220-64-5	 1A, 90 (70)	59973-83-6	54–55 (7)
$HC{\equiv}CC_4H_9$		$CH_2{=}CHCH_2Br$	106-95-6	B	15003-43-7	 1B, 95 (70)	68091-89-4	53–54 (3.5)
$HC{\equiv}CC_3H_7$	627-19-0	$CH_2{=}CHCH_2Cl$		A		 2A, 90 (70)	59937-82-5	47–48 (6)
$HC{\equiv}CC_3H_7$		$CH_2{=}CHCH_2Br$		B		 2B, 80	68091-90-7	
HC≡CPh	536-74-3	$CH_2{=}CHCH_2Cl$		A		 3A, 92 (82)	52917-14-3	95–96 (7.5)
HC≡CPh		$CH_2{=}CHCH_2Cl$[d]		A		3A, 60		
HC≡CPh		$CH_2{=}CHCH_2Br$		B		 3B, 95	68091-91-8	
HC≡CPh			563-47-3	A		 4A, 48	68091-92-9	
HC≡CPh		$CH_3CH{=}CHCH_2Cl$[d]	591-97-9	A		 5A, 27	68091-93-0	
HC≡CPh			563-52-0	A		 6A, 40	68091-94-1	
HC≡CPh			78-88-6	A		 7A, 48	52917-16-5	
$HC{\equiv}CCH_2Cl$	624-65-7	$CH_2{=}CHCH_2Cl$		A		 8A, 72 (50)	68091-95-2	62 (3.8)
$HC{\equiv}CCH_2OH$	107-19-7	$CH_2{=}CHCH_2Cl$		A		 9A-1,[e] 28	68091-96-3	
						 9A-2,[e] 8	68091-97-4	
	15-19-5	$CH_2{=}CHCH_2Cl$		A		 10A, 50	68091-98-5	
$HC{\equiv}CCO_2C$-H_3	922-67-8	$CH_2{=}CHCH_2Cl$		A		 11A-1, ~2[e] 92 (70)	68091-99-6	65–66 (10)

Table I *(continued)*

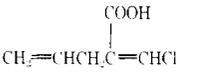
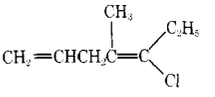
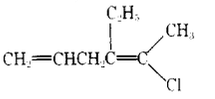
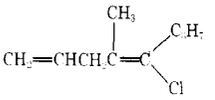
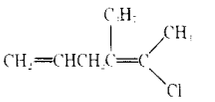
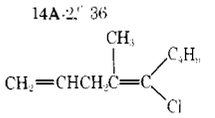
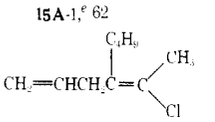
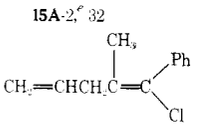
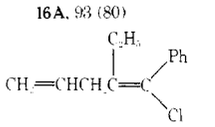
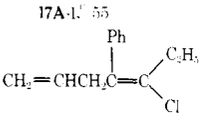
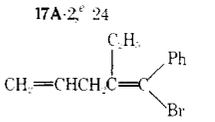
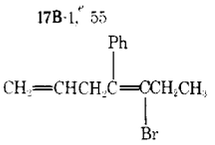
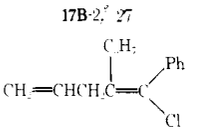
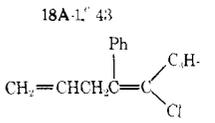
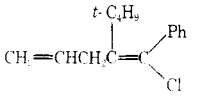
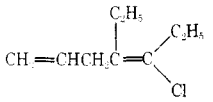
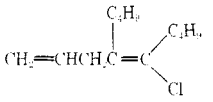
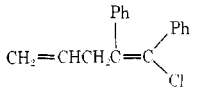
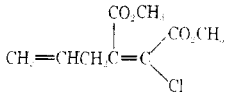
acetylene	registry no.	allyl halide	registry no.	catalyst[b]	registry no.	product, yield,[c] % (isolated yield)	registry no.	bp, °C (mmHg)
$HC{\equiv}CCOOH$	471-25-0	$CH_2{=}CHCH_2Cl$		A		 **12A**, 45	68092-00-2	
$CH_3C{\equiv}CC_2H_5$	627-21-4	$CH_2{=}CHCH_2Cl$		A		 **13A-1**,[e] 60	68092-01-3	
						 **13A-2**,[e] 30	68092-02-4	69–70 (4.5)
$CH_3C{\equiv}CC_3H_7$	764-35-2	$CH_2{=}CHCH_2Cl$		A		 **14A-1**,[f] 56 (75)	68092-03-5	
						 **14A-2**,[f] 36	68092-04-6	57–58 (5)
$CH_3C{\equiv}CC_4H_9$	1119-65-9	$CH_2{=}CHCH_2Cl$		A		 **15A-1**,[e] 62	68092-05-7	
						 **15A-2**,[e] 32	68092-06-8	72–73 (4)
$PhC{\equiv}CCH_3$	673-32-5	$CH_2{=}CHCH_2Cl$		A		 **16A**, 93 (80)	59937-79-0	68–69 (2)
$PhC{\equiv}CC_2H_5$	622-76-4	$CH_2{=}CHCH_2Cl$		A		 **17A-1**,[f] 55	68092-07-9	
						 **17A-2**,[e] 24	68092-08-0	
$PhC{\equiv}CC_2H_5$		$CH_2{=}CHCH_2Br$		B		 **17B-1**,[f] 55	68092-09-1	
						 **17B-2**,[f] 27	68092-10-4	
$PhC{\equiv}CC_3H_7$	4250-81-1	$CH_2{=}CHCH_2Cl$		A		 **18A-1**,[f] 43	68092-11-5	
						 **18A-2**,[e] 23	68092-12-6	

Table I *(continued)*

acetylene	registry no.	allyl halide	registry no.	catalyst[b]	registry no.	product, yield,[c] % (isolated yield)	registry no.	bp, °C (mmHg)
PhC≡C-*t*-C_4H_9	4250-82-2	CH_2=$CHCH_2Cl$		A		 19A, 82[f]	68092-13-7	
C_2H_5C≡C-C_2H_5	928-49-4	CH_2=$CHCH_2Cl$		A		 20A, 90 (82)	59937-84-7	51–52 (2)
C_4H_9C≡C-C_4H_9	1942-46-7	CH_2=$CHCH_2Cl$		A		 21A, 90	68092-14-8	
PhC≡CPh	501-65-5	CH_2=$CHCH_2Cl$		A		 22A, 90	52917-15-4	
CH_3O_2CC≡C-CO_2CH_3	762-42-5	CH_2=$CHCH_2Cl$		A		 23A, 85[f]	68092-15-9	

[a] Reaction with Pd complex (4 mmol), acetylenic compound (80 mmol), and allyl halide (80 mL) at 20 °C for 2 h. Satisfactory analytical data (±0.4% for C, H, Cl, Br) were reported for all new compounds. [b] A is $PdCl_2(PhCN)_2$. B is $PdBr_2(PhCN)_2$. [c] Yields were based on acetylenes used and determined by GC analysis. [d] Nitromethane (30 mL) was the solvent. Reaction with Pd complex (1 mmol), phenylacetylene (10 mmol), and allyl chloride (50 mmol). [e] These isomers could not be well separated by GC and yields were determined by NMR analysis. [f] Reaction time was 24 h.

merization of various acetylenes and allyl halides proceeds smoothly with palladium complex catalysts under mild conditions.[7,8] Recently there appeared selective 1,4-diene syntheses which, however, used mixed metals as the reagent and are stoichiometric with respect to the metals used.[9-12] The present catalytic codimerization provides a facile and useful 1,4-diene synthesis without isomerization to 1,3-diene.[13,14]

We report herein an investigation of the scope of the reaction with a variety of acetylenes and allyl halides together with mechanistic investigations.

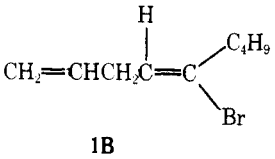
Results and Discussion

Generally acetylenes are more reactive toward palladium than olefins. In order to accomplish the codimerization of an acetylene and an allyl halide, low acetylene concentrations must be maintained during the reaction. If large amounts of the acetylenic compound are added to the allyl halide solution containing a palladium complex catalyst, the acetylene polymerizes rapidly. Since the codimerization is exothermic, it is necessary in all experiments to add acetylenic compounds carefully to the allyl halide solution which is maintained at about 20 °C. Lowering the reaction temperature to −30 °C can prevent the polymerization of acetylene even at high acetylene concentrations and a good yield of a codimer is obtained in spite of a slow reaction rate.

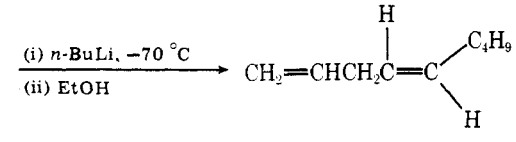
Various palladium compounds, e.g., PdX_2, $PdX_2(PhCN)_2$, $Pd(OAc)_2$–LiX, and (π-allyl-$PdX)_2$ (X = halogen), had catalytic activity for the codimerization. $PdX_2(PhCN)_2$ showed the highest activity.

Twenty acetylenic compounds were treated with seven allyl halides to investigate the scope of the codimerization. The yields of codimers and their properties are shown in Table I. NMR data of the codimers are summarized in Table II which is available as supplementary material.

Terminal Acetylenes. The reaction of 1-hexyne and allyl chloride gave 5-chloro-1,4-nonadiene (**1A**) in almost quantitative yield in the presence of the $PdCl_2(PhCN)_2$ catalyst. Similarly bromide analogue **1B** was obtained by using 1-hexyne, allyl bromide, and $PdBr_2(PhCN)_2$. The structure was determined by IR and NMR spectroscopy and elemental analysis. The configuration about the double bond with respect to the halogen was determined to be *Z* by treatment of **1B** with *n*-BuLi and EtOH[15] to form the known (*E*)-1,4-nonadiene.[9]



1B



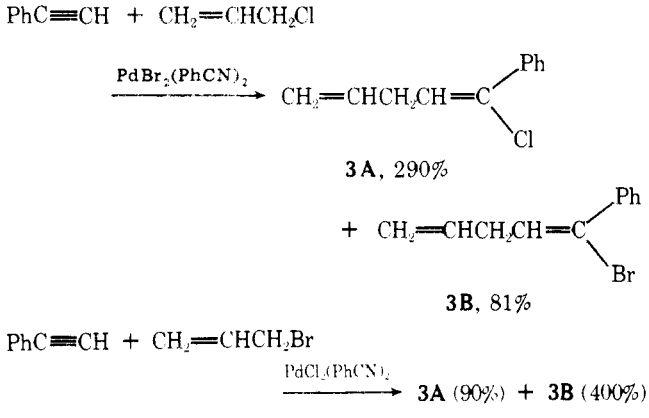
The reaction of phenylacetylene with allyl chloride and allyl bromide gave 1-halogeno-1-phenyl-1,4-pentadienes (**3A, 3B**) respectively, whereas the codimerization of phenylacetylene and allyl iodide with $PdI_2(PhCN)_2$ did not take place. A mixed halide system such as $PdBr_2(PhCN)_2$–allyl chloride and $PdCl_2(PhCN)_2$–allyl bromide gave mixtures of the chloride codimer (**3A,** 290% based on Pd used) and the bromide codimer (**3B,** 81%) and **3A** (90%) and **3B** (400%), respectively. The codimers containing the same halogen as the palladium ligands used were produced in quantitative yield, suggesting that the rate of the halogen exchange reaction between allyl halide and $PdX_2(PhCN)_2$ was much slower than that of the codimerization under the reaction conditions.

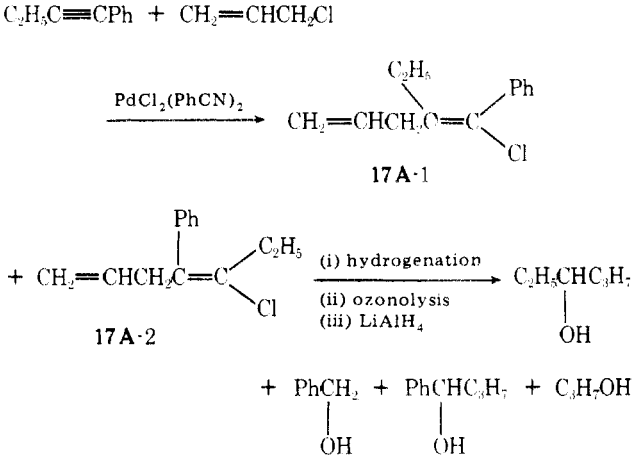
Carboxyl, ester, halogeno, and hydroxyl functional groups on the acetylenic compounds can be tolerated for the codimerization. The reaction of propargyl alcohol with allyl

Table III. Cooligomerization of Acetylene and Allyl Halides[a]

catalyst	solvent	product, yield (%, based on Pd used) (Z) codimer	(E) codimer	cotrimer
$PdCl_2(PhCN)_2$[b]		1110	630	60
$PdCl_2(PhCN)_2$	AcOH	150	trace	120
$PdCl_2(PhCN)_2$	benzene	150	trace	10
$PdCl_2(PhCN)_2$	acetone	48	75	140
$PdCl_2(PhCN)_2$	MeOH	31	150	300
$PdCl_2(PhCN)_2$–LiCl[c]	AcOH	15	120	280
$PdCl_2$–LiCl[c]	AcOH	trace	70	240
$Pd(OAc)_2$–LiCl[c]	AcOH	trace	19	500
$Pd(OAc)_2$–LiCl[d]	AcOH	trace	33	460
$Pd(OAc)_2$–LiBr[e]	AcOH	32	160	490
$Pd(OAc)_2$–LiI[f]	AcOH	170	41	310
$(Et_4N)_2Pd_2Cl_6$	CH_2Cl_2	trace	490	940

[a] Reaction with Pd complex (4 mmol), allyl chloride (120 mmol), and solvent (36 mL) at 20 °C for 2 h. [b] Allyl chloride (45 mL) was used. [c] Molar ratio of Pd complex and LiCl was 1:5. [d] Pd complex–LiCl = 1:10. [e] Allyl bromide was used. Pd complex–LiBr = 1:5. [f] Allyl iodide was used. Pd complex–LiI = 1:5. Reaction time was 48 h.





chloride gave two double bond regioisomers of 2-chloro-2,5-hexadien-1-ol (**9A**-1, linear type) and 1-chloro-2-hydroxymethyl-1,4-pentadiene (**9A**-2, branched type) in the ratio of 3.5:1. Acetylenes containing strong electron-withdrawing substituent such as carboxyl and ester gave exclusively the branched type codimers (**11A, 12A**).

The codimerization can be applied to various allyl halides. Substituted allyl chlorides gave lower yields of the corresponding codimers, compared with allyl chloride probably because of their weaker coordination ability to palladium.

It should be noted that corresponding double bond isomers, 1,3-dienes, could not be observed by GC and NMR spectroscopy in the reaction products. This result shows that both reactants, acetylene and allyl halide, coordinate more strongly to palladium than the 1,4-diene products do under the reaction conditions and it also suggests that the codimerization does not involve a palladium–hydride intermediate.[16]

Disubstituted Acetylenes. The reactions of unsymmetrical acetylenes give mixtures of double bond regioisomers. The regioisomer ratios were influenced by the alkyl group on acetylenic bonds. The reactions of 1-phenyl-1-butyne and allyl halides gave a mixture of 4-halogenophenylmethylene-1-hexenes (**17A**-1, **17B**-1) and 5-halogeno-4-phenyl-1,4-heptadiene (**17A**-2, **17B**-2). The structures of the new compounds were further confirmed by the following chemical behavior. Ozonolysis after the selective hydrogenation of the 1,4-diene codimers to 3-chlorophenylmethylenehexane and 3-chloro-4-phenyl-3-heptene with a polymer anchored Rh catalyst[17] gave four alcohols: 3-hexanol, benzyl alcohol, 1-phenyl-1-butanol, and 1-propanol. Furthermore, treatment of the bromide codimers (**17B**-1, **17B**-2) with *n*-BuLi gave a mixture of 4-phenylmethylene-1-hexene and 4-phenyl-1,4-heptadiene. Similarly the reaction of 1-phenyl-1-pentyne gave two regioisomers (**18A**-1, **18A**-2). It is interesting that the reaction of 3,3-dimethyl-1-phenyl-1-butyne gave 2,2-dimethyl-3-(chlorophenylmethylene)-5-hexene (**19A**) without other regioisomers. The reaction rate was very slow; after 2 h, the yield of the codimer was 10%, and after 48 h the yield reached 82%.

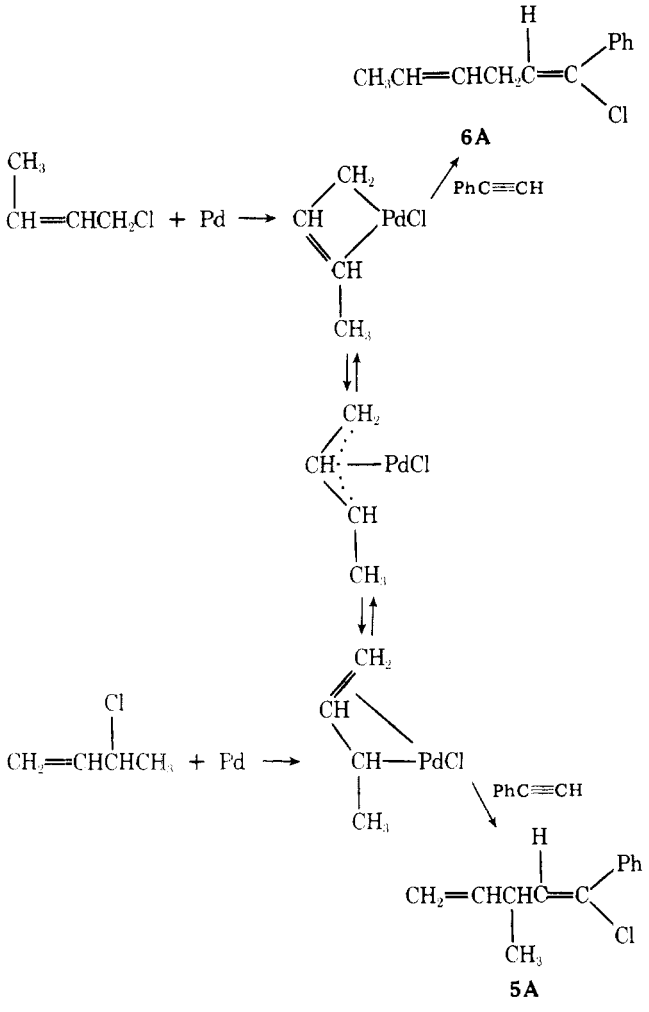
In the case of unsymmetrical alkyl methylacetylenes, the ratios of terminal methyl substituted codimer to internal codimer fall in a range of 4:6–3:7 (**13A, 14A, 15A**).

In the reaction of dimethoxycarbonylacetylene, a longer reaction time is required to attain a high yield since the ester group weakens the coordination of acetylene to palladium owing to electronic factors.

Maitlis reported that disubstituted acetylenes were trimerized to give benzene derivatives with palladium complexes.[18] However, the corresponding benzenes could not be detected under our conditions.

Acetylene. In contrast to the above reactions of substituted acetylenes, the reaction of acetylene and allyl chloride gave a cotrimer as well as codimers, 1-chloro-1,3,6-heptatriene (probably (1*E*,3*Z*) but not definitely established) and (*E*)- and (*Z*)-1-chloro-1,4-pentadienes. The distribution of the three products was remarkably influenced by the palladium complex, solvent, and chloride ion concentration as shown in Table III: (*E*)- and (*Z*)-codimers were selectively formed by $PdCl_2(PhCN)_2$; a dimer complex, $(Et_4N)_2Pd_2Cl_6$, gave (*E*) codimer and cotrimer; $Pd(OAc)_2$–LiCl gave exclusively the cotrimer; the use of methanol solvent yielded more (*E*) codimer than (*Z*) codimer accompanying large amounts of the cotrimer; the addition of LiCl increased the yields of both (*E*) codimer and cotrimer. Generally, in the cases where (*E*) codimer was formed in higher yield than the (*Z*) codimer, the yield of the cotrimer increased. These results suggest that both

Scheme I

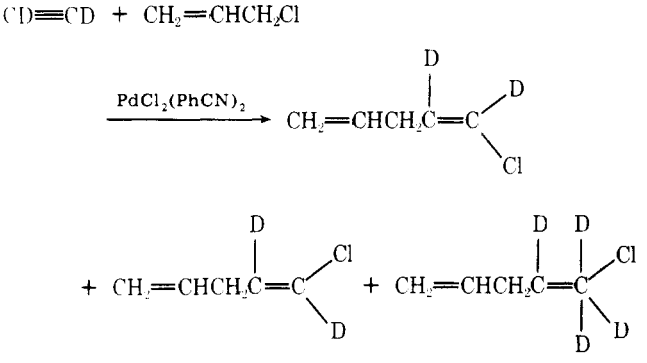


reaction paths for (*E*) codimer and cotrimer might contain a common intermediate species.[19]

In these reactions, it was confirmed that the codimer products were not isomerized under the reaction conditions and the ratio of (*E*) to (*Z*) codimers remained constant during the reactions.

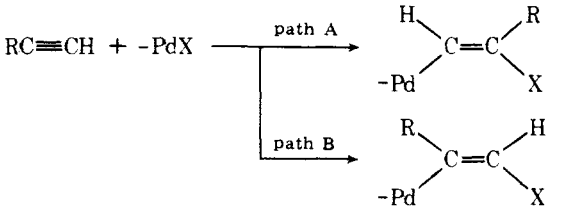
Mechanism. At least two typical mechanisms for the codimerization can be imagined. One is the oxidative addition–reductive elimination mechanism and the other is the insertion–elimination mechanism. In the former mechanism which has been proposed in the carbonylations of acetylene and allyl halide with nickel complexes, an oxidative addition of allyl halide to nickel is the initial step.[20] If the present codimerization would proceed via a π-allyl intermediate formed by the oxidative addition of allyl halide to palladium, we could propose a reaction mechanism involving the insertion of acetylene between the π-allyl moiety and palladium, followed by reductive elimination of hexadienyl and halogen moieties as shown in Scheme I. If the above mechanism would be operative, both codimerizations of 1-chloro-2-butene and 3-chloro-1-butene with phenylacetylene should give the common products **5A** and **6A**, but these two reactions actually gave different products of 1-chloro-3-methyl-1-phenyl-1,4-pentadiene (**5A**) and 1-chloro-1-phenyl-1,4-hexadiene (**6A**), respectively. Therefore, we can rule out the oxidative addition mechanism.

So we would propose an insertion–elimination mechanism for this codimerization as shown in Scheme II. The insertion of acetylene into a palladium–halogen bond occurs as the first step and subsequently allyl halide inserts into a palladium–vinyl bond. The β-halogen elimination by palladium gives a codimer and a palladium–halogen species and then the catalytic cycle is complete. In the case of unsubstituted acetylenes, the cotrimer is formed by the successive insertion of acetylene and allyl halide into the palladium–vinyl bond. The direction of addition of palladium–halogen to the acetylenic bond determines the stereochemistry of the codimers:[21] cis direction leads to (*Z*) codimer while trans direction leads to (*E*) codimer. It can be presumed that both reactions for (*E*) codimer and the cotrimer might proceed via a common intermediate, the (*E*)-palladium–vinyl species. Support for the palladium–vinyl and palladium–butadienyl species (I, II) comes from Maitlis' work, since the reaction sequence to this point in Scheme II is as proposed for the formation of benzene derivatives from substituted acetylenes and the palladium chloride complex.[18,22] Most recently Larock reported that the reaction of vinyl mercury, allyl chloride, and palladium chloride proceeds via a vinyl palladium intermediate to give 1,4-pentadiene.[12]



Furthermore, in the reaction of dideuterioacetylene and an allyl halide, 1,2-dideuteriocodimers and 1,2,3,4-tetradeuteriocotrimer were obtained without deuterium scrambling at allylic groups. The deuterium distribution is quite compatible with this mechanism. Conclusively the codimerization seems to be explained by the insertion–elimination mechanism containing the palladium–halogen bond recycle.[23]

According to the insertion–elimination mechanism, the formation of regioisomers in the terminal acetylene reactions is ascribed to the direction of addition of the palladium–halogen bond to the triple bond as follows. The direction is

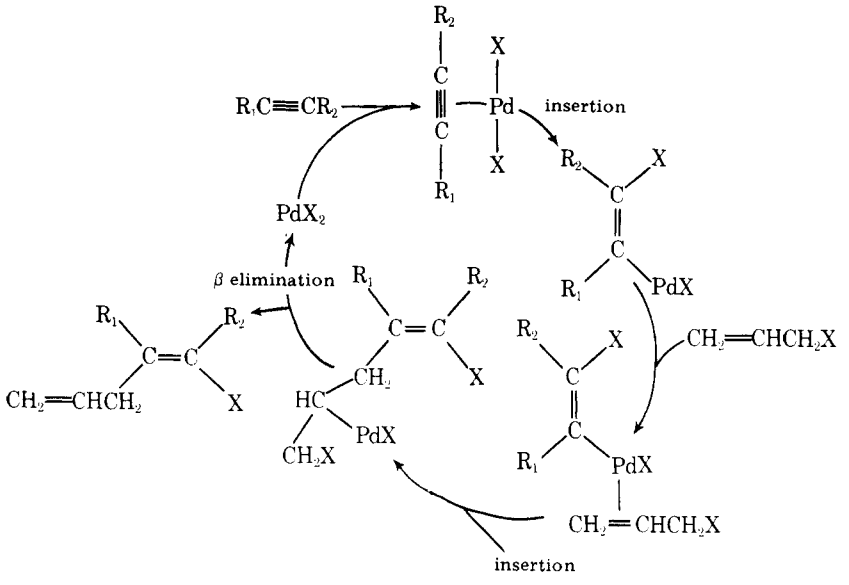


markedly affected by the kinds of substituents attached to the triple bonds. Alkyl and phenyl groups (electron donating) direct palladium exclusively to the β carbon of the triple bond (path A), while carbonyl and ester groups (electron withdrawing) direct palladium to the α carbon (path B). The palladium favors attacking the acetylenic carbon with the higher electron density.[24] Thus it appears that the direction of addition of palladium to acetylene may be strongly controlled by electronic factors.

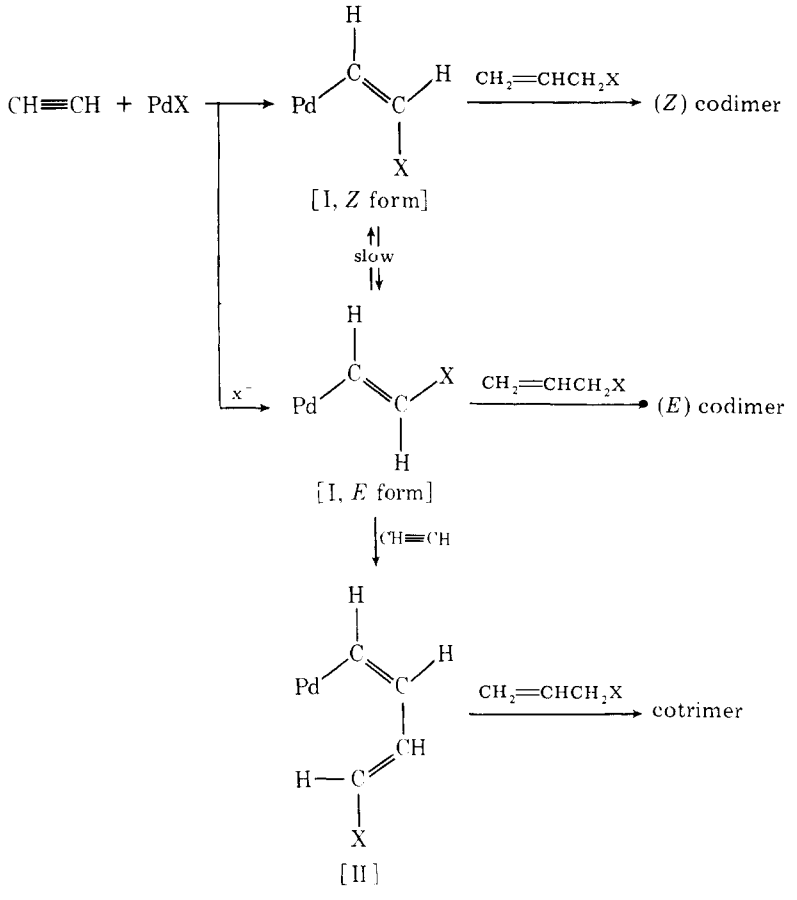
In conclusion, this codimerization provides a facile method for the syntheses of not only 1,4-dienes but also of substituted vinyl halides. We expect that these halogeno-1,4-dienes can be further converted into more useful compounds by the replacement of the halogen atom by other functional groups.[25] In mechanistic aspects, the codimerization proceeds via the palladium–halogen bond recycle mechanism which is different from that of common oligomerizations of acetylenes or olefins involving a metal hydride as an active species.[1]

Scheme II

substituted acetylene reaction



acetylene reaction



Experimental Section

General. GC analyses were run on a shimazu 3BT gas chromatograph. Infrared spectra were recorded using a JASCO Model IR-E spectrometer. Proton magnetic resonance spectra were recorded on JNM-MH-60 or HNM-4H-100 spectrometers. Chemical shifts are reported in parts per million on the δ scale relative to Me_4Si internal standard and coupling constants are in hertz. Elemental analyses were run on a Yanagimoto CHN-CORDER 2-TYPE. Boiling points are uncorrected. All solvents were strictly anhydrous. PdX_2 (X = Cl, Br, and I) was obtained from Wako Pure Chemical Industries, LTD. Other palladium complexes [$PdX_2(PhCN)_2$,[26] $Pd(OAc)_2$,[27] $Pd(acac)_2$,[28] $PdCl_2(PPh_3)_2$,[29] $Pd_2(C_3H_5)_2Cl_2$,[30] and $Pd_2(NEt_4)_2Cl_6$[31]] were prepared by literature procedures. 3-Chloro-1-butene was synthesized by the method of Oae.[32] Other allyl halides were purchased from Wako Pure Chemical Industries, Ltd. and purified by distillation. Acetylenic compounds [1-pentyne,[33] 1-hexyne,[33] 2-heptyne,[34] 5-decyne,[34] 1-phenyl-1-propyne,[34] 1-phenyl-1-butyne,[34] 1-phenyl-1-pentyne,[34] 3,3-dimethyl-1-phenyl-1-butyne,[35] and diphenylacetylene[36]] were prepared by literature procedures. Other acetylenic compounds were commercial grade from Wako Pure Chemical Industries, Ltd. and were purified by distillation. Acetylene was purchased from Fuji Gas Kogyo and dried by passage through a calcium chloride tube before use. Deuterioacetylene was prepared by the reaction of CaC_2 and D_2O.

General Procedure for Codimerizations of Acetylenes and Allyl Halides. The allyl halide and solvent were added to a three-necked flask fitted with a magnetic stirrer bar and a condenser. The palladium catalyst was dissolved in the solution and then acetylenic

compound was added dropwise by a syringe over a period of 1 h while the reaction temperature was maintained at about 20 °C. The mixture was further stirred for 1 h. Allyl halide, unreacted acetylene, and solvent were removed at reduced pressure. The remaining mixture was chromatographed on alumina to remove palladium complexes. The column was eluted with petroleum ether to give codimers.

Codimerization of 1-Hexyne and Allyl Bromide with $PdBr_2(PhCN)_2$. To a mixture of $PdBr_2(PhCN)_2$ (1.81 g, 4 mmol) and allyl bromide (80 mL) was added dropwise 1-hexyne (6.56 g, 80 mmol) with stirring over a period of 1 h and the mixture was allowed to stir for an additional 1 h. The gas chromatograph of the resulting mixture showed that the starting acetylene was completely consumed and 5-bromo-1,4-nonadiene (**1B**) was selectively formed in 95% yield. Allyl bromide was removed at reduced pressure. The oily residue was chromatographed on an alumina column (80 g). The codimer was eluted with petroleum ether. Evaporation of the ether and distillation gave 12 g of **1B** at 53–54 °C (3.5 mmHg).

Hydrogen Bromine Exchange Reaction in 1B, 3B, and 17B. The exchange reaction was carried out by the method of Panek.[15] The exchange reaction in **1B** is representative. **1B** (0.91 g, 4.1 mmol) was added by syringe to a stirred and cooled (dry ice–acetone) mixture of THF (5.2 mL) and *n*-BuLi (3.0 mL of 1.6 N hexane solution, 4.8 mmol). The reaction mixture was stirred for 5 min and then cooled ethanol was added. GC analysis and the NMR spectrum of (*E*)-1,4-nonadiene were superimposable with those of an authentic sample:[9] IR (neat) 993, 970, 914 cm^{-1}; NMR (CCl_4) δ 0.92 (t, 3 H, J = 7 Hz, CH_3), 1.16–1.52 (m, 4 H, $C_2\mathbf{H}_4CH_3$), 1.80–2.20 (m, 2 H, $=CHC\mathbf{H}_2$), 2.60–2.84 (m, 2 H, $=CHC\mathbf{H}_2CH=$), 4.84–6.01 (ABC m, 3 H, $CH_2=CH$), and 5.34–5.50 (m, 2 H, $CH=CH$).

Using the same procedure as for **1B**, the reaction of **3B** gave (*E*)-1-phenyl-1,4-pentadiene: IR (neat) 990, 960, 908, 754, 692 cm^{-1}; NMR (CCl_4) δ 2.89 (t, 2 H, J = 6 Hz, CH_2), 4.92–6.00 (ABC m, 3 H, $CH_2=CH$), 6.01 (d–t, J = 16.6 Hz, 1 H, $CH_2C\mathbf{H}=$), 6.35 (d, J = 16 Hz, 1 H, $=C\mathbf{H}(Ph)$), and 7.00–7.30 (m, 5 H, Ph). Similarly the reaction of **17B** gave a 1:2.3 mixture of 4-phenyl-1,4-heptadiene and 4-phenylmethylene-1-hexene. 4-Phenyl-1,4-heptadiene: NMR (CCl_4) δ 0.94 (t, 3 H, J = 7 Hz, CH_3), 1.94 (quintet, 2 H, J = 7 Hz, $C\mathbf{H}_2CH_3$), 3.00 (d, 2 H, J = 7 Hz, CH_2), 4.80–6.00 (ABC m, 3 H, $CH_2=CH$), 6.18 (s, 1 H, $=CH(Ph)$), and 7.12 (s, 5 H, Ph). 4-Phenylmethylene-1-hexene: NMR (CCl_4) δ 1.06 (t, 3 H, J = 7 Hz, CH_3), 2.15 (q, 2 H, J = 7 Hz, $C\mathbf{H}_2CH_3$), 2.85 (d, 2 H, J = 7 Hz, CH_2), 4.80–6.00 (ABC m, 3 H, $CH_2=CH$), 6.18 (s, 1 H, $=C\mathbf{H}(Ph)$), and 7.12 (s, 5 H, Ph).

Partial Hydrogenation of 14A, 17A, and 19A, Followed by Ozonolyses. The codimerization of 2-hexyne and allyl chloride with $PdCl_2(PhCN)_2$ was carried out under the same conditions as for 1-hexyne. After normal workup, distillation gave a mixture of two regioisomers (**14A**-1, **14A**-2, 9.48 g, 75%). In spite of elaborate effort, the two regioisomers could not be separated by GC methods (Apiezon grease L, SE-30, PEG-2000). Therefore, the ratio of the two isomers was determined by NMR spectroscopy. The hydrogenation of a mixture of two regioisomers (**14A**-1, **14A**-2, 2.73 g, 17.3 mmol) with polymer anchored Rh catalyst[17] (0.16 g) in CH_2Cl_2 (20 mL) was carried out under a H_2 atmosphere at room temperature. When H_2 absorption reached 387 mL (equimole to codimer used), the catalyst was separated. The filtrate containing corresponding monoenes was directly ozonolyzed. After the complete consumption of the monoenes was confirmed by GC analysis, the resulting solution was treated with $LiAlH_4$ to give a mixture of ethyl alcohol, 1-butanol, 2-pentanol, and 4-heptanol. The distribution of the four alcohols (ethyl alcohol + 4-heptanol:1-butanol + 2-pentanol = 1:1.5) was consistent with the regioisomer ratio calculated by NMR analysis.

Using the same procedure as ozonolysis of **14A, 19A** was selectively hydrogenated to 3-chlorophenylmethylene-2,2-dimethylhexane, which was further ozonolyzed. The complete consumption of the starting olefin was checked by GC analysis. The resulting solution was treated with $LiAlH_4$. GC analysis showed an equimolar formation of benzyl alcohol and 2,2-dimethyl-3-hexanol. Other alcohols such as 2,2-dimethyl-1-propanol and 1-phenyl-1-butanol could not be detected.

Similarly a mixture of **17A**-1 and **17A**-2 gave four alcohols: 1-propanol, 3-hexanol, benzyl alcohol, and 1-phenyl-1-butanol.

Codimerization of Acetylene and Allyl Chloride with $PdCl_2(PhCN)_2$. Acetylene was slowly bubbled into the allyl chloride solution (45 mL) containing $PdCl_2(PhCN)_2$ (1.52 g, 4 mmol) with stirring at 20 °C for 4 h. GC analysis showed the presence of (*Z*)-1-chloro-1,4-pentadiene (1110%, based on Pd), (*E*)-1-chloro-1,4-pentadiene (630%, based on Pd), and 1-chloro-1,3,6-heptatriene (60%, based on Pd). Distillation gave a mixture of the codimers (5 g). Samples of two codimers were collected by preparative GC (Apiezon grease L) for spectral identification. (*Z*)-1-Chloro-1,4-pentadiene: IR (CCl_4) 985, 914 ($CH_2=CH$), 690 ((*Z*)-$CH=CH$) cm^{-1}; NMR (CCl_4) δ 2.78–3.13 (m, 2 H, CH_2), 4.80–5.24 (m, 2 H, $CH_2=$), and 5.40–6.13 (m, 3 H, other olefinic protons). (*E*)-1-Chloro-1,4-pentadiene: IR (CCl_4) 985, 914 ($CH_2=CH$), 938 ((*E*)-$CH=CH$) cm^{-1}; NMR (CCl_4) δ 2.60–3.00 (m, 2 H, CH_2), 4.78–5.22 (m, 2 H, $CH_2=$), and 5.40–6.14 (m, 3 H, other olefinic protons).

Selective Cotrimerization of Acetylenes and Allyl Chloride with $Pd(OAc)_2$–LiCl. To a solution of $Pd(OAc)_2$ (2.25 g, 10 mmol) and LiCl (2.12 g, 50 mmol) in AcOH (90 mL) was added allyl chloride (23 g, 0.3 mol). The reaction mixture was stirred and a stream of acetylene was bubbled at 20 °C for 2 h. GC analysis showed 1-chloro-1,3,6-heptatriene (500%, based on Pd) and 1-chloro-1,4-pentadiene (19%, based on Pd). The reaction mixture was poured into water. After the ethereal extract was neutralized, and concentrated, the residue was distilled to give a pure cotrimer (3.51 g): bp 34–35 °C (7 mmHg); UV (MeOH) λ_{max} 237 nm (ϵ_{max} 26 700); IR (neat) 1640, 1585 (C=CC=C), 990, 913 ($CH_2=CH$), 973 ((*E*)-$CH=CH$), and 713 ((*Z*)-$CH=CH$) cm^{-1}; NMR (CCl_4) δ 2.88 (t, 2 H, J = 7 Hz, CH_2), 4.80–5.20 (m, 2 H, $CH_2=$), and 5.50–6.60 (m, 5 H, other olefinic protons); mass spectrum m/e 128 (M^+). Anal. Calcd for C_7H_9Cl: C, 65.38; H, 7.07. Found: C, 65.53; H, 6.93%.

The hydrogenation of the cotrimer over the polymer-anchored Rh catalyst selectively gave 1-chloro-1,3-heptadiene: UV (MeOH) λ_{max} 237 nm; IR (neat) 970 ((*E*)-$CH=CH$), 714 ((*Z*)-$CH=CH$) cm^{-1}; NMR (CCl_4) δ 0.94 (t, 3 H, J = 7 Hz, CH_3), 1.20–1.75 (m, 2 H, $C\mathbf{H}_2CH_3$), 2.00–2.30 (m, 2 H, CH_2), and 5.30–6.80 (m, 4 **H**, olefinic protons).

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Registry No.—Acetylene, 74-86-2; (*Z*)-1-chloro-1,4-pentadiene, 52917-17-6; (*E*)-1-chloro-1,4-pentadiene, 52917-18-7; 1-chloro-1,3,6-heptatriene, 57365-44-3; palladium acetate, 59453-92-8; lithium chloride, 7447-41-8; lithium bromide, 7550-35-8; lithium iodide, 10377-51-2; palladium chloride, 7647-10-1; bis(tetraethylammonium)hexachloropalladate, 58108-71-4.

Supplementary Material Available: Table II listing full NMR data for compounds **1–23** (4 pages). Ordering information is given on any current masthead page.

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Preparation of Harringtonine from Cephalotaxine

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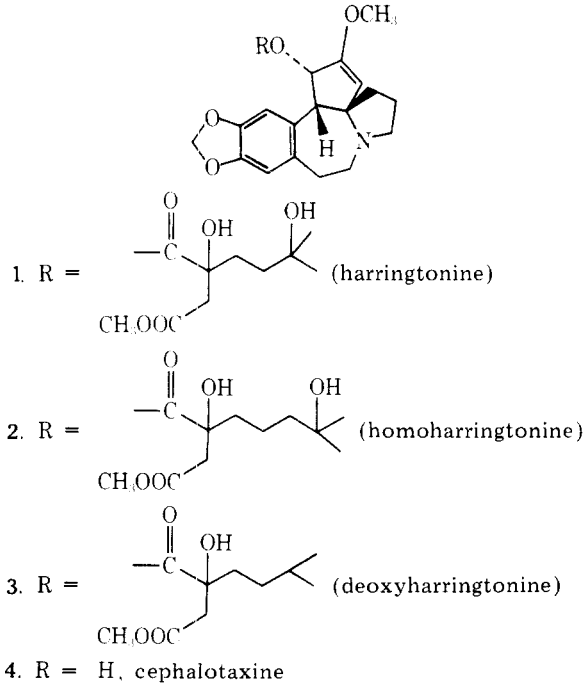
Use of racemic **5** as a side-chain synthon provides a three-step conversion of *l*-cephalotaxine (**4**) into a readily separable, ~1:1 mixture of the clinically useful anticancer drug harringtonine (**1**) and its side-chain epimer. The synthesis of **5** is described.

Harringtonine (**1**) and its congeners were first characterized approximately 10 years ago and shown to exhibit anticancer activity in in vivo systems.[2-4] More recently, workers in the People's Republic of China have established that harringtonine and its homologue homoharringtonine (**2**) are efficacious in the treatment of human cancers.[5,6]



The parent alkaloid, cephalotaxine (**4**), was first synthesized in 1972[4,7] and is now relatively accessible by either isolation or total synthesis.[8] Harringtonine (**1**) and its natural homologue **2** are much less available, however, and clinical evaluation of these esters has not been undertaken in the United States due to lack of material. Numerous groups have attempted to prepare **1** from **4**, but no satisfactory solution has yet been achieved.[9,10] We now report a conversion of cephalotaxine (**4**) into harringtonine (**1**) which is a substantial improvement over existing methods[10b] and offers a potential means of alleviating the present scarcity of **1**. The approach utilizes **5** as a side-chain synthon.[11]

Use of racemic **5** provides a three-step conversion of *l*-cephalotaxine into a readily separable (LC, C_{18} μ-Bondapac column)[12] 1:1 mixture of harringtonine (**1**) and its side-chain epimer (**1a**) in an overall, incompletely optimized yield of approximately 35% (Scheme I).[13] Since the conversion of **4** into the mixture of **1** and its epimer is unaccompanied by asymmetric induction, use of the appropriate antipode (vide infra) of **5** should provide pure **1** in similar overall yield.

Lactone acid chloride **5** is available by the operationally straightforward sequence outlined in Scheme II. The minor, undesired Diels–Alder adduct **9b** is removed most easily by fractional crystallization[15] after saponification of **9** to the mixture of hydroxy acids **10**.[16] The conversion of **11** to **16** is most conveniently conducted without purification of intermediates and proceeds in 37% overall yield. The selective

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