XXVIb was converted in 53% yield to XXIXb: bp 82–84° (20 mm); n^{25}D 1.4621 [lit.[23] bp 78° (20 mm)].

General Preparation of Quaternary Ammonium Iodides. The general procedure used was to dissolve the amine in ether and add an excess of methyl iodide. The resulting mixture was stirred overnight at 25°, and the solid product which had precipitated was collected by filtration and was recrystallized from ethanol.

***N,N,N*-Trimethyl-2,3-dimethylcyclopentylammonium-*cis*-2-d_1 Iodide (XIa).** Amine Xa was converted in 90% yield to XIa, mp 288–290° (lit.[3] mp 289–291°).

***N,N,N*-Trimethyl-2-spiro[4.5]decylammonium Iodide (XIV).** Amine XIII was converted in 80% yield to XIV, mp 222°.

Anal. Calcd for $C_{13}H_{26}NI$: C, 48.3; H, 8.1; N, 4.3; I, 39.3. Found: C, 48.0; H, 8.3; N, 4.4; I, 39.9.

***N,N,N*-Trimethyl-2-spiro[4.5]decylammonium-*cis*-3-d_1 Iodide (XIVa).** Amine XIIIa was converted in 85% yield to XIVa, mp 213°. This compound was compared with the hydrogen analog XIV.

***N,N,N*-Trimethylcyclopentylammonium-*trans*-2-d_1 Iodide (XXXb).** Amine XXVIIb was converted in 94% yield to XXXb, mp 249–253° dec (lit.[24] mp 260°).

***N,N,N*-Trimethylcyclohexylammonium-*trans*-2-d_1 Iodide (XXXIb).** Amine XXVIIIb was converted in 94% yield to XXXIb, mp 276–277° dec (lit.[25] mp 278–278.2°).

***N,N,N*-Trimethylcycloheptylammonium-*trans*-2-d_1 Iodide (XXXIIb).** Amine XXIXb was converted in 91% yield to XXXIIb, mp 252° dec (lit.[17] mp 259°).

Quaternary Ammonium Hydroxides and Hofmann Pyrolysis. The conversion of the quaternary iodides to the corresponding hydroxides was accomplished by passage of an aqueous solution of the iodide over a column of Dowex 1-X8 basic resin and elution with water. The water was evaporated under vacuum from the hydroxide, keeping the temperature below 40°. The hydroxide was then pyrolyzed at 130–150° (50 mm). The olefin was collected, washed with a small amount of cold dilute sulfuric acid, followed by several washings with water, and was then dried. Each olefin was then analyzed and collected by gas chromatography on a 2-ft silicone rubber column or a 6-ft column of 40% ethylene glycol saturated with silver nitrate on Chromosorb W (60–80 mesh). Each olefin was analyzed for deuterium in a mass spectrometer at low voltage.

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Stereochemical Control in Wittig Olefin Synthesis. Preparation of the Pink Bollworm Sex Pheromone Mixture, Gossyplure[1]

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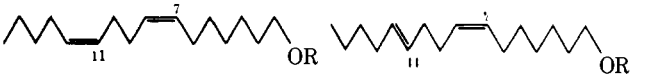
Abstract: Stereochemical control of the Wittig reaction of the primary aldehyde **6** with the nonstabilized alkylide, triphenylphosphonium *n*-pentylide **7**, is achieved by controlled partial equilibration of the intermediate adducts. These conditions are applied to the direct synthesis of the mixture of insect sex pheromones, "gossyplure", which is a 1:1 mixture of (7*Z*,11*Z*)- and (7*Z*,11*E*)-7,11-hexadecadien-1-yl acetate (**1a** and **2a**, respectively). The difunctionalized intermediate ethyl (*Z*)-8-oxo-4-octenoate (**6**) is conveniently prepared from (*Z*,*Z*)-1,5-cyclooctadiene (**3**). Simple Wittig reaction conditions are also outlined which give predominantly the cis olefin product **8a**.

The sex pheromone of the female pink bollworm moth, *Pectinophora gossypiella* (Saunders), has been recently identified as a ca. 1:1 mixture of (7*Z*,11*Z*)- and (7*Z*,11*E*)-7,11-hexadecadien-1-yl acetate (gossyplure).[2-5] The 1:1 mixture of the isomers **1a** and **2a** was by far the most attractive to males in the field.[2,3] Addition of as little as 10% of either the 7*E*,11*Z* or the 7*E*,11*E* isomer greatly diminished the attraction of the 1:1 mixture of 7*Z*,11*Z* (**1a**) and 7*Z*,11*E* (**2a**) isomers.[3]



1a, R = Ac
b, R = CH(Me)OEt
c, R = H

2a, R = Ac
b, R = CH(Me)OEt
c, R = H

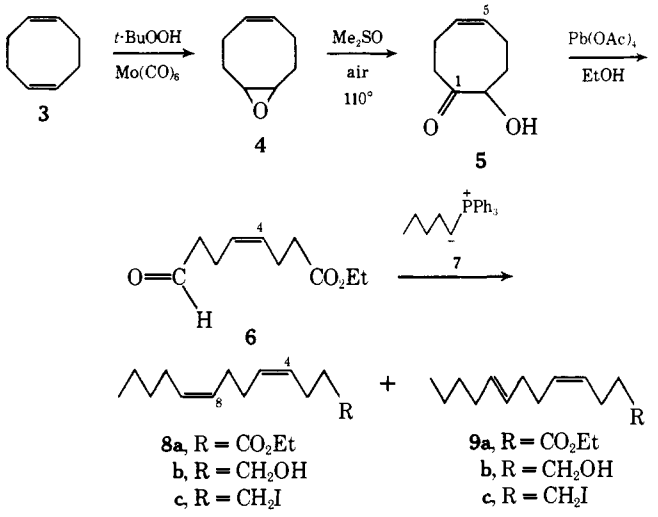
Although **1a** and **2a** have now been prepared separately by conventional routes via acetylenic intermediates,[3,5-7] we

decided to prepare directly the required 1:1 mixture of cis and trans isomers by a single synthetic scheme involving stereochemical control of the Wittig olefin reaction. Since both the 7*E* isomers of gossyplure inhibit the attraction of pink bollworm males to the pheromone,[3] we decided to define the stereochemistry at this double bond by choosing a starting material already possessing a completely cis olefin double bond.

We describe here our work on the controlled equilibration of the intermediate adducts in the Wittig reaction and the application of this technique to the synthesis of gossyplure, the 1:1 mixture of **1a** and **2a.**

Results and Discussion

We introduced the critical C-7 double bond in gossyplure in entirely the cis configuration by taking advantage of the stereochemistry present in the readily available (*Z,Z*)-1,5-cyclooctadiene (**3**). This diene seemed to be a potentially ideal starting material since selective nonsymmetrical cleavage of one double bond would provide not only the required functional groups but also the cis double bond. Thus oxidation of **3** at 0° with 1 equiv of *m*-chloroperbenzoic acid in dichloromethane gave a mixture of the monoepoxide **4** (73%), unreacted **3** (13%), and 14% of the diepoxide of **3** (cf. ref 8). Distillation of this product gave the pure monoepoxide **4.** Alternately, **4** was prepared by oxidation of **3** with *tert*-butyl hydroperoxide in the presence of molybdenum hexacarbonyl.[9] This latter method gave mostly **4** (65%) with some diepoxide (9%) and was preferable to the first method since distillation of the crude oxidation mixture, without any work-up, gave **4** directly. Conversion of the monoexpoxide **4** to the α-ketol **5** was carried out by bubbling air through a solution of **4** in dimethyl sulfoxide at 110° (48 to 60 hr),[10] followed by chromatography of the crude product (50% isolated yield of **5**). No transannular interaction of the olefin with the epoxide group was noticed during this presumably acid-catalyzed oxidation. Lead tetraacetate (1 equiv) cleavage of the α-ketol **5** in benzene-ethanol[11] gave the pure aldehyde ester **6** in 91% yield. The above conversion of a symmetrical cyclic olefin to a difunctionalized product, in which the functional groups are dissimilar in reactivity, could be of general utility in organic synthesis.



With the synthesis of the key intermediate **6** completed, we then set out to achieve the required stereochemical control of the Wittig olefin reaction. The effect of the reaction conditions on the stereochemical outcome of the Wittig reaction has been extensively studied.[12-15] Thus, it is known that, when saturated aliphatic nonstabilized triphenylphosphonium ylides react with primary aliphatic aldehydes in nonpolar solvents (such as benzene or THF) at 0° in the absence of inorganic ions ("salt-free"), predominantly (>90%) cis olefins are isolated from the Wittig condensations.[12,13a,15] The same result is obtained, with nonstabilized alkylides and aliphatic aldehydes, in the presence (or absence) of lithium salts if the reaction is carried out in a dipolar aprotic solvent such as dimethylformamide,[13] dimethyl sulfoxide,[16a,b,e] or hexamethylphosphoramide.[6c,16b-d] In nonpolar solvents, the stereochemistry of the olefin product is dependent on the nature of the inorganic salt present.[12,13a] In the presence of LiI and especially lithium tetraphenylborate, more trans olefin is obtained than with LiBr or LiCl. Schlosser[12] tentatively interpreted these results, for nonpolar solvents, by assuming that, in salt-free solution, the alkylide and aliphatic aldehyde react essentially irreversibly to give a "betaine" (e.g., **10**)[17] with predominantly the erythro configuration (and hence cis olefin product), with the rate of decomposition of the "betaine" to the product being slower than its rate of formation. Schlosser postulated that, in the presence of lithium salts, the initial *erythro*-"betaine" adduct is partially converted to the thermodynamically more stable *threo*-"betaine" via reversion to the starting aldehyde and ylide, resulting in an increase in the proportion of the trans isomer in the olefin product.

Schlosser and Christmann were able to demonstrate the reversibility of the formation of the Wittig intermediate in the presence of soluble lithium salts, with the reaction of triphenylphosphonium ethylide and benzaldehyde in benzene.[12b,c] They also noticed that, when a sample of the isolated β-hydroxyphosphonium bromide salt (betaine-hydrobromide, erythro and threo diastereoisomers, 89:11 respectively; prepared from triphenylphosphonium ethylide and benzaldehyde, followed by HBr) was treated at 0° with lithium *tert*-butoxide in a variety of solvents, the use of a *protic* solvent such as *tert*-butyl alcohol in ether increased the proportion of trans olefin in the product.[12c] Thus they concluded that alcohols also promote reversible betaine dissociation to reactants in a manner analogous to the role of lithium salts, but to a greater extent, and hence increase the proportion of the trans isomer in the product. However, these authors were unable at that time to satisfactorily explain[12] in these reactions the thermodynamic preference for the threo diastereomer in the betaine-lithium halide adduct, or the reason for the initial predominant formation of *erythro*-betaine or *erythro*-oxaphosphetane[17] and hence the cis stereoselectivity of the Wittig reaction. Equilibration of these diastereoisomeric Wittig intermediates via reversible betaine dissociation to the reactants was found by Schlosser and his coworkers to be too slow to be practical as a route to pure trans olefins and was postulated to give a possible maximum of only 80-90% of the trans olefin.[12a,c] Thus they developed a highly stereoselective trans olefin route whereby the primary Wittig intermediate,[17] with predominantly the erythro configuration, is α metallated (in the presence of soluble lithium salts), and the resulting intermediate β-oxidophosphorus ylide ("betaine ylide") is protonated to generate the Wittig intermediate with the threo configuration which then gives the trans olefin.[12,18]

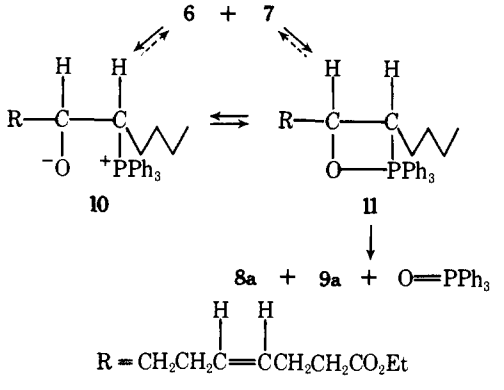
In light of these earlier results, it remained for us to determine whether or not the relatively unstable Wittig intermediate[17] derived from an aliphatic aldehyde and a nonstabilized ylide could be partially equilibrated and, if so, whether this reaction could be controlled to yield precise mixtures of cis and trans olefins. We have expanded on the above observations[12-18] and have developed a simple procedure for the controlled partial equilibration of the Wittig intermediates, which in the present case gives directly a 1:1 mixture of **8a** and **9a.** Table I summarizes our results on the

Table I. Reaction of Ethyl (*Z*)-8-Oxo-4-octenoate (6) with Triphenylphosphonium *n*-Pentylide (7)

Entry	Reaction conditions: Ylide formation[a] Base, solvent, temp, time in min	Reaction conditions: Olefin formation (after addition of 6)[b] Temp, time in min[c]	Product: Isomer ratio[d] 8a:9a	Product: Isolated yield,[e] %
1	*t*-BuOK, THF, 25°, 30	25°, 50	94:6	69
2	NaH, DMF, 25°, 120	25°, 120	94:6	59
3	*n*-BuLi, ether, 25°, 60; ether removed in vacuo; then DMF, 25°	25°, 120	94:6	68
4	$NaNH_2$, NH_3(liq), −33°, 105; NH_3 removed; then benzene and filtration	0°, 120 (benzene:hexane, 1:1)	94:6	52
5	NaOEt, DMF, 25°, 60	25°, 120 then 60°, 4 days	92:8	10[f]
6	*n*-BuLi, benzene, 25°, 60	25°, 120	87:13	49
7	*n*-BuLi, THF, −20°, 60	25°, 60	86:14	57
8	*n*-BuLi, ether–1 equiv of *t*-BuOH, 25°, 90	25°, 60	82:18	45
9	*n*-BuLi, ether, 25°, 90	25°, 120	78:22	61
10	*n*-BuLi, ether, 25°, 30; then −78°	−78°, 30; then addition of 1.1 equiv of $LiN(CHMe_2)_2$, −78 to −50°, 90	78:22	36[g]
11	*n*-BuLi, ether, 25°, 30; then −40°	−50°, 75; then addition of *t*-BuOH, −50°, 4.5 hr; then 25°, 12 hr	78:22	67
12	*n*-BuLi, ether, 25°, 30; then −40°	−40°, 80; then addition of $(Et)_3COH$, −40°, 3.3 hr; then 25°, 12 hr	75:25	67
13	*n*-BuLi, ether, 25°, 30; then −40°	−40°, 60; then addition of 2-propanol, −40°, 3 hr; then 25°, 60	71:29[h]	53
14	*n*-BuLi, ether, 25°, 30; then −40°	−40°, 80; then addition of EtOH, −40°, 10; then 25°, 60	49:51	63
15	*n*-BuLi, ether, 0°, 30; then −78°	−78°, 60; then addition of EtOH, −78 to −50°, 4.5 hr; then 25°, 12 hr	31:69	54
16	*n*-BuLi, ether, 25°, 30; then −40°	−40°, 90; then addition of MeOH, −40°, 4 hr	25:75[i]	35

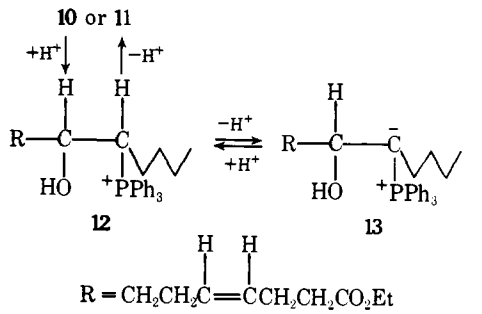
[a] *n*-Pentyltriphenylphosphonium bromide was used as the starting salt in all cases; an excess of ylide (1.2–2 equiv) over aldehyde 6 was used in all cases. [b] Reactions were generally quenched with water prior to work-up; cf. C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963). [c] Time in minutes unless otherwise specified. [d] Determined by GLC analysis of the diepoxide derivatives of 8a and 9a. The isomer ratio was confirmed in a number of cases by GLC analysis of the derived acetates 1a and 2a and their corresponding benzoates, and also by GLC and HPLC analysis of the benzoates of 8b and 9b.[25,30] [e] Yield after TLC purification and/or distillation. [f] The low yield in this experiment could have been due to the use of commercial "dry" NaOEt (cf. ref 13). [g] A β-keto-ester condensation product was also isolated from this reaction. [h] Partial transesterification occurred in this reaction. The product was reconverted to the ethyl ester (NaOEt in ethanol) before GLC analysis. [i] Complete transesterification occurred in this experiment.

effect of solvent, temperature, inorganic salts, and base on the isomer ratio in the product, from the Wittig reaction of the aliphatic aldehyde **6** with the *n*-pentylide **7**. A normal Wittig reaction in ether in the presence of lithium bromide (entry 9, Table I) gave a 78:22 ratio of **8a:9a**, respectively. However, when the ylide **7** (prepared from the phosphonium bromide salt with *n*-butyllithium) was allowed to react in ether with the aldehyde **6** at −40° for 1 to 1.5 hr, followed by the slow addition of ethanol to the intermediate adduct (**10** or **11**), and the resulting reaction mixture was allowed to remain ca. 10 min at −40° before warming to room temperature, then a 1:1 mixture of **8a** and **9a** was obtained (entry 14, Table I). This result was reproducible at



−40°, and the equilibration time after the addition of the ethanol was not very critical. Times from 10 min to 1 hr at −40° gave ca. 1:1 mixtures of **8a** and **9a**. Even after 5 hr at −40°, a mixture of **8a** and **9a** in the ratio of 46:54, respectively, was obtained, suggesting that the rate of decomposition of the intermediate to product olefin is reasonably fast at −40° under these conditions using ethanol. Longer times (e.g., entry 15, Table I) at lower temperatures gave increasing proportions of the trans isomer **9a**, up to a maximum of ca. 75%. Methanol gave a similar result to the use of ethanol, but equilibration appeared to be faster, and longer times even at −40° (entry 16, Table I) gave a higher proportion of the trans isomer. *tert*-Butyl alcohol and 3-ethyl-3-pentanol had little or no effect on the reaction under these conditions (cf. entry 9 with 11 and 12, Table I; cf. ref 12b,c), whereas isopropyl alcohol had only a small effect (entry 13, Table I).

The ethanol or methanol is obviously facilitating partial equilibration of the intermediate adduct (**10** or **11**). The equilibration of the Wittig intermediate could occur either via its reversible formation from the starting aldehyde and ylide (cf. ref 12) or via reversible removal, by nonbulky al-

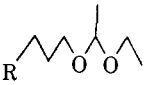


koxides, of the proton on the carbon adjacent to the phosphorus atom in the adduct or more likely in a protonated adduct (such as the β-hydroxyphosphonium intermediate **12**). The first possibility, reversible adduct formation from the reactants, does not seem likely in the presence of excess ethanol when a nonstabilized alkylide such as **7** is involved, as **7** would be readily protonated to the salt under these conditions if it formed. Indeed reaction of the aldehyde **6** with the phosphonium bromide salt of **7** in ether–ethanol in the presence of lithium ethoxide at −40° under the conditions of the controlled equilibration reaction (cf. entry 14, Table I) gave no trace of **8a** or **9a**. An unsuccessful attempt was made to demonstrate the reversibility of adduct formation (cf. ref 12b,c). Thus the ylide **7** was treated with 1.2 equiv of the aldehyde **6** at −40° in ether and, after 75 min (cf. entry 14, Table I; no ylide color), 1.1 equiv of a second aldehyde, 10-undecen-1-al, was added followed by ethanol. Workup as before (after 5 hr at −40°) gave no detectable (<1%) amount of the compound from the reaction of **7** with the second aldehyde. The diene ester product, however, was a mixture of **8a** and **9a** in the ratio 54:46, respectively, indicating that partial equilibration had still occurred. The equilibration probably occurs via the exchange, by lithium alkoxide in ether–alcohol, of the proton on the carbon adjacent to the phosphorus atom in a protonated betaine (i.e., the β-hydroxyphosphonium salt **12** gives reversibly the β-hydroxy ylide **13**).[19] The lack of any equilibration when the Wittig intermediate was treated at −78° with 1.1 equiv of the sterically hindered base lithium diisopropylamide (entry 10, Table I) suggests the possible importance of the protic medium in the above experiments.[20] Partial equilibration in the presence of ethanol-*d* (EtOD), instead of ethanol, at −40° (cf. entry 14, Table I) gave a mixture of **8a** and **9a** (46:54, respectively) with deuterium incorporated into the generated double bond. The NMR and mass spectra of the product showed the incorporation of ca. 65% of a deuterium atom equivalent per molecule. This result supports the α-proton exchange mechanism rather than reversible adduct dissociation to the reactants, especially in view of the lack of **8a** or **9a** product from the lithium ethoxide–aldehyde–phosphonium salt experiment described above. In this context, treatment of *n*-pentyltriphenylphosphonium bromide in ether–ethanol-*d* with lithium ethoxide under the reaction conditions (−40°, then room temperature) gave ca. 70% deuterium exchange of the hydrogen atoms at the position adjacent to the phosphorus atom of the salt. Repetition of this experiment, but quenching at −40° with HBr after 1 hr, gave <5% deuterium exchange of the α hydrogens.

This general approach to the stereochemical control of the Wittig reaction to give specific mixtures[21] of cis and trans olefins promises to be useful, especially in pheromone synthesis, where such specific ratios of isomers are critically important. Even though up to 75% of the trans isomer **9a** can be obtained with the alcohol procedure at low temperature (entry 16, Table I), this equilibration method is unlikely to give greater than 80–90% of the trans olefin (cf. ref 12c) with these reactants.

Incidental to the above development of reaction conditions for the controlled equilibration of the adducts, we examined a number of Wittig reaction conditions expected to give predominantly cis olefin (cf. ref 12, 13, 15, 16). Schlosser's "salt-free" conditions (entry 4, Table I) do indeed give mostly the cis olefin **8a**. However, several other sets of conditions are as selective for cis olefin and are much less tedious as laboratory procedures. For example, potassium *tert*-butoxide in THF at room temperature (cf. ref 22) gave a *Z*:*E* ratio of 94:6 (entry 1, Table I), as also did NaH in dimethylformamide (entry 2, Table I). Schlosser's stereoselective trans olefin route through α metallation of the "betaine" adduct with an alkyl- or aryllithium reagent to give the β-oxidophosphorus ylide ("betaine ylide")[12,18] could not be used with the substrate **6** because of the presence of the ester function. In an attempt to overcome this limitation, the Wittig intermediate (**10** or **11**) was treated at −78° with 1.1 equiv of lithium diisopropylamide (entry 10, Table I), but no equilibration occurred (a β-ketoester condensation product was isolated from this reaction, indicating some removal of a proton α to the ester group), in contrast to the results obtained in the presence of ethanol discussed above.[20]

To complete the synthesis of gossyplure, a functionalized three-carbon unit was coupled with the appropriate derivative of **8a** + **9a**. Thus, reduction of the 1:1 mixture of the esters **8a** and **9a** (entry 14, Table I) with $LiAlH_4$ gave the alcohols **8b** and **9b**, which were converted to the corresponding iodides **8c** and **9c** (88% yield from esters) via the corresponding mesylates. The iodides were then coupled in ether–THF at −20° with the lithium dialkylcuprate complex prepared from the lithium reagent **14a**,[23,24] to give the mixture



14a, R = Li
b, R = Mg

of acetals **1b** and **2b**. Mild acidic hydrolysis of **1b** plus **2b** then gave the 1:1 mixture of the alcohols **1c** and **2c** in 82% overall yield from **8c** plus **9c**. Acetylation of the alcohol mixture gave gossyplure (1:1 mixture of **1a** and **2a**) in a purity of 99%.[25]

We also found that the coupling of the useful lithium reagent **14a** with primary halides proceeded satisfactorily in the presence of catalytic quantities of Cu(I).[26] For example, addition of 1-bromononane to a solution of 1.1 equiv of **14a** and 0.1 equiv of lithium dichlorocuprate in ether–THF at 0° (1 hr), followed by acid hydrolysis, gave 64% isolated yield (after TLC) of pure 1-dodecanol. Similarly, coupling of the Grignard reagent **14b**[27] with 1 equiv of 1-bromononane in THF in the presence of 0.05 equiv of dilithium tetrachlorocuprate (0°, 4 hr), followed by acid hydrolysis of the acetal group, gave 1-dodecanol in 52% isolated yield. A significant solvent effect was noted in the coupling of 1-iodooctane with the lithium dialkylcuprate complex prepared from **14a**. The iodide was completely consumed in a coupling run with 2 equiv of ate complex in ether–THF after 15 min at −20° whereas, with 2 equiv in diethyl ether alone, some 1-iodooctane remained after 18 hr at 0° (cf. ref 28). The lithium reagent **14a** could be prepared readily in ether at 0 to −10° in 70–80% yields (with 1.2 equiv of lithium–1% sodium) and the Grignard reagent **14b** could be obtained in THF at 0° in ~65% yield.

Experimental Section

Preparative thin-layer chromatography was in general carried out on 1 m × 20 cm glass plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. NMR spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200 G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at 20 or 70 eV ionization potential. Gas-liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. All solvents were dried over activated molecular sieves.

(*Z*)-1,2-Epoxy-5-cyclooctene (4). A. *m*-Chloroperbenzoic Acid. To a solution of 21.6 g (0.20 mol) of (*Z*,*Z*)-1,5-cyclooctadiene (**3**) in 400 ml of dichloromethane, cooled in an ice bath, was slowly added 40.6 g (0.20 mol) of 85% *m*-chloroperbenzoic acid in 400 ml of dichloromethane, maintaining the temperature at <10°. The suspension was stirred at 0–5° for 3 hr and at room temperature

overnight and then was filtered, and the filtrate was washed with aqueous sodium sulfite solution, 2 *M* Na_2CO_3 solution, and brine and dried ($CaSO_4$) and the solvent was removed in vacuo. GLC analysis of the product showed the presence of 13% of the diene **3**, 73% of the monoepoxide **4** and 14% of the diepoxide. Careful distillation through a Vigreux column gave 12 g (48% yield) of the monoepoxide **4**:[8] bp 95–100° (10 mm); NMR ($CDCl_3$) δ 3.03 (br m, 2, H-1 and H-2) and 5.62 ppm (br m, 2, HC=CH).

B. *tert*-Butyl Hydroperoxide. To a solution of 3.24 g (30 mmol) of **3** in 10 ml of benzene containing 80 mg (0.3 mmol) of molybdenum hexacarbonyl, heated under reflux in a N_2 atmosphere, was added, over 30 min, 3.16 g (33 mmol) of 94% *tert*-butyl hydroperoxide. After the mixture had been heated for 3 hr under reflux, the oxidation had ceased, and GLC analysis showed the presence of the diene **3**, the monoepoxide **4**, and the diepoxide in the ratio 26:65:9, respectively. Direct distillation through a Vigreux column gave 1.49 g (40% yield) of **4.**

(*Z*)-2-Hydroxy-5-cyclooctene-1-one (5). A solution of 4.0 g (32.2 mmol) of 1,2-epoxy-5-cyclooctene (**4**) in 15 ml of dimethyl sulfoxide was heated at 110° for 48 hr, while air was slowly bubbled through the solution. The reaction mixture was cooled and then was poured into ice water, and the mixture was extracted with chloroform. The chloroform extracts were washed with saturated brine and were dried ($CaSO_4$). The residue, after removal of solvent in vacuo, was purified by chromatography on six 1 m × 20 cm preparative silica plates impregnated with Rhodamine 6G (developed with 30% ethyl acetate in hexane) to give 2.25 g (16.1 mmol, 50% yield) of (*Z*)-2-hydroxy-5-cyclooctene-1-one (**5**): bp (bath, short path) 55° (0.1 mm); ir (CCl_4) 3520 (OH), 3020 (HC=CH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.33 (m, 1, H-2) and 5.72 ppm (m, 2, H-5 and H-6).

Anal. ($C_8H_{12}O_2$) C, H.

Ethyl (*Z*)-8-Oxo-4-octenoate (6). To 206 mg (1.47 mmol) of the ketol **5** in 5 ml of ethanol–benzene (3:7, respectively) was added in portions 800 mg (1.53 mmol) of 85% lead tetraacetate (from Arapahoe Chemicals; wet with glacial acetic acid) After 3 hr at room temperature, the mixture was filtered, and the solid was washed several times with ether. The combined filtrates were then washed with aqueous sodium sulfite, 2 *M* aqueous Na_2CO_3, and brine and were dried ($CaSO_4$). After solvent removal in vacuo, 245 mg (1.33 mmol, 91% yield) of pure ester aldehyde **6** was obtained: bp (bath, short path) 70° (0.05 mm); ir (CCl_4) 3010 (HC=CH), 2800 and 2700 (CHO), 1730 cm^{-1} (ester C=O and aldehyde C=O); NMR δ 1.27 (t, 3, *J* = 7 Hz, CH_3CH_2O), 4.15 (q, 2, *J* = 7 Hz, CH_3CH_2O), 5.43 (br t, 2, H-4 and H-5), and 9.85 ppm (t, 1, *J* = 1 Hz, H-8).

Anal. ($C_{10}H_{16}O_3$) C, H.

Ethyl 4,8-Tridecadienoate (8a plus 9a; Entry 14, Table I). The ylide was prepared by suspending 3.47 g (8.4 mmol) of dry *n*-pentyltriphenylphosphonium bromide in 50 ml of anhydrous ether under a N_2 atmosphere and then adding 4.8 ml (8.0 mmol) of 1.67 *M* *n*-butyllithium in hexane with stirring. After the mixture had been stirred for 30 min, the orange solution was cooled to −40°, and 1.26 g (6.84 mmol) of the aldehyde ester **6** in 5 ml ether was added. The suspension was stirred for 80 min at −40°, and then 40 ml ethanol was added dropwise over about 5 min (a heavy gum precipitated on addition of the ethanol which was most easily redissolved if overhead mechanical stirring was used). The cooling bath was removed 10 min after the addition of the ethanol, and the solution was warmed to 25° and was stirred for 1 hr. The mixture was then poured into ether–hexane (3:1), and saturated brine was added. The organic phase was dried ($CaSO_4$), and the solvent was removed in vacuo. The residue was treated with pentane and the mixture filtered to remove most of the Ph_3PO. Both GLC and TLC analyses of the pentane-soluble product indicated a diene ester of high purity (>90%).[29] A 5-mg sample of the crude diene ester in 0.5 ml of CH_2Cl_2 was treated with an excess of *m*-chloroperbenzoic acid (25 mg) at 0° for 16 hr. The diepoxide derivatives, after a simple work-up which included aqueous sodium sulfite and sodium carbonate washes, were then analyzed by GLC.[30] In this manner, the diene ester product was shown to be a 49:51 mixture of the 4*Z*,8*Z* and 4*Z*,8*E* isomers, **8a** and **9a**, respectively.

The pentane soluble crude product was purified on three 1 m × 20 cm silica plates impregnated with Rhodamine 6G (developed in 5% ethyl acetate in hexane) to give 1.03 g (4.32 mmol, 63% yield) of esters (**8a** plus **9a**): bp (bath, short path) 65° (0.05 mm); ir (CCl_4) 1730 cm^{-1} (C=O); NMR δ 0.88 (t, 3, *J* = 5.5 Hz, CH_3CH_2), 1.26 (t, 3, *J* = 7 Hz CH_3CH_2O), 4.15 (q, 2, *J* = 7 Hz, CH_3CH_2O), and 5.43 ppm (br m, 4, HC=CH).

Anal. ($C_{15}H_{26}O_2$) C, H.

4,8-Tridecadien-1-ol (8b plus 9b). To 1.0 g (4.2 mmol) of the esters **8a** plus **9a** in 15 ml of anhydrous ether at 20° under a N_2 atmosphere was added 0.6 ml (2.58 mmol) of 4.3 *M* $LiAlH_4$ in ether with stirring. After 3 hr, excess reagent was destroyed by the dropwise addition of saturated aqueous Na_2SO_4, and the reaction mixture was transferred to a separatory funnel containing additional ether and 2% aqueous HCl. The layers were separated, and the ether phase was washed with saturated $NaHCO_3$ and brine and then was dried (Na_2SO_4). Removal of the solvent gave 760 mg (3.9 mmol, 93% yield) of diene alcohols (**8b** plus **9b**): bp (bath, short path) 70° (0.05 mm); ir (CCl_4) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.90 (t, 3, *J* = 5.5 Hz, CH_3CH_2), 3.67 (t, 2, *J* = 6 Hz, H-1), and 5.45 ppm (m, 4, HC=CH).

Anal. ($C_{13}H_{24}O$) C, H.

4,8-Tridecadien-1-yl Methanesulfonates. The mesylates were prepared by the dropwise addtion of 0.33 ml (480 mg, 4.2 mmol) of methanesulfonyl chloride to a solution of 746 mg (3.8 mmol) of the diene alcohols (**8b** plus **9b**) and 0.76 ml (555 mg, 5.5 mmol) of triethylamine in 20 ml of dichloromethane at −10° under a N_2 atmosphere with stirring. After 1.5 hr, the reaction was quenched by the addition of ice, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine and was dried (Na_2SO_4). Removal of the solvent in vacuo gave 1.032 g (3.76 mmol, 99% yield) of the mesylates: ir (CCl_4) 1370, 1350, and 1180 (OSO_2CH_3); NMR ($CDCl_3$) δ 0.88 (t, 3, *J* = 5.5 Hz, CH_3CH_2), 3.02 (s, 3, CH_3SO_3), 4.25 (t, 2, *J* = 6 Hz, H-1), and 5.43 ppm (br m, 4, HC=CH).

Anal. ($C_{14}H_{26}O_3S$) C, H, S.

1-Iodo-4,8-tridecadienes (8c plus 9c). To 1.0 g (3.64 mmol) of the mesylates in 25 ml of acetone under a N_2 atmosphere was added 750 mg (5.0 mmol) of NaI. After the solution had been heated at 60° for 20 hr, the heating bath was removed, and hexane and water were added to the suspension. The aqueous phase was further extracted with hexane, and the combined organic layers were washed with 1% aqueous $NaHCO_3$ and brine and then were dried (Na_2SO_4). The solvent was removed in vacuo to give 1.07 g (3.5 mmol, 96% yield) of iodides (**8c** plus **9c**): NMR ($CDCl_3$) δ 0.90 (t, 3, *J* = 5.5 Hz, CH_3CH_2), 3.20 (t, 2, *J* = 6.5 Hz, H-1), and 5.43 ppm (m, 4, HC=CH).

Anal. ($C_{13}H_{23}I$) C, H, I.

7,11-Hexadecadien-1-ols (1c plus 2c). To 1.03 g (5.4 mmol) of CuI suspended in 15 ml of anhydrous tetrahydrofuran (THF) at −20° under a N_2 atmosphere was added 20 ml (10.8 mmol) of 0.54 *M* 3-[(1-ethoxy)ethoxy]propyllithium (**14a**)[23,31] in ether with stirring. After 15 min at −20°, an aliquot of the black solution gave a negative Gilman color test,[32] and 0.90 g (2.94 mmol) of iodides (**8c** plus **9c**) in 5 ml THF was added. The reaction was quenched after 1 hr at −20° by the addition of saturated aqueous NH_4Cl, and diethyl ether was added to the mixture, and the phases were separated. The organic phase was washed with saturated sodium chloride solution and was dried ($CaSO_4$).

The residue, after solvent removal in vacuo, was redissolved in 30 ml of THF, and 20 ml water containing 250 mg of trichloroacetic acid was added, and the solution was allowed to stand for 20 hr at room temperature and was then heated at 60° under a N_2 atmosphere for 1 hr. The cooled solution was then poured into a mixture of ether and 2 *M* aqueous Na_2CO_3. The layers were separated, and the organic layer was washed with brine and was then dried ($CaSO_4$). After solvent removal in vacuo, the residue was purified on two 1 m × 20 cm preparative silica plates impregnated with Rhodamine 6G (developed in 20% ether in hexane) to give 570 mg (2.4 mmol, 82% yield from iodides) of the diene alcohols (**1c** plus **2c**): bp (bath, short path) 95° (0.025 mm); ir (CCl_4) 3610 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.90 (t, 3, *J* = 5.5 Hz, CH_3CH_2), 3.63 (t, 2, *J* = 6 Hz, H-1), and 5.40 ppm (m, 4, HC=CH).

Anal. ($C_{16}H_{30}O$) C, H.

Gossyplure (1a plus 2a, 1:1). To the diene alcohols (**1c** plus **2c**) (520 mg, 2.18 mmol) in 3 ml pyridine was added 1.5 ml of acetic anhydride and the solution stirred overnight under a N_2 atmosphere. Ice was added to the mixture and, after 2 hr, the reaction was poured into hexane–ether (9:1). The organic layer was washed with 5% aqueous HCl, 2 *M* aqueous Na_2CO_3, and brine. After the

extract was dried ($CaSO_4$), the solvent was removed in vacuo, and the residue was distilled to yield 526 mg (1.88 mmol, 86% yield) of the diene acetates, shown by GLC analysis[25] to be a 1:1 mixture of the 7*Z*,11*Z* and 7*Z*,11*E* isomers (**1a** and **2a**, respectively) in an overall purity of 99%: bp (bath, short path) 80° (0.025 mm); ir (CCl_4) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.88 (t, 3, J = 5.5 Hz, CH_3CH_2), 2.05 (s, 3, CH_3CO), 4.05 (t, 2, J = 6 Hz, H-1), and 5.40 ppm (m, 4, HC=CH).

Anal. ($C_{18}H_{32}O_2$) C, H.

Wittig Reactions of Ethyl (*Z*)-8-Oxo-4-octenoate (6) with Triphenylphosphonium *n*-Pentylide (7). A. t-BuOK in THF (Entry 1, Table I). To 620 mg (1.5 mmol) of *n*-pentyltriphenylphosphonium bromide suspended in 7 ml of dry tetrahydrofuran (THF) at room temperature under a N_2 atmosphere was added 2.65 ml (1.4 mmol) of 0.53 *M* *t*-BuOK in THF. After the mixture had been stirred for 30 min, 128 mg (0.7 mmol) of the aldehyde ester **6** in 1 ml of THF was added. After 50 min, 0.5 ml of water was added with stirring and, after a further 1 hr, the mixture was poured into ether-saturated brine. The organic layer was dried, and the solvent was removed in vacuo. The hexane soluble portion of the product was purified by chromatography on silica gel preparative thin layer plates (20 × 20 mm; Rhodamine 6G impregnated; developed with 4% ethyl acetate in hexane) to give 115 mg (0.48 mmol, 69% yield) of a mixture of **8a** and **9a** (ratio of 94:6 by GLC analysis of a sample which was epoxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 at 0° overnight).[30]

B. Sodium Hydride in Dimethylformamide (Entry 2, Table I). To 40 mg (1.67 mmol) of NaH (oil-free; washed with pentane) under N_2 was added 5 ml of dimethylformamide and 700 mg (1.7 mmol) of phosphonium salt at room temperature with stirring. After 2 hr, 180 mg (0.98 mmol) of **6** in 1 ml of dimethylformamide was slowly added. After a further 2 hr, water was added followed by ether and brine. The organic layer was dried ($CaSO_4$), and the solvent was removed in vacuo (GLC analysis of an epoxidized sample[30] showed a mixture of **8a** and **9a** in the ratio 94:6). Short path distillation [bp (bath) 65° (0.03 mm)] gave 138 mg (0.58 mmol, 59% yield) of product.

C. *n*-BuLi in Ether, then Dimethylformamide (Entry 3, Table I). To 413 mg (1 mmol) of the salt in 10 ml ether under argon was added 0.57 ml (0.95 mmol) of 1.67 *M* *n*-butyllithium in hexane. After 1 hr the ether was removed in vacuo, and 7 ml of dimethylformamide was added. To this solution was added 108 mg (0.59 mmol) of **6** with stirring. After 2 hr water was added, and the mixture was extracted with hexane and worked up in the normal manner. Short path distillation of the product gave 94 mg (0.4 mmol, 68% yield) of a mixture of **8a** and **9a** (ratio 94:6, respectively).[30]

D. Salt-free Ylide (Entry 4, Table I) (cf. ref 12c, 15). To 150 ml of liquid NH_3 (distilled from Na) was added 75 mg of ferric nitrate hexahydrate and 460 mg (20 mmol) of Na with stirring at −78°. After 2 hr the mixture was warmed to reflux (Dry Ice condenser), and 8.26 g (20 mmol) of phosphonium bromide was added with stirring. After 1.75 hr the Dry Ice condensor was removed and the NH_3 allowed to evaporate under N_2. To the residue was added 75 ml of dry benzene, and the mixture was heated under reflux for 1.5 hr and then was allowed to cool. The mixture was filtered in a Schlenk tube under N_2 through a coarse glass frit covered with dry Celite to give an orange-red benzene solution of the ylide **7**.

To 253 mg (1.37 mmol) of **6** in 2.5 ml of benzene and 2.5 ml of hexane at 0° under N_2 was added, with stirring, an excess of the salt-free ylide solution above. After 2 hr the solution was warmed to room temperature and worked up by addition of ether and brine. The organic phase was dried ($CaSO_4$), the solvent removed, and the residue purified by preparative TLC on silica gel plates to give 169 mg (0.71 mmol, 52% yield) of a mixture of **8a** and **9a** in the ratio 94:6, respectively.[30]

E. *n*-Butyllithium in Benzene (Entry 6, Table I). To 413 mg (1 mmol) of the phosphonium bromide suspended in 10 ml of dry benzene under argon at room temperature was added 0.57 ml (0.95 mmol) of 1.67 *M* *n*-butyllithium in hexane with stirring. After 1 hr, 118 mg (0.64 mmol) of **6** in 0.5 ml of benzene was added and, after a further 2 hr, water was added, and the organic layer was washed with water and dried ($CaSO_4$), and the solvent was removed in vacuo. The residue was extracted thoroughly with hexane, and the hexane solution filtered, and the solvent removed from the filtrate in vacuo. The diene ester product was then short path distilled [bp (bath) 65° (0.05 mm)] to give 75 mg (0.315 mmol, 49% yield) of a mixture of **8a** and **9a** (87:13, respectively).[30]

F. *n*-Butyllithium in THF (Entry 7, Table I). To 455 mg (1.1 mmol) of the salt suspended in 7 ml of THF under N_2 at −20° was added 0.68 ml (1.05 mmol) of 1.55 *M* *n*-butyllithium in hexane. After 1 hr the solution was warmed to room temperature, and 110 mg (0.60 mmol) of **6** in 2 ml of THF was added. After 1 hr, 0.5 ml of water was added and, after a further 30 min, the mixture was poured into ether and brine. The organic phase was washed with brine and dried ($CaSO_4$), and the solvent was removed in vacuo. The residue was extracted with hexane, and the hexane-soluble fraction was short path distilled to give 81 mg (0.34 mmol, 57% yield) of **8a** plus **9a** (86:14 respectively).[30]

G. *n*-Butyllithium in Ether–*tert*-Butyl Alcohol (Entry 8, Table I). To a suspension of 413 mg (1 mmol) of the phosphonium salt in 10 ml of ether containing 0.1 ml (1 mmol) of *tert*-butyl alcohol at room temperature under argon was added 0.57 ml (0.95 mmol) of 1.67 *M* *n*-butyllithium in hexane. After the mixture had been stirred for 1.5 hr, 120 mg (0.65 mmol) of **6** in 0.5 ml ether was added (immediately a precipitate formed). After 1 hr, water was added and the mixture worked up as in E above to give 70 mg (0.29 mmol, 45% yield) of **8a** plus **9a** (82:18, respectively).[30]

H. *n*-Butyllithium in Ether (Entry 9, Table I). To 413 mg (1 mmol) of the phosphonium salt suspended in 10 ml of ether at 25° under N_2 was added, with stirring, 0.57 ml (0.95 mmol) of 1.67 *M* *n*-butyllithium in hexane. After 1.5 hr, 120 mg (0.65 mmol) of **6** in 0.5 ml of ether was added (an immediate white precipitate formed). After the mixture had been stirred for 2 hr at room temperature, water was added, and the mixture was worked up as described in E above, to give (after short path distillation) 95 mg (0.40 mmol, 61% yield) of **8a** plus **9a** (78:22, respectively).[30]

I. Attempted Equilibration with $LiN(CHMe_2)_2$ (Entry 10, Table I). To 420 mg (1.02 mmol) of *n*-pentyltriphenylphosphonium bromide suspended in 8 ml of ether at room temperature under N_2 was added 0.62 ml (0.96 mmol) of 1.55 *M* *n*-butyllithium in hexane with stirring. After 30 min, the orange solution was cooled to −78°, and 175 mg (0.95 mmol) of **6** in 1 ml of ether was added. The reaction mixture was stirred for another 30 min (the color of the mixture was pale yellow), and then 2 ml (1.06 mmol) of 0.53 *M* lithium diisopropylamide in ether was added (a slight darkening of the color of the mixture occurred). The temperature was raised −50° over 1.5 hr, and then the reaction was quenched by the addition of 2 ml of water. The reaction was warmed to room temperature, was stirred for 1 hr, and then was poured into additional ether. The organic layer was washed with brine and was dried ($CaSO_4$), and the ether was removed in vacuo. Preparative TLC purification (4% ethyl acetate in hexane) of the pentane-soluble fraction gave two bands. The less polar band gave 80 mg (0.34 mmol, 35% yield) of the diene esters **8a** and **9a** (ratio 78:22, respectively).[30] The more polar product (50 mg) was tentatively identified from its spectral analyses as the ester condensation product, ethyl 3-oxo-2-(2,6-undecadienyl)-6,10-pentadecadienoate: ir (CCl_4) 3000 (HC=CH), 1745 (ester C=O), and 1720 cm^{-1} (ketone C=O); NMR ($CDCl_3$) δ 0.88 (br t, 6, J = 5.5 Hz, CH_3), 3.45 [t, 1, J = 7 Hz, C(O)-C*H*(CH_2R)$CO_2CH_2CH_3$], 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), and 5.38 ppm (br m, 8, HC=CH).

J. Prolonged Ethanol Equilibration (Entry 15, Table I). To a suspension of 413 mg (1 mmol) of the phosphonium salt in 6 ml of ether at 0° under N_2 was added 0.6 ml (0.96 mmol) of 1.60 *M* *n*-butyllithium in hexane. After the mixture was stirred for 0.5 hr, it was cooled to −78°, and 121mg (0.66 mmol) of **6** in 0.3 ml of ether was add l. After 1 hr at −78°, 5 ml of ethanol was added, and the temperature of the cooling bath was allowed to rise to −50° over 1.5 hr. After a further 3 hr at −50°, the mixture was allowed to slowly warm to room temperature overnight. Addition of water and work-up as described in E above, followed by purification by preparative TLC, gave 85 mg (0.36 mmol, 54% yield) of **8a** plus **9a** (31:69 respectively).[30]

K. Prolonged Methanol Equilibration (Entry 16, Table I). To 455 mg (1.1 mmol) of the phosphonium bromide suspended in 7 ml of ether at 25° under N_2 was added 0.68 ml (1.05 mmol) of 1.55 *M* *n*-butyllithium in hexane. After the mixture was stirred for 30 min, it was cooled to −40°, and 94 mg (0.51 mmol) of 6 in 0.5 ml ether was added dropwise. After 1.5 hr at −40°, 5 ml of methanol was slowly added. After 4 hr at −40 to −45°, 1 ml of water was added, and the reaction mixture was allowed to come to room tempera-

ture. After a further 1 hr, the mixture was poured into ether and the organic layer washed with brine, dried ($CaSO_4$), and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel TLC plates to give 40 mg (0.18 mmol, 35% yield) of the methyl esters corresponding to **8a** and **9a** (1:3, respectively).[30] Complete transesterification occurred under these reaction conditions.

Attempted Wittig Reaction with LiOEt in EtOH–Ether. To a mixture of 1 ml of ethanol and 1 ml of ether was added 0.28 ml (0.45 mmol) of 1.6 *M* *n*-butyllithium in hexane under N_2. In another flask, 207 mg (0.50 mmol) of the phosphonium bromide was added to 2 ml of ether and 2 ml of ethanol along with 60 mg (0.33 mmol) of **6** (under N_2) and the mixture cooled to −40° with stirring. The above LiOEt solution was then added and the mixture stirred at −40° for 2 hr. TLC indicated no reaction at all (including no aldol products) so the mixture was brought to room temperature over 1.5 hr and was stirred at 25° for 3 hr and then was worked up in the usual way. TLC analysis showed the absence of any **8a** or **9a**. The only product isolated after preparative TLC was the dehydrated aldol product from self-condensation of **6**.

Attempted Demonstration of the Reversibility of Wittig Adduct Formation. To 223 mg (0.54 mmol) of *n*-pentyltriphenylphosphonium bromide suspended in 3 ml of ether at room temperature under N_2 was added, with stirring, 0.31 ml (0.50 mmol) of 1.6 *M* *n*-butyllithium in hexane. After 30 min the solution was cooled to −40°, and 110 mg (0.60 mmol) of **6** in 0.5 ml of ether was added. After a further 75 min (the suspension was colorless), 94 mg (0.56 mmol) of 10-undecen-1-al (from Givaudan Corp) in 0.5 ml of ether was added. After 5 min at −40°, 2 ml of ethanol was added dropwise and, after another 5 hr at −40°, the reaction mixture was brought to room temperature and was stirred for 20 min. The mixture was poured into ether–brine and the organic phase washed with brine and dried ($CaSO_4$), and the solvent was removed. Both GLC and TLC analysis (before solvent removal) showed <1% of the C-16 diene (authentic sample of which was prepared from 10-undecen-1-al and ylide **7**) and the presence of 10-undecen-1-al and of **6**. Purification by TLC gave 83 mg (0.35 mmol, 58% yield) of a mixture of **8a** and **9a** (ratio 54:46, respectively).[30]

Partial Equilibration with Ethanol-*d*. To 455 mg (1.1 mmol) of the phosphonium salt in 4 ml of ether at room temperature under N_2 was added 0.63 ml (1.0 mmol) of 1.6 *M* *n*-butyllithium in hexane. After 30 min the solution was cooled to −40°, and 110 mg (0.6 mmol) of **6** in 0.5 ml of ether was added. After 105 min at −40°, 5 ml of EtOD was added dropwise, and the mixture was kept at −40° for 1 hr and then warmed to room temperature. After 30 min the mixture was worked up as described above for entry 14, Table I, to give 67 mg (0.28 mmol, 47% yield) of a mixture of **8a** and **9a** in the ratio 46:54, respectively.[30] Integration of the NMR spectrum ($CDCl_3$) showed signals at 5.43 ppm for only ca. 3.2 olefinic H. Careful analysis of the M^+, $M^+ + 1$, and $M^+ + 2$ peaks in the mass spectrum (with respect to the M^+ and $M^+ + 1$ peaks of undeuterated **8a** + **9a**) showed incorporation of ca. 65% of a deuterium atom equivalent per molecule. The product was treated with NaOEt in ethanol overnight to remove any possible deuterium α to the ester group and then reanalyzed by its NMR and mass spectra, with identical results.

Deuterium Exchange in *n*-Pentyltriphenylphosphonium Bromide. To 413 mg (1 mmol) of the phosphonium bromide in 1.5 ml of ether was added 1.5 ml of EtOD under N_2 and the solution cooled to −40°. To this solution was added a solution of lithium ethoxide (previously prepared by adding 1 ml of 1.6 *M* *n*-butyllithium in hexane to 1.5 ml EtOD and 1.5 ml of ether). After 45 min at −40°, the solution was warmed to room temperature and was stirred for 30 min. Then 0.22 ml (1.94 mmol of HBr) of 8.8 *M* aqueous HBr (47%) was added dropwise. The solvent was then removed in vacuo and the residue dried by azeotropic distillation with $CDCl_3$ and then by heating at 70° under vacuum (0.05 mm) overnight. NMR analysis ($CDCl_3$) of the recovered salt showed considerable (ca. 70%) deuterium exchange of the hydrogens at the position adjacent to the phosphorus atom (α-H absorb at 3.67 ppm).

Repetition of the above exchange experiment at −40° for 60 min, but quenching *at −40°* with 47% HBr, gave <5% deuterium exchange of the α hydrogens in the recovered salt.

1-Dodecanol from 1-Bromononane. A. *Via* Lithium Reagent 14a. To 5 ml of anhydrous THF at −20° under N_2 was added 5 ml (1.85 mmol) of 0.37 *M* 3-[(1-ethoxy)ethoxy]propyllithium[23] in ether and 0.185 ml (0.185 mmol) of 1 *M* $LiCuCl_2$ in THF. Then 352 mg (1.70 mmol) of 1-bromononane in 1 ml THF was added, and the bath temperature was allowed to warm to 0°. After 1 hr, no bromide remained (by TLC analysis), and the reaction was quenched by the addition of saturated aqueous NH_4Cl. Ether was added to the mixture, and the layers were separated. The organic layer was washed with brine and was dried ($CaSO_4$), and the solvent was removed in vacuo.

The residue was dissolved in 15 ml of THF and 10 ml of water containing 100 mg of trichloroacetic acid, and the solution was stirred for 24 hr at room temperature. The reaction was added to ether, and the organic layer was washed with aqueous $NaHCO_3$ and brine and was dried ($CaSO_4$). The solvent was removed in vacuo, and the product was purified by preparative TLC to give 203 mg (1.09 mmol, 64% yield) of 1-dodecanol, identical with an authentic sample.

B. *Via* The Grignard Reagent 14b. The Grignard reagent was prepared in 65% yield from Mg turnings and 1 equiv of the bromo acetal[23] in THF at 0–10° under an argon atmosphere. To 6 ml (2.04 mmol) of 0.34 *M* Grignard reagent **14b** in THF at 0°, under N_2, was added 0.3 ml (0.1 mmol) of 0.33 *M* Li_2CuCl_4 in THF. Then 414 mg (2 mmol) of 1-bromononane in 2 ml THF was added, and the temperature was maintained at 0–10° for 4 hr. The reaction was quenched by the addition of 5 ml of saturated aqueous NH_4Cl and was worked up and the acetal group hydrolyzed, as in A, to give (after preparative TLC) 192 mg (1.03 mmol, 52% yield) of pure 1-dodecanol.

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References and Notes

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Stereochemistry of β-Replacement Reactions Catalyzed by Tyrosine Phenol-Lyase

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Abstract: The stereochemistry of one of the β-replacement reactions catalyzed by tyrosine phenol-lyase has been elucidated by studying the reaction of tyrosine (stereospecifically deuterated at C-3) with resorcinol, catalyzed by the purified enzyme from *Escherichia intermedia*. The configuration of deuterium in the product, 2,4-dihydroxy-L-phenylalanine, was elucidated by nmr comparison with a stereospecifically synthesized sample. The results show that the exchange occurs with retention of configuration at C-3. A mechanism involving an enzyme-bound aminoacrylate moiety is discussed.

Tyrosine phenol-lyase (L-tyrosine phenol-lyase (deaminating) EC 4.1.99.2, formerly known as β-tyrosinase) is a pyridoxal phosphate-dependent multifunctional enzyme which catalyzes α,β elimination (eq 1-4),[4,5] β replacement (eq 5 and 6),[6,7] racemization (eq 7),[8] and the reverse of α,β eliminations (eq 8 and 9)[9,10] to form L-tyrosine or its derivatives from pyruvic acid, ammonia, and phenols.

L-tyrosine + H_2O ⟶ phenol + pyruvic acid + NH_3 (1)

S-methyl-L-cysteine + H_2O ⟶ methylmercaptan + pyruvic acid + NH_3 (2)

L-cysteine + H_2O ⟶ H_2S + pyruvic acid + NH_3 (3)

L-serine ⟶ pyruvic acid + NH_3 (4)

L-tyrosine + pyrocatechol ⟶ 3,4-dihydroxyphenyl-L-alanine + phenol (5)

S-methyl-L-cysteine + resorcinol ⟶ 2,4-dihydroxyphenyl-L-alanine + phenol (6)

L(D)-alanine ⟶ DL-alanine (7)

phenol + pyruvic acid + NH_3 ⟶ L-tyrosine + H_2O (8)

pyrocatechol + pyruvic acid + NH_3 ⟶ 3,4-dihydroxyphenyl-L-alanine (9)

The function of tyrosine phenol-lyase including the synthesis of 2,4-dihydroxyphenyl-L-alanine from tyrosine and