$OCCH_3$), 2.17–1.58 (m, 2, CH_2), 1.34 (t, J = 6 Hz, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 186.998 (carbonyl), 72.359 (CHCl), 69.056 (CH-OH), 51.169 (CH_2CO), 38.449 (CH_3CO), 35.232 (CH_2), 21.781 (CH_3); IR (neat) ν 3600–3200 (hydroxy) 1706 (carbonyl) cm^{-1}. Anal. Calcd: C, 51.07; H, 7.96. Found: C, 51.27; H, 7.63.

Reaction of Tributylbenzyltin with α-Bromoacetophenone. To a solution of 600 mg (3.00 mmol) of α-bromoacetophenone and 560 mg (3.00 mmol) of tributylbenzyltin in 2 mL of THF was added 150 mg (0.140 mmol) of benzylchlorobis(triphenylphosphine)palladium. The yellow solution was stirred at 63 °C in a capped Schlenk tube under argon for 20 h. The black reaction mixture was then allowed to cool to 25 °C and the solvent and the volatile products were distilled under reduced pressure into a cold (−50 °C) receiver containing 3.00 mmol bromine in 1 mL carbon tetrachloride solution. The bromination mixture was allowed to warm to 25 °C and was then stirred for an additional 2 h. After evaporation of the solvent, 515 mg (80.0%) of 1,2-dibromobutane was obtained as determined by the GC of this fraction (oven 100 °C, R_f 6.5 min). The nonvolatile residue of the reaction mixture contained acetophenone (313 mg, 87.0%) and dibutylbenzyltin bromide (1.2 g, 99.0%). Yields were determined by ^1H NMR integrations using dichloromethane as an internal standard. The nonvolatile residue was chromatographed (silica gel) with n-hexane. Dibutylbenzyltin bromide eluted with the first 5-mL fraction: bp 100–116 °C (0.08 mm) [lit.[38] 140–155 °C (1 mm)]; ^1H NMR ($CDCl_3$) δ 6.94 (s, 5, aromatic), 2.70 (s, 2, benzylic), 1.65–0.63 (m, 14, butylene); ^{13}C NMR ($CDCl_3$) δ 138.947, 128.379, 126.861, 123.942 (aromatic), 27.781, 26.321 (CH_2), 25.737 ($PhCH_2Sn$), 17.096 (CH_2Sn), 13.301 (CH_3).

Determination of Enantiomeric Excess of 4 Formed in a Reaction Catalyzed by Dichlorobis[(+)-neomenthyldiphenylphosphine)palladium(II). A reaction between tributylacetonylstannane (**3**) and α-bromoacetophenone (**2**) was carried out at 25 °C for 90 h. After workup and purification of the product as described for racemic **4**, a part of the product (36 mg, 0.19 mmol) was dissolved in chloroform-d in an NMR tube and 89.6 mg (0.075 mmol) of tris[((3-heptafluoropropyl)-hydroxymethylene)-α-camphorato]europium(III), $(hfdc)_3Eu(III)$, shift reagent was added (the molar ratio of 2.5:1 was found to give optimum separation between the methyl signals of the two enantiomers). The two methyl signals were separated by 6.6 Hz and were integrated to give a ratio of 109/75 equivalent to 19% ee.

(38) Bychkov, V. T.; Vyazankin, N. S. *Zh. Obshch. Khim.* **1965**, *35*, 687.

Acknowledgment. This work was supported by a Grant CHE8003336 from the National Science Foundation. We wish to thank Dr. Forrest K. Sheffy for helpful discussions and his aid in the preparation of the manuscript.

Registry No. **1**, 22784-59-4; **2**, 70-11-1; **2**-α,α-d_2, 87372-49-4; **3**, 14583-98-3; (±)-**4**, 87372-50-7; (+)-**4**, 87411-83-4; (−)-**4**, 87372-51-8; **4**-3,3-d_2, 87372-52-9; **5**, 7393-43-3; **6**, 15336-98-8; **7**, 20924-82-7; **8**, 2114-00-3; **9**, 87372-53-0; **10**, 87372-54-1; **11a**, 58283-61-7; **11b**, 87372-55-2; **12**, 24401-36-3; **13a**, 21433-91-0; **13b**, 19842-57-0; **14**, 17392-08-4; **15**, 87372-56-3; (diphos)$PdCl_2$, 19978-61-1; ((+)-diop)$PdCl_2$, 59634-23-0; (R-camp)$_2PdCl_2$, 87372-48-3; ((+)-nmdpp)$_2PdCl_2$, 78251-24-8; α-bromocyclobutyl phenyl ketone, 51175-78-1; 3-bromo-2-butanone, 814-75-5; 3-chloro-2-butanone, 4091-39-8; α-bromocyclohexanone, 822-85-5; β-chloropropiophenone, 936-59-4; γ-chlorobutyrophenone, 939-52-6; 5-chloro-2-pentanone, 5891-21-4; α-bromobutyraldehyde, 24764-97-4; α-bromo-α-methylpropiophenone, 10409-54-8; 1-phenyl-1-acetonyl-5-oxaspiro[2.3]hexane, 87372-57-4; 2,3-dimethyl-2-acetonyloxirane, 87372-58-5; 1-acetonyl-7-oxabicyclo[4.1.0]heptane, 87372-59-6; 2-phenyl-2-allyloxetane, 87372-60-9; 2-phenyl-2-allyltetrahydrofuran, 87372-61-0; 2-methyl-2-allyltetrahydrofuran, 87372-62-1; 2-acetonyl-3-ethyloxirane, 87372-63-2; 2-allyl-3-ethyloxirane, 58325-53-4; α-chloroacetophenone, 532-27-4; α-chlorobutyraldehyde, 28832-55-5; dichlorobis(benzonitrile)palladium(II), 14220-64-5.

Synthetic Utility of the Palladium-Catalyzed Coupling Reaction of Acid Chlorides with Organotins

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Received February 23, 1983

The palladium coupling of acid chlorides with unsymmetrical organotin reagents R''_3SnR' can be carried out in chloroform under mild conditions in high yields to give the ketone RCOR′ in which only one of the four organic groups on tin appears in the ketone product. Alkyl partners (R″ = methyl or butyl) on tin serve as anchoring groups and do not transfer. When R′ is acetylenic, vinyl, aryl, methoxymethylene, allyl, or benzyl, transmetalation takes place preferentially, resulting in coupling with the acyl group from the acid chloride. The reaction is tolerant of functional groups both on the acid chloride and the tin reagent. A palladium-catalyzed coupling reaction of an organotin reagent bearing acrylate functionality with an acid chloride serves as a method to introduce both a ketone and an acrylate functionality into a carbon framework. The coupling reaction of 4-(*tert*-butyldiphenylsiloxy)pentanoyl chloride with benzyl 3-(tributylstannyl)acrylate gave a 71% yield of benzyl 7-(*tert*-butyldiphenylsiloxy)-4-oxo-2-octenoate, a precursor to the macrolide antibiotic pyrenophorin.

Introduction

The synthesis of ketones by the palladium-catalyzed coupling reaction of acid chlorides with organotin reagents[1,2] has been shown to be a mild, selective reaction that generally gives greater than 85% yields.[1] The reaction is especially useful in that other functionalies on the acid chloride such as ester, nitrile, nitro, halo, and aldehyde can survive the reaction unaltered. However, the solvent originally used in these reactions was hexamethylphosphoric triamide (HMPA), which not only makes workup difficult in certain reactions but also is a carcinogen.[3]

In the coupling reaction, the tetraorganotin reagent transfers the first organic group on tin rapidly, but the second leaves about 100 times slower from R''_3SnCl. Thus,

(1) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636; *J. Org. Chem.* **1979**, *44*, 1613.

(2) (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) *J. Organomet. Chem.* **1977**, *129*, C36.

(3) Lee, K. P.; Trochimowicz, H. J. *Toxicol. Appl. Pharmacol.* **1982**, *62*, 90.

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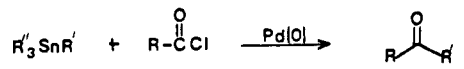


with a stoichiometric amount of tetraorganotin, only one group is transferred. The single transfer is not troublesome if a relatively simple organic group, for example, methyl, is to be transferred, since a relatively inexpensive, available tin reagent, tetramethyltin, can be utilized. This reaction has, in fact, been used for the synthesis of a key methyl ketone intermediate in the total synthesis of (±)-quadrone.[4] If the partner on tin is more expensive or difficult to synthesize, however, then the utilization of only one of the four groups on tin would be a distinct disadvantage. Fortunately, different types of groups on tin transfer selectively, the simple alkyl group serving as the anchor and transferring at the slowest rate. This was shown earlier to be the case for triphenylmethyltin, benzyltrimethyltin, and vinyltributyltin, in which the phenyl, benzyl, and vinyl groups, respectively, transferred selectively. More recently, the selective transfer of the acetylenic group from tin has been shown to be selective over butyl.[5] In a separate study,[6] we have shown that the order of transfer is R′ = PhC≡C > *n*-PrC≡C > PhCH=CH ≈ CH_2=CH > Ph > $PhCH_2$ > CH_3OCH_2 > CH_3 > *n*-Bu. Here we report the palladium-catalyzed coupling reaction in a more convenient solvent, chloroform, and have utilized various unsymmetrical tin reagents, R′SnR''_3, in selectively transferring one of the groups, R′.

Results and Discussion

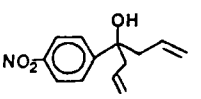
Alkyl-, Aryl-, Vinyl-, Acetylenic, and (Methoxymethyl)tins. The coupling reactions of the acid chlorides with the tin reagents were carried out in chloroform at 65 °C for 12–24 h, with the precipitation of palladium metal signaling the end of the reaction, as occurred in the reactions with HMPA as a solvent.[1] The yields were not quite as high as with the HMPA solvent, but the workup was simpler (Table I). The reaction of tetramethyltin with 4-bromobenzoyl chloride occurred without methylation at the aryl bromide site (entry 1b), indicating that the reaction in chloroform is more selective than that in HMPA, in which a 26% yield of 4-methylacetophenone was obtained as a byproduct.[1] Additionally, primary alkyl bromides survived the reaction conditions, and no methylation or elimination occurred in the reaction with 6-bromohexanoyl chloride (entry 1c). The reaction of tetrabutyltin with benzoyl chloride gave an 85% yield of valerophenone (entry 1d).

Unsymmetrical organotin reagents could be utilized effectively in chloroform with the selective transfer of phenyl (entries 2a–g) taking place in preference to methyl or butyl. The yields of phenyl ketones were good both for aroyl chlorides and ω-bromoalkanoyl chlorides, with no reaction occurring at the primary bromide site. The use of 0.5 equiv of diphenyldibutyltin with 4-nitrobenzoyl chloride gave an 80% yield of 4-nitrobenzophenone, both phenyl groups on tin being transferred effectively (entry 2g).

Unsymmetrical alkenyltin reagents gave good yields of α,β-unsaturated ketones (entries 3a–h), the unsubstituted vinyltin reagent requiring only 1–12 h for reaction. Substitution of an α-methyl group on the vinyl carbon attached to tin required longer reaction times (72 h, entry 3e), and the coupling with 2-butenyltributyltin was the only reaction in which the transfer of the anchoring butyl group took place to some extent (6%) in place of vinyl. The vinyl group transfers with retention of geometry at the double bond, as in the case of the (*Z*)-2-butenyltin reagent. However, isomerization of α,β-unsaturated ketones takes place rapidly, and the thermodynamic product ultimately is observed in the coupling product.[6] Thus, (*Z*)-benzyl 3-(tributylstannyl)propenoate yields (*E*)-benzyl 4-phenyl-4-oxo-2-butenoate. The vinyl group can carry the ester or protected alcohol functionality into the coupled product.

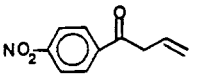
The reaction of alkynyltrimethyltin reagents with benzoyl chloride gave good yields of 1-alkynyl ketones either in chloroform or HMPA (entries 4a–c). The yield obtained for 1,3-diphenyl-2-propyn-1-one was higher in chloroform than in HMPA, consistent with the report[5] that better yields of 1-alkynyl ketones were obtained in dichloroethane than in HMPA. Some selectivity of the methoxymethyl group over methyl or butyl are observed in coupling reactions involving these unsymmetrical tin reagents (entries 5a and 5b).

Allyltins. When allyltrimethyltin was allowed to react with 4-nitrobenzoyl chloride in the presence of benzylchlorobis(triphenylphosphine)palladium(II) (**1**), the product isolated was a diallyl alcohol (**2**) formed by further

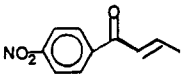


2

allyl addition to the expected allyl ketone. It is known that the allyl group of an allyltin compound undergoes addition to an aldehyde in the presence of Lewis acid catalysts.[7] Thus, it is probable that the palladium catalyst was acting as a Lewis acid and participated in the formation of **2**. The reaction was conducted with tetrakis(triphenylphosphine)palladium(0) in order to circumvent this problem. In tetrahydrofuran this catalyst gave a 90:10 mixture of 1-(4-nitrophenyl)-3-buten-1-one (**3**) and 1-(4-nitrophenyl)-2-buten-1-one (**4**) in 83% yield. Thus, selective allyl transfer occurred as in the rhodium-catalyzed coupling reactions of acid chlorides and allyltin compounds.[2b]

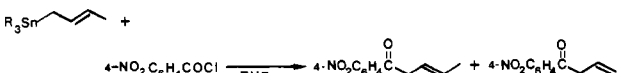


3



4

The reaction of 4-nitrobenzoyl chloride with crotyltrimethyltin was carried out with 0.6 mol % in tetrakis(triphenylphosphine)palladium(0) at 65 °C to give a 50:50 mixture of crotyl ketone **5** and the coupling product of allylic rearrangement (**6**). With the crotyltributyltin reagent, in the presence of 1 mol % of **1**, the ratio of **5** to **6** was 30:70. Lowering the reaction temperature to 50 °C with this reagent produced predominately the product of allylic transposition (**5**:**6** = 17:83).



Cat.	R	T°C	5	6
$(Ph_3P)_4Pd$	Me	65	50	50
1	Bu	65	30	70
1	Bu	50	17	83

Although there is insufficient information to speculate about the mechanism, most electrophilic cleavage reactions

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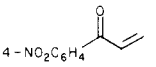
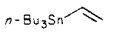
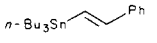
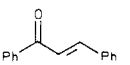
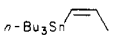
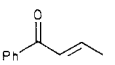
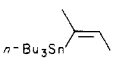
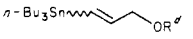
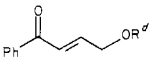
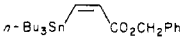
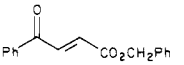
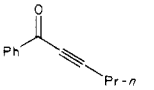
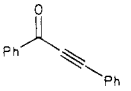
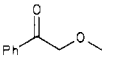
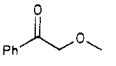
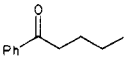
(5) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.
(6) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129.
(7) Pereyre, M.; Quintard, J. P. *Pure Appl. Chem.* **1981**, *53*, 2401.

Table I. Synthesis of Ketones from Acid Chlorides and Organotin Reagents[a]

entry	RCOCl	R'SnR$_3$''	reaction time, h	RCOR'	yield,[b] %
1a	4-$NO_2C_6H_4COCl$	Me_4Sn	24	4-$NO_2C_6H_4COMe$	95
1b	4-BrC_6H_4COCl		24	4-BrC_6H_4COMe	60
1c	$Br(CH_2)_5COCl$		24	$Br(CH_2)_5COMe$	45
1d	PhCOCl	n-Bu_4Sn	40	PhCO-n-Bu	85
2a	4-$NO_2C_6H_4COCl$	$PhSnMe_3$	18	4-$NO_2C_6H_4COPh$	97
2b	$Br(CH_2)_5COCl$		2	$Br(CH_2)_5COPh$	98
2c		PhSn-n-Bu_3	2	$Br(CH_2)_5COPh$	89
2d	$Br(CH_2)_{10}COCl$	$PhSnMe_3$	5	$Br(CH_2)_{10}COPh$	87
2e	PhCOCl	4-$MeOC_6H_4Sn$-n-Bu_3	5	4-$MeOC_6H_4COPh$	85
2f		3-$CF_3C_6H_4Sn$-n-Bu_3	5	3-$CF_3C_6H_4COPh$	64
2g	4-$NO_2C_6H_4COCl$	Ph_2Sn-n-Bu_2	18	4-$NO_2C_6H_4COPh$	80
3a	PhCOCl		18		88
3b	4-$NO_2C_6H_4COCl$		0.33		88
3c	PhCOCl		0.33		71
3d			24		82
3e			4.5		74
3f		 75:25 Z/E	72	 70:30 Z/E	63[c]
3g			24		78
3h			20		55
4a	PhCOCl	$Me_3SnC{\equiv}C$-n-Pr	23		70
4b		$Me_3SnC{\equiv}CPh$	16		87, 64[e]
5a	PhCOCl	$Me_3SnCH_2OCH_3$	18		48
					16
5b		n-$Bu_3SnCH_2OCH_3$	18		36
					14

[a] Reactions were carried out in 5 mL of chloroform at 65 °C for 12–24 h, with 5 mmol of acid chloride, 5.2 mmol of organotin reagent, and 0.02 × 10^{-2} mmol (0.4 mol %) of benzylchlorobis(triphenylphosphine)palladium(II) (1), unless otherwise noted. [b] Isolated yields. [c] A 6% yield of valerophenone was isolated. [d] R = $SiMe_2$-t-Bu. [e] HMPA solvent.

of allyltin compounds are presumed to occur by allylic transposition (S_E2') reactions.[8–10]

Benzyltins. The selective transfer of a benzyl group from benzyltrimethyltin has been reported to give a 91.5% yield of desoxybenzoin in the reaction with benzoyl chloride in the presence of 1 in HMPA.[1] Repeating the reaction in the presence of 0.45 mol % of 1 gave a 10:90 mixture of desoxybenzoin to acetophenone (Table II). The use of benzyltributyltin under identical conditions gave a 15:85 mixture of desoxybenzoin to valerophenone. Thus, under these conditions the transfer of methyl and butyl groups was somewhat favored over the benzyl group. When chloroform was substituted as the solvent, the formation of methyl and butyl ketones again predominated.

When the reaction of benzyltributyltin and benzoyl chloride was conducted in the presence of 4 mol % of 1 in HMPA, the reaction occurred with very good selectivity of benzyl transfer and gave a 93:7 mixture of desoxy-

(8) Mangravite, J. A.; Verdone, J. A.; Kuivila, H. G. *J. Organomet. Chem.* **1976**, *104*, 303.
(9) Gielen, M.; Nasielski, J. *Bull. Soc. Chem. Belg.* **1962**, *71*, 32.
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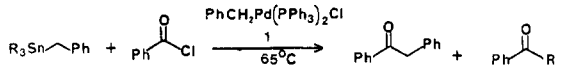
Table II. Palladium-Catalyzed Coupling of Benzyltins with Benzoyl Chloride



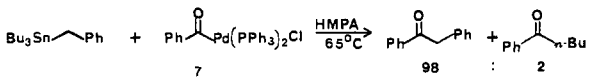
R	catalyst, mol %	solvent	$PhCOCH_2Ph$:PhCOR[a]	conversion,[b] %
Me	0.45	HMPA	10:90	100
Bu	0.45	HMPA	15:85	60
Me	0.45	$CHCl_3$	16:84	53
Bu	0.45	$CHCl_3$	15:85	40
Bu	4.0	HMPA	93:7[c]	84[d]
Me	4.0	HMPA	60:40	100

[a] Product ratio determined by ^1H NMR. [b] Conversion of organotin as determined by ^1H NMR. [c] Product ratio determined by HPLC by comparison to a know mixture of the two ketones. [d] Isolated yield of desoxybenzoin.

benzoin to acetophenone. When benzyltrimethyltin was utilized, a 60:40 mixture of desoxybenzoin to acetophenone was obtained.

The effect of catalyst concentration on the selectivity of benzyl transfer from an unsymmetrical organotin is quite unusual, since according to the proposed mechanism,[1] the catalytic intermediate that reacts with the organotin, benzoylchlorobis(triphenylphosphine)palladium(II) (7), should be formed in the reaction and react with the organotin reagent, regardless of the catalyst concentration. When stoichiometric reactions between benzyltrialkyltins and 7 were carried out, the reaction of benzyltributyltin and 7 in HMPA at 65 °C afforded desoxybenzoin exclusively while the reaction of benzyltrimethyltin and 7 gave a 70:30 mixture of desoxybenzoin to acetophenone. These product ratios are approximately the same as those observed in the catalytic reactions containing 4 mol % of 1. This indicates that in the catalytic reactions between benzoyl chloride and the benzyltrialkyltins with 4 mol % of 1, the benzoylpalladium complex 7 probably was formed and reacted with the organotins predominantly at the benzyl group.

A reaction between benzyltributyltin and 7 was carried out in HMPA with the benzoylpalladium complex 7,

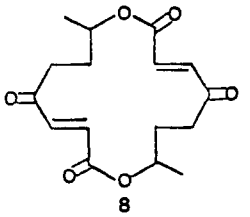


present in a concentration of 6.6×10^{-3} M, corresponding to the same concentration (0.45 mol %) at which 1 was introduced in the catalytic reactions. The reaction gave a 98:2 mixture of desoxybenzoin to valerophenone as measured by HPLC. Thus, the acylpalladium chloride complex 7 reacts with the benzyltin selectively at the benzyl group regardless of its concentration. In the 0.45 mol % catalytic reaction, the identical acylpalladium chloride complex must not be formed, since the benzyl group is not selectively transferred under these conditions.

Different transfer orders of organic groups on tin to platinum(II) complexes have been observed, depending on the structure of the complex. With benzyltrimethyltin, predominate benzyl transfer takes place to dichloro(cyclooctadiene)platinum(II), while methyl transfer predominates in reactions with bis(trifluoroacetato)bis(phosphine)platinum(II).[11,12] The electrophilic cleavage reactions of benzyltrimethyltin also can result in selective benzyl or methyl cleavage, depending on the electrophile.[13]

Synthesis of a Pyrenophorin Precursor. The 2-alkenoic functionality occurs widely in many natural products, particularly antibiotic natural macrolides such as pyrenophorin,[14] vermiculin,[15] elaiophylin,[16] colletodio,[17] grahamimycin A_1,[18] and mycinolide IV.[19] For the synthesis of such products the synthesis of a reagent containing an acrylic building block that could be coupled with other carbon frameworks was a particularly desirable objective.

The synthesis of the macrolide antibiotic (±)-pyrenophorin (8)[14] has been achieved by several routes,[20,21] including the dimerization of the ketal or dithiane-protected hydroxy acid 2.[22,23]



8

The coupling of the appropriately functionalized acid chloride 9 with the 3-(tributylstannyl)acrylate reagent 10 to yield ketone 11 was envisaged as a relatively simple, direct route to the key pyrenophorin precursor (12, Scheme I). Because the palladium-catalyzed ketone synthesis is mild and will tolerate a wide variety of functional groups on both the acid chloride and the organotin coupling partners, this coupling method has the advantage that the acrylate functionality can be introduced directly to yield the 4-oxo-2-alkenoate unit with minimal protection.

The base hydrolysis of γ-valerolactone produced the salt, which was converted to the bissilyl-protected hydroxy acid. Hydrolysis gave the silyl-protected acid a 71% yield from γ-valerolactone. Treatment of the silyl-protected acid with oxalyl chloride gave the corresponding acid chloride 9, which was used without further purification. The *tert*-butyldiphenylsilyl protecting group was required during conversion of the acid to the acid chloride, as other protecting groups such as allyl, *tert*-butyldimethylsilyl, and THP were extruded with concomitant regeneration of γ-valerolactone.

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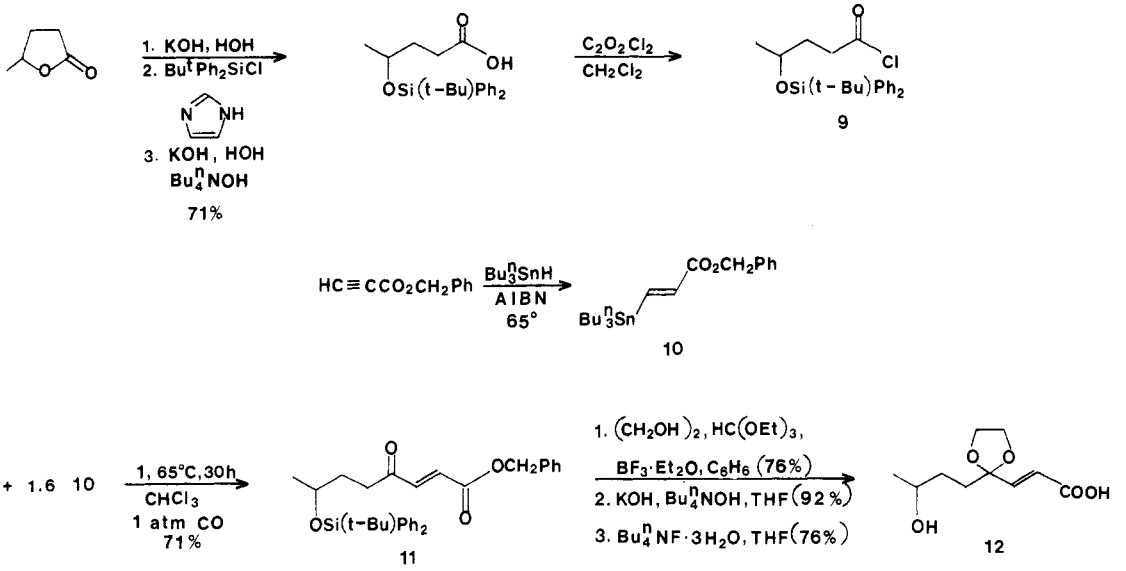
Scheme I



Of a number of available methods[24,25] for the synthesis of the organotin coupling partner, the radical hydrostannation of benzyl propiolate was carried out to give a mixture of *E* and *Z* isomers **4** in 90% yield. Use of the benzyl ester suppressed the polar addition product, 2-(tributylstannyl)acrylate, which is formed in the hydrostannation of methyl propiolate.[26] The *E* isomer **10** was separated from the *Z* isomer by medium-pressure LC.

When the coupling reaction was carried out under the standard reaction conditions utilizing a slight excess of the tin reagent (1.2 equiv), only a 32–40% yield of ketone **11** could be obtained. When this reaction was carried out for 30 h with 1.6 equiv of **10** under 1 atm of carbon monoxide, it gave **11**, which was obtained in a 71% yield from the acid chloride **9** after purification by LC. The carbon monoxide was necessary for the higher yield since lower yields were obtained under these same conditions in the absence of carbon monoxide. Presumably this was due to some decarbonylation of the acylpalladium catalytic intermediate prior to coupling, which was suppressed in the presence of carbon monoxide.

The ketalization of **11** gave the ketal in 76% yield. The basic hydrolysis of the ester followed by silyl deprotection with tetrabutylammonium fluoride gave **12**[20] in 70% yield from the ketal.

The overall yield of **12** from γ-valerolactone was 27%. Since the *R* and *S* enantiomers of valerolactone are both available,[27] no reactions enroute to **12** involve bond breaking at the chiral center and the Mitsunobu reactions[28] for the dimerization of **12** is highly stereospecific, both enantiomers of **12** and the naturally occurring (*R,R*)-pyrenophorin should be available by this method.

Experimental Section

All melting points and boiling points are uncorrected. Tetrahydrofuran (THF), diethyl ether, and benzene were freshly distilled under nitrogen from sodium benzophenone prior to use. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over 13X molecular sieves under argon. Chloroform was passed through a short basic alumina column prior to use in the coupling reactions. Gas chromatographic analyses were carried out on a Varian Model 3700 using a 10% OV-101 Chromasorb W-80/100, 2 m × $^1/_8$ in. column and helium as a carrier gas. HPLC analyses were carried out on Waters Models 6000A and M-45 pumps with a solvent programer and a Model 440 absorbance detector. A μBondapak-C18 column was utilized for reverse-phase HPLC analyses, and a μPorasil column was utilized for normal-phase HPLC analyses. Radial chromatography was carried out with a Chromatotron (Harrison Research Co.). Flash chromatography was carried out according to the published procedure.[29] The ^{1}H NMR spectra were obtained on Varian Model EM-360 and JEOL Model FX-100 spectrometers, with tetramethylsilane as the internal standard. The ^{13}C NMR spectra were obtained on a JEOL FX-100 spectrometer, with deuteriochloroform as the internal standard. Infrared spectra were obtained on a Beckman Model 4250 spectrometer. The mass spectra were obtained on a VG Micromass 16F spectrometer. The elemental analyses were performed by Micro-Tech Laboratories. High-resolution mass spectra were obtained by the Midwest Regional Center for Mass Spectrometry, Lincoln, NE.

Tin Reagents. The following tin reagents used in this study were prepared according to known procedures: phenyltrimethyltin,[30] phenyltributyltin,[31] (4-methoxyphenyl)tributyltin,[32] [3-(trifluoromethyl)phenyl]tributyltin,[33] dibutyldiphenyltin,[34] trimethylvinyltin,[35] tributylvinyltin,[35] (phenylethynyl)trimethyltin,[36] 1-pentynyltrimethyltin,[36] allyltrimethyltin,[37] crotyltrimethyltin,[38] and crotyltributyltin.[39]

(*E*)-β-Styryltributyltin. A mixture of 5.82 g (20.0 mmol) of tributyltin hydride, 1.95 g (19.0 mmol) of phenylacetylene, and 0.14 g (0.085 mmol) of azobis(isobutyronitrile) was heated slowly to 50 °C and maintained at that temperature for 24 h. The reaction mixture was cooled, a white precipitate was removed by filtration through a Celite pad, and the liquid was distilled to give 6.50 g (84%) of (*E*)-β-styryltributyltin: bp 134 °C (0.1 mmHg) [lit.[31] bp 122–125 °C (0.1 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 0.7–1.6 (m, 27), 6.9 (s, 2, =CH), 7.2–7.4 (m, 5); ^{13}C NMR ($CDCl_3$) δ 9.74, 13.8, 27.4, 29.2, 125.9, 127.3, 128.3, 129.3, 138.7, 146.0.

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(Z)-1-Propenyltributyltin. This compound was prepared by the reaction of propenylmagnesium bromide and tributyltin chloride following a procedure for the preparation of tributylvinyltin:[35] bp 77–78 °C (0.25 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.7–1.6 (m, 27), 1.7 (d, 3, J = 7 Hz, =CCH_3), 5.7 (m, 1, =CHSn), 6.4 (m, 1, =C*H*CH_3). The ^{1}H NMR spectrum in the vinyl region matched the published data for (Z)-1-propenyltrimethyltin.[40]

2-Buten-2-yltributyltin. A solution of 22.3 g (0.165 mol) of 2-chloro-2-butene in 30 mL of THF was added to 12.2 g (0.500 mol) of magnesium in 75 mL of THF. The solution was heated at the reflux temperature for 5 h, cooled, treated with 48.8 g (0.150 mol) of tributyltin chloride, and stirred at ambient temperature for 10 h. The reaction was quenched with an aqueous ammonium chloride solution. The organic layer was separated and washed with 75 mL of saturated aqueous sodium bicarbonate and brine, then dried (Na_2SO_4), concentrated, and distilled to give 36.0 g (70%) of product as a mixture of E and Z isomers: bp 114 °C (1.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.4–2.2 (m, 32), 5.63 (m, 1, =CH, E isomer), 6.10 (m, 1, =CH, Z isomer) [the ratio of Z to E was 75:25]; ^{13}C NMR ($CDCl_3$) δ 9.16, 9.92, 13.7, 17.5, 19.8, 26.8, 27.0, 27.5, 28.0, 29.4, 134.3, 134.5, 138.4, 138.8. The isomer assignment was based on comparison of the chemical shifts of the vinyl protons to the vinyl protons published for (E)- and (Z)-2-butenyltrimethyltin.[41] Anal. Calcd for $C_{16}H_{34}Sn$: C, 55.68; H, 9.93. Found: C, 55.79; H, 9.68.

Benzyl 3-(Tributylstannyl)propenoate. A mixture of 6.6 g (23 mmol) of tributyltin hydride, 4.0 g (25 mmol) of benzyl propiolate,[42] and 0.16 g (0.92 mmol) of azobis(isobutyronitrile) was heated slowly to 65 °C and then kept at that temperature for 15 h. The reaction mixture was purified on a 10-cm gravity column (silica gel, ethyl acetate/hexane, 10:90), followed by separation by medium-pressure LC (silica gel, ethyl acetate/hexane, 2:98) to give 6.0 g (60%) of the Z isomer: ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 27), 5.1 (s, 2, $-CH_2O_2C-$), 6.7 (d, 1, J = 12 Hz, =CH), 7.15 (d, 1, J = 12 Hz, =CH), 7.3 (br s, 5); ^{13}C NMR ($CDCl_3$) δ 11.2, 13.9, 27.4, 29.3, 66.3, 128.2, 128.3, 134.9, 135.9, 157.9, 167.3 ($-CO_2R$); IR (neat) 1710 cm^{-1} (ester C=O). Anal. Calcd for $C_{22}H_{36}O_2Sn$: C, 58.56; H, 8.04. Found: C, 58.93; H, 8.09. Further elution gave 2.9 g (29%) of the E isomer (**10**): ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 27), 5.1 (s, 2, $-CH_2O_2C-$), 6.3 (d, 1, J = 20 Hz, =CH), 7.3 (br s, 5), 7.8 (d, 1, J = 20 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 9.74, 13.7, 27.3, 29.0, 66.1, 128.0, 128.1, 128.3, 135.8, 153.1, 164.3 (CO_2R); IR (neat) 1720 cm^{-1} (ester C=O). Anal. Calcd for $C_{22}H_{36}O_2Sn$: C, 58.56; H, 8.04. Found: C, 58.69; H, 8.49.

1-(Tributylstannyl)-3-(*tert*-butyldimethylsiloxy)-1-propene. A mixture of 8.7 g (30 mmol) of tributyltin hydride, 5.1 g (30 mmol) of 3-(*tert*-butyldimethylsiloxy)-1-propyne,[5] and 50 mg (0.30 mmol) of azobis(isobutyronitrile) was slowly heated to 100 °C and maintained at 100 °C for 3 h. The reaction mixture was cooled, partitioned between ether and water, washed with aqueous sodium bicarbonate and brine, and then dried (Na_2SO_4). The solution was concentrated and distilled to give 9.6 g (72%) of product as a colorless liquid: bp 128 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.3 (s, 6, CH_3Si), 0.8–1.9 (m, 36), 4.3 (d, J = 2 Hz, $-CH_2O-$, Z isomer), 6.1 (s, 2, =CH, E isomer) (the E to Z isomer ratio was 85:15). Anal. Calcd for $C_{21}H_{46}OSiSn$: C, 54.57; H, 10.05. Found: C, 54.17; H, 9.67.

(Methoxymethyl)trimethyltin. Lithium trimethylstannate was prepared from 10.0 g (50.0 mmol) of trimethyltin chloride and 2.1 g (0.30 mol) of lithium in 65 mL of THF.[43] The lithium trimethylstannate solution was transferred away from the excess lithium metal with a cannula and cooled to 0 °C. To the solution was added 4.0 g (50 mmol) of chloromethyl methyl ether in 10 mL of THF, followed by stirring at ambient temperature for 12 h. The reaction mixture was quenched with 70 mL of water, and the aqueous layer was separated and washed with two 20-mL ether portions. The combined organic layer was washed with brine and then dried (Na_2SO_4) and distilled to give 4.2 g (41%) of (methoxymethyl)trimethyltin as a colorless liquid: bp 123 °C (650 mmHg) [lit.[44] bp 59.5 °C (65 mmHg)]; ^{1}H NMR (CCl_4) δ 0.3 (s, 9, CH_3Sn), 3.2 (s, 3, CH_3O), 3.6 (s, 2, $SnCH_2O$); ^{13}C NMR ($CDCl_3$) δ −10.6 (CH_3Sn), 62.7, 65.0. The ^{1}H NMR spectrum matched the published data.[44]

(Methoxymethyl)tributyltin. This compound was made by a procedure analogous to that for the preparation of (methoxymethyl)trimethyltin;[44] however, the lithium tributylstannate was prepared from the reaction of tributyltin hydride with lithium diisopropylamide.[45] The product was purified by flash chromatography (silica gel), eluting with pentane to remove nonpolar side products, followed by methylene chloride to give (methoxymethyl)tributyltin, after removal of the solvent, in 41% yield: ^{1}H NMR ($CDCl_3$) δ 0.65–1.7 (m, 27), 3.3 (s, 3, CH_3O), 3.7 (s, 2, $SnCH_2O$); ^{13}C NMR ($CDCl_3$) δ 8.98, 13.7, 27.4, 29.2, 63.1, 64.3. Anal. Calcd for $C_{14}H_{32}OSn$: C, 50.18; H, 9.63. Found: C, 50.09; H, 9.37.

Acid Chlorides. Acid chlorides either were obtained commercially or prepared according to known procedures and distilled before use: 4-nitrobenzoyl chloride,[46] 4-bromobenzoyl chloride,[47] 6-bromohexanoyl chloride,[46] and 6-bromoundecanoyl chloride.[46]

General Procedure for Ketone Preparation in HMPA. The procedure followed for the reaction of the acid chlorides with tetraorganotins to yield ketones has been described.[1]

General Procedure for Ketone Preparations Utilizing Derivatives of Trimethyltin in Chloroform. A solution of 5.0 mmol of the acid chloride and 15–20 mg ($2.0–2.6 \times 10^{-2}$ mmol) of benzylchlorobis(triphenylphosphine)palladium(II) (**1**)[48] in 1 mL of chloroform was treated with 5.2 mmol of the organotin in 4 mL of chloroform. The yellow solution was heated at 65 °C with stirring under an air atmosphere in a tube sealed by a Teflon vacuum stopcock until palladium metal precipitated (1–24 h). The solution was cooled to room temperature, poured into 30 mL of ether, extracted with 2 × 20 mL of water, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography or crystallization.

General Procedure for Ketone Preparation Utilizing Derivatives of Tributyltin in Chloform. The reactions were conducted in the same fashion as with the organotrimethyltin compounds. After precipitation of palladium metal, the reaction mixture was poured into 30 mL of ether, washed with 30 mL of water, then with 30 mL of a half-saturated aqueous potassium fluoride solution with vigorous shaking, and allowed to stand 15–30 min. The resulting white precipitate of tributyltin fluoride was removed by filtration, and the organic layer was separated and again washed with aqueous potassium fluoride. The second wash usually resulted in much less precipitation of tributyltin fluoride, from which the organic layer could be decanted. The organic layer was washed with brine and then dried ($MgSO_4$) and concentrated. The residue was treated with ethyl acetate, which resulted in additional tributyltin fluoride precipitate and was removed by filtration with a Celite pad. The mother liquor was purified by chromatography or crystallization.

Ketones. Ketone products were isolated according to the general procedures. Yields and reaction times are listed in Table I. Known ketones were identified either by comparison with authentic samples or by comparison with data reported: 4-bromoacetophenone,[49] 1-phenyl-2-propen-1-one,[50] 1,3-diphenylpropyn-1-one,[51] 4-methoxyacetophenone,[52] 3-(trifluoromethyl)-acetophenone.[53]

7-Bromo-2-heptanone. The product was purified by column chromatography (alumina, ether) to give 7-bromo-2-heptanone

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in 45% yield. The product was further purified by distillation: bp 68–70 °C (0.8 mmHg) [lit.[54] bp 107–108 °C (8 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 1.4–1.9 (m, 6), 2.2 (s, 3, O=CCH_3), 2.45 (t, 2, J = 6 Hz, O=CCH_2), 3.4 (t, 2, J = 8 Hz, CH_2Br); IR (neat) 1725 cm^{-1} (C=O). Anal. Calcd for $C_7H_{13}BrO$: C, 43.55; H, 6.79. Found: C, 43.69; H, 6.77.

6-Bromo-1-phenyl-1-hexanone. The product was purified by column chromatography (alumina, ether) to give 6-bromo-1-phenyl-1-hexanone as a white solid in 98% yield: mp 37.5–38 °C; ^{1}H NMR ($CDCl_3$) δ 1.6–2.1 (m, 6), 2.9 (t, 2, J = 7 Hz, O=CCH_2), 3.4 (t, 2, J = 7 Hz, CH_2Br), 7.4–7.7 (m, 3), 7.9–8.1 (m, 2); ^{13}C NMR ($CDCl_3$) δ 23.0, 27.6, 32.4, 33.4, 37.9, 127.5, 128.1, 132.4, 136.5, 199.0 (C=O); IR (KBr) 1690 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.93. Found: C, 56.29; H, 5.87.

11-Bromo-1-phenyl-1-undecanone. The product was purified by column chromatography (alumina, methylene chloride) to give 11-bromo-1-phenyl-1-undecanone as an off-white solid in 87% yield. The product was recrystallized from ethanol to give beige plates: mp 53.5–54.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.9–2.0 (m, 16), 2.9 (t, 2, J = 7 Hz, O=CCH_2), 3.3 (t, 2, J = 7 Hz, CH_2Br), 7.1–7.6 (m, 3), 7.8–8.0 (m, 2); ^{13}C NMR ($CDCl_3$) δ 24.3, 28.1, 28.7, 29.4, 34.0, 32.8, 38.6, 127.9, 128.3, 132.6, 136.9, 200.1 (C=O). Anal. Calcd for $C_{17}H_{25}BrO$: C, 62.77; H, 7.75. Found: C, 62.75; H, 7.96.

1-(4-Nitrophenyl)-2-propen-1-one. The product was recrystallized from chloroform/hexane to give 1-(4-nitrophenyl)-2-propen-1-one as a yellow solid in 88% yield: mp 87–89 °C [lit.[55] 88–90 °C]; ^{1}H NMR ($CDCl_3$) δ 6.0 (dd, 1, J = 10, 2 Hz, CH=), 6.4 (dd, 1, J = 18, 2 Hz, CH=), 7.1 (dd, 1, J = 18, 10 Hz, O=CCH=), 8.0 (d, 2, J = 9 Hz), 8.3 (d, 2, J = 9 Hz); IR (KBr) 1670 cm^{-1} (C=O). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98. Found: C, 61.23; H, 4.11.

1-Phenyl-2-buten-1-one. The product was purified by flash chromatography to give the E isomer in 40% yield: ^{1}H NMR ($CDCl_3$) δ 1.97 (d, 3, J = 5.5 Hz, CH_3C=), 6.9–7.3 (m, 2, =CH), 7.3–7.6 (m, 3), 7.8–8.0 (m, 2); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 127.2, 128.2, 132.3, 137.6, 144.6, 190.3 (C=O). Further elution of the column gave the Z isomer in 33% yield: ^{1}H NMR ($CDCl_3$) δ 2.1 (dd, 3, J = 7, 1.7 Hz, CH_3C=), 6.4 (dq, 1, J = 11.5, 7 Hz, CH=), 6.8 (dd, 1, J = 11.5, 1.7 Hz, CH=), 7.3–7.5 (m, 3), 7.8–8.0 (m, 2); ^{13}C NMR ($CDCl_3$) δ 16.1 (CH_3), 124.9, 127.9, 128.1, 132.2, 143.4, 191.4 (C=O); IR (neat) 1680 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{10}O$: C, 82.17; H, 6.90. Found: C, 81.35; H, 6.92. The ^{1}H NMR spectrum for each isomer matched the published data.[56]

2-Methyl-1-phenyl-2-buten-1-one. This compound was prepared from benzoyl chloride and a 25:75 mixture of (*E*)- to (*Z*)-2-butenyltributyltin according to the general procedure. The product was purified by medium-pressure LC (silica gel), by eluting with one column volume of hexane followed by 1.5:98.5 ethyl acetate/hexane to give a 6% yield of valerophenone. Further elution gave the E isomer in 19% yield: ^{1}H NMR ($CDCl_3$) δ 1.5 (d, J = 7 Hz, =CCH_3), 1.95 (s, 3, =C(C=O)CH_3), 5.8 (q, J = 7 Hz, CH=), 7.3–7.7 (m, 5); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 20.8 (CH_3), 126.3, 128.3, 128.7, 129.0, 132.7, 136.0, 199.7 (C=O); IR (neat) 1650 cm^{-1} (C=O). Further elution gave the Z isomer in 43% yield: ^{1}H NMR ($CDCl_3$) δ 1.8 (d, 3, J = 7 Hz, =CCH_3), 1.9 (s, 3, =C(C=O)CH_3), 6.4 (q, 1, J = 7 Hz, CH=), 7.3–7.7 (m, 5); ^{13}C NMR ($CDCl_3$) δ 11.9 (CH_3), 14.5 (CH_3), 127.6, 128.7, 130.8, 137.1, 138.4, 140.8, 198.0 (C=O); IR (neat) 1645 cm^{-1} (C=O). The ^{1}H NMR spectrum for the Z isomer matched the published data for an isomer of 2-methyl-1-phenyl-2-buten-1-one, which was misassigned as the E isomer.[57]

The isomers were assigned by analogy to the relative shifts of the vinyl protons of the corresponding tin reagents. Also, the chemical shifts observed for the γ-methyl groups (Z, 1.8; E, 1.5) are consistent with the chemical shifts for (*E*)- and (*Z*)-1-phenyl-2-buten-1-one.[56] The ^{13}C chemical shifts for the γ-methyl carbons (Z, 11.9; E, 20.8) are consistent with these methyls being Z and E, respectively, to a carbonyl group.[58]

(*E*)-Benzyl 4-Phenyl-4-oxo-2-butenoate. This compound was prepared by a modified general procedure utilizing 1.5 equiv of (*Z*)-benzyl-3-(tributylstannyl)propenoate and benzoyl chloride in the presence of 2 mol % of 1.[48] Purification was carried out by medium-pressure LC (silica gel, ethyl acetate/hexane, 10:90) to give the E isomer as a clear liquid in 55% yield: ^{1}H NMR ($CDCl_3$) δ 5.3 (s, 2, OCH_2Ph), 6.9 (d, 1, J = 16 Hz, CH=), 7.3–7.6 (m, 8), 7.8–8.0 (m, 3); ^{13}C NMR ($CDCl_3$) δ 67.0 (OCH_2), 128.1, 128.4, 128.6, 131.9, 133.6, 135.1, 136.6, 165.0 (CO_2R), 189.0 (C=O); IR (neat) 1675 (C=O), 1725 (ester C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.51; H, 5.47.

4-(*tert*-Butyldimethylsiloxy)-1-phenyl-2-buten-1-one. This compound was prepared from benzoyl chloride and an 85:15 mixture of (*E*)- to (*Z*)-1-(tributylstannyl)-3-(*tert*-butyldimethylsiloxy)-1-propene in the presence of 1 mol % of 1 according to the general procedure. Purification was carried out by medium-pressure LC (silica gel, ethyl acetate/hexane, 5:95) to give the E isomer in 65% yield: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 6, $SiCH_3$), 0.9 (s, 9, $SiCCH_3$), 4.4 (m, 2, $-CH_2O-$), 7.1 (br s, 2, =CH), 7.3–7.6 (m, 3), 7.9–8.1 (m, 2); ^{13}C NMR ($CDCl_3$) δ −5.4 ($SiCH_3$), 18.3, 25.8, 62.5 (CH_2O), 123.1, 128.2, 132.3, 137.6, 147.2, 189.7 (C=O); IR (neat) 1670 cm^{-1} (C=O); MS parent, m/e 276.1546, calcd for $C_{16}H_{24}O_2Si$, 276.1625. Further elution of the column gave the Z isomer in 12% yield: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 6, CH_3), 0.9 (s, 9, $SiCCH_3$), 4.5 (m, 2, OCH_2), 5.8 (m, 1, CH=), 6.2 (m, 1, CH=), 7.3–7.6 (m, 3), 7.9–8.1 (m, 2).

Coupling of Allyltrimethyltin with 4-Nitrobenzoyl Chloride To Give 3 and 4. A solution of 1.25 g (6.20 mmol) of allyltrimethyltin, 1.12 g (6.00 mmol) of 4-nitrobenzoyl chloride, and 40 mg (0.034 mmol) of tetrakis(triphenylphosphine)palladium(0)[59] was degassed and heated at 65 °C for 22 h. The reaction mixture was poured into 20 mL of ether, washed with 3 × 30 mL of water, and then dried (Na_2SO_4). The solvents were removed to give 0.90 g (83%) of a 90:10 mixture of **3** and **4** as measured by ^{1}H NMR: ^{1}H NMR (of **3**) ($CDCl_3$) δ 3.8 (dm, 2, J = 7 Hz, CH_2C=), 5.1 (dm, 1, J = 6 Hz, CH=), 5.35 (m, 1), 5.7–6.2 (m, 1), 8.1 (d, 2, J = 9 Hz). An ether solution of the product mixture was stirred over potassium carbonate, filtered, and concentrated to give **4**: ^{1}H NMR ($CDCl_3$) δ 2.05 (d, 2, J = 5.5 Hz, CH_3C=), 6.9–7.3 (m, 2), 8.0 (d, 2, J = 9 Hz), 8.3 (d, 2, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 18.8 (CH_3), 123.5, 127.0, 129.2, 142.6, 147.2, 149.8, 188.9 (C=O); IR ($CHCl_3$) 1675 cm^{-1} (C=O); MS parent, m/e 191.0582, calcd for $C_{10}H_9NO_3$, 191.0583.

Coupling of Crotyltrimethyltin with 4-Nitrobenzoyl Chloride To Give 5 and 6. A solution of 0.68 g (3.1 mmol) of crotyltrimethyltin, 0.56 g (3.0 mmol) of 4-nitrobenzoyl chloride, and 20 mg (1.7×10^{-2} mmol) of tetrakis(triphenylphosphine)-palladium(0)[59] in 2.5 mL of THF was degassed by three freeze–pump–thaw cycles. The solution was heated at 65 °C for 42 h, poured into ether, and washed with two portions of water. The organic layer was dried ($MgSO_4$), concentrated, and purified by flash chromatography (silica gel, ether/hexane, 1:3) to give 0.32 g (52%) of a mixture of **5** and **6** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3, J = 7 Hz, CH_3, **6**), 1.7 (m, 3, CH_3, **5**), 3.7 (m, 2, CH_2C=O, **5**), 4.2 (q, 1, J = 7 Hz, CHC=O, **6**), 5.1 (m), 5.3 (m), 5.6–6.3 (m), 8.2 (m, 4); IR ($CHCl_3$) 1685 cm^{-1} (C=O) (ratio of **5** to **6** is 50:50); MS parent, m/e 205.0743, calcd for $C_{11}H_{11}NO_3$, 205.0739. Further purification of the product mixture by medium-pressure LC (silica gel, ethyl acetate/hexane, 3:97) gave the rearranged isomer of **6**, 1-(4-nitrophenyl)-2-methyl-2-buten-1-one, as white needles: ^{1}H NMR ($CDCl_3$) δ 1.93, (d, 3, J = 5 Hz, =$CHCH_3$), 2.0 (s, 3, =CCH_3), 6.44 (d of m, 1, J = 5.5 Hz), 7.7 (d, 2, J = 8 Hz), 8.2 (d, 2, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 11.5, 14.9, 122.9, 129.4, 137.3, 143.8, 144.3, 148.7, 196.2 (C=O).

General Procedure for the Coupling of Benzyltributyltin and Benzoyl Chloride. A solution of 5.2 mmol of the substituted benzyltributyltin, 5.0 mmol of benzoyl chloride, and 150 mg (0.200 mmol) of benzylchlorobis(triphenylphosphine)palladium(II)[48] (**1**) in 5 mL of HMPA was stirred at 65 °C for 20–24 h. The reaction mixture had precipitated palladium metal by this time. The reaction mixture was diluted with 30 mL ether and washed with 3 × 30 mL of water, followed by 30 mL of a half-saturated aqueous potassium fluoride solution. The white precipitate of tributyltin

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fluoride was removed by filtration, and the mother liquor was washed with brine and concentrated. The residue was treated with 20 mL of ethyl acetate, and the undissolved tributyltin fluoride was removed by filtration. The mother liquor was dried ($MgSO_4$), concentrated, and purified by chromatography and/or recrystallization. All ketone products showed only one peak by HPLC.

General Procedure for Reactions of Benzyltrialkyltins with 7. (a) In HMPA. A solution of 0.772 g (1.00 mmol) of benzoylchlorobis(triphenylphosphine)palladium(II) (**7**)[60] in 1 mL of HMPA was treated with 1.0 mmol of the organotin in 1.5 mL HMPA. The yellow solution was heated at 65 °C under an air atmosphere in a sealed tube. Palladium metal precipitated from the reaction mixture within 1 h, and the mixture was heated a total of 12 h. The reaction mixture was poured into 50 mL of ether and washed with 3 × 50 mL of water. The organic layer was filtered through a Celite pad, dried ($MgSO_4$), and concentrated, and the residue was analyzed by ^1H NMR. **(b) In $CDCl_3$.** A solution of 0.30 mmol of the organotin in 1 mL of $CDCl_3$ in a ^1H NMR tube was treated with 116 mg (0.150 mmol) of **7**. The reaction mixture was heated at 65 °C in an oil bath. Periodically, the ^1H NMR tube was removed and cooled to ambient temperature, and the ^1H NMR spectrum of the reaction mixture was obtained.

Reaction of Benzyltributyltin with Benzoylchlorobis(triphenylphosphine)palladium(II) (7) at High Dilution. A solution of 25 mg (0.033 mmol) of **7** and 34.6 mg (0.130 mmol) of triphenylphosphine in 4.0 mL of HMPA was heated at 65 °C with 126 mg (0.330 mmol) of benzyltributyltin in 1.0 mL of HMPA. The reaction was stopped after 6 h, poured into 30 mL of water, and extracted with 2 × 30 mL of hexane. The hexane layer was passed through a Celite pad and analyzed by HPLC (ethyl acetate/hexane, 98:2, 2 mL/min). The reaction mixture showed a peak corresponding to desoxybenzoin at t_r 6.9 min and a peak corresponding to valerophenone at t_r 3.9 min. The product ratio of desoxybenzoin to valerophenone was found to be 98:2 by comparison to a mixture of known amounts of authentic samples of the two ketones.

4-(*tert*-Butyldiphenylsiloxy)pentanoic Acid. To 5.0 g (0.050 mol) of γ-valerolactone was added 20.6 mL of 2.43 N aqueous potassium hydroxide, standardized by titration with potassium hydrogen phthalate. The solution was stirred at room temperature for 12 h. To the solution was added 50 mL of benzene, and the flask was fitted with a Dean–Stark condenser. The water was removed by azeotroping over a period of 12 h. The benzene was removed in vacuo to give the potassium salt as a white solid.

A mixture of 4.90 g (8.24 mmol) of the potassium salt in 20 mL THF, 50 mL of 2.4 N aqueous potassium hydroxide, and 6 mL of tetrabutylammonium hydroxide was heated at the reflux temperature for 15 h. The reaction mixture was acidified with 50% aqueous hydrochloric acid and extracted with ether. The ethereal layer was dried ($MgSO_4$) and concentrated to give a viscous oil. The oil was dissolved in 20 mL pentane, and 10% sodium hydroxide was added dropwise as the sodium salt precipitated. The pentane layer was removed from the precipitate by pipet, and the precipitate was washed again with 2 × 30 mL of pentane. The solid was acidified with 10% hydrochloric acid, and the aqueous layer was extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated, and the precipitation from pentane with 10% sodium hydroxide was repeated. The resulting clear colorless oil was further purified by flash chromatography (silica gel; ethyl acetate/hexane/methanol 25:70:5) to give 2.17 g (74%) of 4-(*tert*-butyldiphenylsiloxy)pentanoic acid as a clear oil: ^1H NMR ($CDCl_3$) δ 1.05 (d, 3, J = 6 Hz, CH_3), 1.05 (s, 9, $SiCCH_3$), 1.8 (m, 2), 2.45 (dd, 2, J = 7.6, 8.1 Hz, CH_2CO_2H), 3.95 (hext, 1, J = 6 Hz, CHOSi), 7.2–7.4 (m, 6), 7.5–7.7 (m, 4); ^{13}C NMR ($CDCl_3$) δ 19.4, 23.1, 27.1, 29.9, 33.9, 68.4 (CHOSi), 127.3, 127.5, 129.4, 133.9, 134.5, 135.7, 180.2 (CO_2H); IR (neat) 2900 (acid OH) 1705 (acid C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_3Si$: C, 70.74; H, 7.92. Found: C, 71.49; H, 8.07.

4-(*tert*-Butyldiphenylsiloxy)pentanoyl Chloride (9). A solution of 1.19 g (3.45 mmol) of 4-(*tert*-butyldiphenylsiloxy)-pentanoic acid was dissolved in 25 mL of methylene chloride and was treated with 0.44 mL (5.1 mmol) of oxalyl chloride and stirred overnight. The volatiles were removed in vacuo to give **9**, which was used in the coupling reactions without further purification.

Benzyl 7-(*tert*-Butyldiphenylsiloxy)-4-oxo-2-octenoate (11). A solution of **9** prepared from 200 mg (0.561 mmol) of the corresponding acid, 253 mg (0.561 mmol) of **10**, and 10 mg of **1** in 2 mL of chloroform was flushed with a stream of CO for 5 min. The reaction mixture was heated at 65 °C for 18 h, an additional 150 mg (0.33 mmol) of **10** was added, and the reaction mixture was heated an additional 12 h. The reaction mixture was poured into ether and washed with 3 × 15 mL of water. The organic layer was washed with two portions of aqueous potassium fluoride, and the resulting solid was removed by filtration. The filtrate was dried ($MgSO_4$), concentrated, and purified by medium-pressure LC (silica gel, ethyl acetate/hexane, 10:90) to give 200 mg (59%) of **11** as a clear liquid: ^1H NMR ($CDCl_3$) δ 1.1 (d, 3, J = 6 Hz), 1.1 (s, 9), 1.6–1.9 (m, 2), 2.6 (t, 2, J = 8 Hz, CH_2C=O), 3.9 (hext, 1, J = 6 Hz, CHOSi), 5.2 (s, 2, OCH_2Ph), 6.6 (d, 1, J = 16 Hz, =CH), 7.0 (d, 1, J = 16 Hz, =CH), 7.3–7.5 (m, 11), 7.6–7.8 (m, 4); ^{13}C NMR ($CDCl_3$) δ 19.3, 23.3, 27.1, 32.7, 37.1, 67.0, 68.4, 127.3, 128.3, 128.4, 129.4, 129.5, 130.0, 133.9, 134.2, 134.6, 135.1, 135.6, 139.5, 165.0 (CO_2R), 199.1 (C=O); IR (neat) 1695 (C=O), 1725 (ester C=O) cm^{-1}. Anal. Calcd for $C_{31}H_{36}O_4Si$: C, 74.36; H, 7.25. Found: C, 74.70; H, 7.55.

Benzyl 7-(*tert*-Butyldiphenylsiloxy)-4,4-(ethylenedioxy)-2-octenoate. A solution of 430 mg (0.860 mmol) of **11**, 112 mg (1.80 mmol) of ethylene glycol, and 0.27 mL (240 mg, 1.6 mmol) of ethyl orthoformate in 5 mL of benzene was treated with 2 drops of boron trifluoride etherate. The reaction mixture was heated at the reflux temperature for 24 h, poured into 40 mL of saturated aqueous sodium bicarbonate, and extracted with ether. The organic layer was dried ($MgSO_4$), concentrated, and purified by medium-pressure LC (silica gel, ethyl acetate/hexane, 10:90) to give 355 mg (76%) of product as a clear colorless oil: ^1H NMR ($CDCl_3$) δ 1.0 (s, 9), 1.0 (d, 3, J = 6 Hz), 1.6–1.9 (m, 4), 3.8 (br s, 5), 5.2 (s, 2, OCH_2Ph), 6.1 (d, 1, J = 16 Hz, =CH), 6.7 (d, 1, J = 16 Hz, =CH), 7.3–7.5 (m, 11), 7.6–7.8 (m, 4); ^{13}C NMR δ 19.3, 23.2, 27.2, 32.6, 33.2, 64.8, 66.4, 69.1, 108.2, 121.1, 127.2, 127.3, 128.1, 128.4, 129.3, 134.2, 134.6, 135.7, 146.8, 165.7; IR (neat) 1720 cm^{-1} (CO_2R). Anal. Calcd for $C_{33}H_{40}O_5Si$: C, 72.76; H, 7.40. Found: C, 72.77; H, 7.47.

4,4-(Ethylenedioxy)-7-hydroxy-2-octenoic Acid (12). A solution of 240 mg (0.440 mmol) of benzyl 7-(*tert*-butyldiphenylsiloxy)-4,4-(ethylenedioxy)-2-octenoate in 5 mL of THF, 3.5 mL of 2.4 N potassium hydroxide, and 1 drop of tetrabutylammonium hydroxide was heated at the reflux temperature for 20 h. The reaction mixture was poured into a bilayer of 20 mL of water and 40 mL of ether. The aqueous layer was acidified with 10% aqueous hydrochloric acid. The organic layer was separated and washed with 2 × 30 mL of water and brine. The organic layer was dried ($MgSO_4$) and concentrated to give 220 mg of a 55:45 mixture of product and benzyl alcohol as determined by ^1H NMR. This corresponds to a 184 mg (92%) crude yield of product, which was carried on without further purification: ^1H NMR ($CDCl_3$) δ 1.1 (s, 9), 1.1 (d, 9, J = 6 Hz), 1.8 (m, 2), 3.9 (br s, 5), 6.1 (d, 1, J = 16 Hz, =CH), 6.8 (d, 1, J = 16 Hz, =CH), 7.4–7.9 (m, 10).

A solution of 184 mg (0.405 mmol) of the acid contaminated with 36 mg of benzyl alcohol and 315 mg (1.00 mmol) of tetrabutylammonium fluoride trihydrate in 3 mL of THF was heated at the reflux temperature for 44 h. The reaction mixture was poured into 20 mL of pH 3 buffer (0.2 M sodium hydrogen phosphate/0.1 M citric acid, 1:4). The aqueous layer was extracted with 3 × 30 mL of ether. The organic layer was washed with 25 mL of 1% aqueous sodium hydroxide and back-washed once with ether, and then the base layer was acidified with 10% hydrochloric acid, followed by a pH 3 buffer. The aqueous layer was extracted with 3 × 40 mL of ether. The ether layer was dried ($MgSO_4$) and concentrated to give 66 mg (76%) of **12** as a viscous oil: ^1H NMR ($CDCl_3$) δ 1.2 (d, 3, J = 6 Hz, CH_3), 1.4–2.1 (m, 4), 3.8 (m, 1, CHOH), 4.0 (s, 4, $-OCH_2CH_2O-$), 5.8 (br s, 2, OH, CO_2H), 6.0 (d, 1, J = 16 Hz, =CH), 6.8 (d, 1, J = 16 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 23.3, 22.3, 33.7, 64.9, 67.8, 108.0, 121.4, 147.6, 169.7 (CO_2H). The ^1H NMR and ^{13}C NMR spectra matched the published data.[20]

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Registry No. 1, 22784-59-4; 3, 87305-64-4; 4, 87305-65-5; 5, 87305-66-6; 6, 87305-67-7; 6 (2-ene), 87305-73-5; 7, 29158-91-6; 9, 87305-68-8; 9 (acid), 87305-75-7; (*E*)-10, 86633-19-4; (*Z*)-10, 86633-18-3; (*E*)-11, 87305-69-9; (*E*)-11 (ethylene ketal), 87305-76-8; (*E*)-12, 87334-71-2; (*E*)-12 (silyl), 87305-77-9; $(PPh_3)_4Pd$, 14221-01-3; $4\text{-}NO_2C_6H_4COCl$, 122-04-3; $4\text{-}BrC_6H_4COCl$, 586-75-4; $Br(CH_2)_5COCl$, 22809-37-6; PhCOCl, 98-88-4; $Br(CH_2)_{10}COCl$, 15949-84-5; $Me_3SnCH_2CH{=}CH_2$, 762-73-2; Me_4Sn, 594-27-4; *n*-Bu_4Sn, 1461-25-2; $PhSnMe_3$, 934-56-5; PhSn-*n*-Bu_3, 960-16-7; $4\text{-}MeOC_6H_4Sn\text{-}n\text{-}Bu_3$, 70744-47-7; $3\text{-}CF_3C_6H_4Sn\text{-}n\text{-}Bu_3$, 53566-38-4; $Ph_2Sn\text{-}n\text{-}Bu_2$, 6452-61-5; $Me_3SnCH{=}CH_2$, 754-06-3; *n*-$Bu_3SnCH{=}CH_2$, 7486-35-3; (*E*)-*n*-$Bu_3SnCH{=}CHPh$, 66680-88-4; (*Z*)-*n*-$Bu_3SnCH{=}CHCH_3$, 66680-84-0; (*E*)-*n*-$Bu_3SnC(CH_3){=}CHCH_3$, 86633-14-9; (*Z*)-*n*-$Bu_3SnC(CH_3){=}CHCH_3$, 86633-15-0; (*E*)-*n*-$Bu_3SnCH{=}CHCH_2OSiMe_2Bu\text{-}t$, 86633-16-1; (*Z*)-*n*-$Bu_3SnCH{=}CHCH_2OSiMe_2Bu\text{-}t$, 86646-19-7; $Me_3SnC{\equiv}C\text{-}n\text{-}Pr$, 1118-50-9; $Me_3SnC{\equiv}CPh$, 1199-95-7; $Me_3SnCH_2OCH_3$, 4649-80-3; *n*-$Bu_3SnCH_2OCH_3$, 27490-32-0; Me_3SnCH_2Ph, 4314-94-7; *n*-Bu_3SnCH_2Ph, 28493-54-1; $Me_3SnCH_2CH{=}CHCH_3$, 43133-16-0; $4\text{-}NO_2C_6H_4COMe$, 100-19-6; $4\text{-}BrC_6H_4COMe$, 99-90-1; $Br(CH_2)_5COMe$, 50775-02-5; PhCOBu, 1009-14-9; $4\text{-}NO_2C_6H_4COPh$, 1144-74-7; $Br(CH_2)_5COPh$, 82777-11-5; $Br(CH_2)_{10}COPh$, 87305-70-2; $4\text{-}MeOC_6H_4COPh$, 611-94-9; $3\text{-}CF_3C_6H_4COPh$, 728-81-4; $PhCOCH{=}CH_2$, 768-03-6; $4\text{-}NO_2C_6H_4COCH{=}CH_2$, 22731-72-2; (*E*)-$PhCOCH{=}CHPh$, 614-47-1; (*E*)-$PhCOCH{=}CHCH_3$, 35845-66-0; (*Z*)-$PhCOCH{=}CHCH_3$, 35660-91-4; (*E*)-$PhCOC(CH_3){=}CHCH_3$, 20047-50-1; (*Z*)-$PhCOC(CH_3){=}CHCH_3$, 20047-49-8; (*E*)-$PhCOCH{=}CHCH_2OSiMe_2Bu\text{-}t$, 87305-71-3; (*Z*)-$PhCOCH{=}CHCH_2OSiMe_2Bu\text{-}t$, 87305-78-0; (*E*)-$PhCOCH{=}CHCO_2CH_2Ph$, 87305-72-4; $PhCOC{\equiv}C\text{-}n\text{-}Pr$, 65236-43-3; $PhCOC{\equiv}CPh$, 7338-94-5; $PhCOCH_2OCH_3$, 4079-52-1; $PhCOCH_3$, 98-86-2; $PhCOCH_2Ph$, 451-40-1; *n*-Bu_3SnH, 688-73-3; $PhC{\equiv}CH$, 536-74-3; $BrCH{=}CHCH_3$, 590-14-7; *n*-Bu_3SnCl, 1461-22-9; $CH_3CCl{=}CHCH_3$, 4461-41-0; $HC{\equiv}CCO_2CH_2Ph$, 14447-01-9; $HC{\equiv}CCH_2OSiMe_2Bu\text{-}t$, 76782-82-6; Me_3SnLi, 17946-71-3; CH_3OCH_2Cl, 107-30-2; *n*-Bu_3SnLi, 21308-48-5; $CH_3CHOH(CH_2)_2CO_2K$, 87305-74-6; γ-valerolactone, 108-29-2.

Organic Reactions at High Pressure. A Robinson Annulation Sequence Initiated by Michael Addition of Activated Cycloalkanones with Hindered Enones[1]

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Activated cycloalkanones (ring size = five, six, seven) undergo Michael addition to β,β-disubstituted enones and subsequent aldol cyclization at 15 kbar (1.5 GPa) pressure in acetonitrile containing triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene to afford 50–90% yields of bicyclic ketals. Rearrangement of these aldols under catalytic acid conditions gives >80% yields of the fused Robinson annulation products.

The classical Robinson annulation reaction[3] still remains an important method for fusing a cyclohexenone ring onto a preexisting cyclic ketone and has found extensive use in the synthesis of a variety of natural products.[4] The original procedure involved the sequential Michael addition of a ketone or keto ester enolate to a vinyl ketone, aldol ring closure of the intermediate 1,4-adduct, and dehydration of the resulting ketol (see eq 1). Despite subsequent modifications designed to overcome the limitations of the reaction,[4] a survey of the literature reveals that its applicability is confined to cases where the vinyl ketone possesses no more than one group in the β-position, and, indeed, in this limiting example only a low yield of product is obtained.

Recently, the use of elevated pressures to overcome steric inhibition in cycloaddition reactions has been demonstrated.[6] In light of this success, it was expected that the Robinson annulation of the enolates of doubly activated systems with hindered enones might be similarly accelerated since both the Michael reaction[7,8] and the aldol

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(3) (a) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285–1288. (b) Dufen, E. C.; McQuillin, F. J.; Robinson, R. *Ibid.* **1937**, 53–60.

(4) For two thorough reviews of the Robinson annulation, see (a) Gawley, R. E. *Synthesis* **1976**, 777–794. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31.

(5) To date, only one report of successful (46%) base-catalyzed (2 N KOH in ethanol) Robinson annulation to mesityl oxide has appeared that employed the highly stabilized enolate of 2-hydroxycyclohexanone: Colonge, J.; Brison, P. *Bull. Soc. Chim. Fr.* **1962**, 98–101. This experiment, in our hands, failed to yield the Robinson-annulated product but gave instead a 52% yield of 7-acetyl-8,8-dimethyl-9-oxabicyclo[4.3.0]non-6-ene: bp 95–98 °C (1 mm); IR (thin film) 1650 cm^{-1}; ^1H NMR (90 MHz) δ 4.57 (dd, *J* = 7, 11 Hz, 1), 3.16 (m, 1), 2.33 (s, 3), 2.32–1.29 (complex, 7), 1.41 (s, 3), 1.34 (s, 3); UV (EtOH) 255 nm (ε 7040), 219 (5070); MS, *m/e* 194 (parent). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 73.98; H, 9.21.

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(8) Several reports have appeared that demonstrate the use of elevated pressures in promoting Michael condensations; see the following: Matsumoto, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1013–1014. (b) Matsumoto, K. *Ibid.* **1981**, *20*, 770–771. (c) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673–1676. (d) Dauben, W. G.; Gerdes, J. M. *Tetrahedron Lett.* **1983**, 3841–3844.

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