REVIEWS

The Robinson Annelation and Related Reactions

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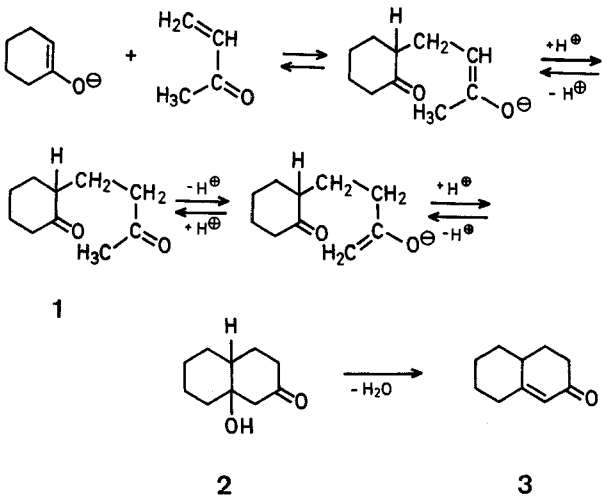
Annelation reactions related to the Robinson reaction are reviewed with an emphasis being placed on the regiochemistry and stereochemistry obtained in the annelation sequence. Annelations employing ring formation by a "3'-oxobutyl" side chain, or its functional equivalent are covered, and examples of experimental procedures have been selected to provide guidelines for application of a given sequence to other molecules.

Es wird eine Übersicht über die Robinson-Annelierung und verwandte Reaktionen unter Verwendung der 3-Oxobutyl- oder äquivalenter Gruppen gegeben. Regioselektivität und Stereochemie der Reaktionsfolgen werden besonders berücksichtigt. Es wurden solche Arbeitsvorschriften ausgewählt, die sich auch auf andere Verbindungen übertragen lassen sollten.

1. Introduction*

The Robinson annelation, since its introduction forty years ago[1,2], with its subsequent modifications, has been one of the most widely used synthetic tools in organic chemistry[3–10]. The original procedure involved nucleophilic attack of a ketone or ketoester enolate, in a Michael reaction[9,10], on a vinyl ketone to produce the intermediate "3'-oxobutyl" Michael adduct **1**. Subsequent aldol-type ring closure to keto alcohol **2**, followed by dehydration, produces the annelation product: an octalone such as **3** (see Table 1).



1

2 **3**

While the process is of great value, it is nevertheless subject to some restrictions:

(a) Methyl vinyl ketone (the most commonly used Michael acceptor) tends to polymerize;

(b) Alkylation usually occurs at the more highly substituted α-carbon;

(c) Dialkylation occurs readily.

It is, no doubt, at least partially as a result of these restrictions that the aforementioned "modifications" have been evolved, so that these restrictions might be overcome. Virtually all of the modifications involve the preparation of the initial Michael adduct, **1**, or its functionalized equivalent, by some means

* Since the acceptance of this manuscript, another review has appeared: M. E. Jung, *Tetrahedron* **32**, 3 (1976).

[1] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285.
[2] E. C. DuFeu, F. J. McQuillin, R. Robinson, *J. Chem. Soc.* **1937**, 53.
[3] G. Stork, *Pure Appl. Chem.* **9**, 131 (1964).
[4] L. Velluz, J. Valls, G. Nominé, *Angew. Chem.* **77**, 185 (1965); *Angew. Chem. Int. Ed. Engl.* **4**, 181 (1965).
[5] I. V. Torgov, *Pure. Appl. Chem.* **6**, 525 (1963).
[6] B. P. Mundy, *J. Chem. Ed.* **50**, 110 (1973).
[7] E. Wenkert, et. al., *J. Am. Chem. Soc.* **86**, 2038 (1964).
[8] S. Danishefsky, P. Cain, A. Nagel, *J. Am. Chem. Soc.* **97**, 380 (1975).
[9] H. O. House, *Modern Synthetic Reactions*, 2nd Edit, W. A. Benjamin Inc., Menlo Park, Calif., 1972.
[10] E. D. Bergmann, D. Ginsburg, R. Pappo, *Org. React.* **10**, 179 (1959).

which maximizes yield, minimizes side reactions, or which can be accomplished under relatively mild conditions. These various methods may be classified in two categories: (a) those involving reaction of a Michael acceptor[10] with the nucleophile, and (b) those involving reaction of the nucleophile with an alkyl halide. Either type of reagent could either contain a carbonyl group or some latent carbonyl function[11,12]. In the latter case, the carbonyl moiety would be unmasked after attachment to the ketone substrate. Another possibility is that of creating the side-chain ketone carbonyl group via addition of one or more carbon atoms to an existing side chain to produce the 3′-oxobutyl side chain needed for annelation. However, this discussion will be limited to only those methods which involve simultaneous introduction of all of the 3′-oxobutyl side chain carbon atoms.

The experimental procedures included here have been selected not only to illustrate various annelation sequences, but also to provide details of, for example, several methods of enolate generation (i.e., generation with alkoxide, regiospecific generation via enol ethers and enol esters, etc.), and several methods of cyclization. Thus a fair amount of flexibility is available allowing the adoption of an annelation sequence to many different circumstances. As is noted for each individual procedure (footnote 26), all experimental procedures included in this review should be carried out under an inert atmosphere.

2. The Robinson Annelation

Robinson originally demonstrated the utility of this procedure using an assortment of substituted vinyl ketones (c.f., Table 1, entries 1–6)[1,2], but had little success in obtaining annelation products when employing the parent compound, methyl vinyl ketone, as the electrophilic reactant[2]. Instead, it was found by both Robinson and others that success could be achieved via the use of a quaternized Mannich base[13] to generate the reagent *in situ* (see Table 1)[2,14,15]. Subsequently, 1,4-dimethoxy-2-butanone was employed as an *in situ* methoxymethyl vinyl ketone precursor[16].

Table 1. The Robinson Annelation

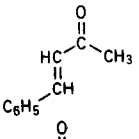
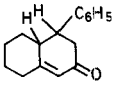
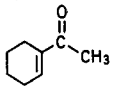
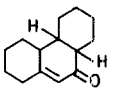
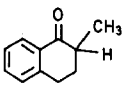
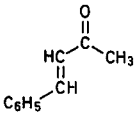
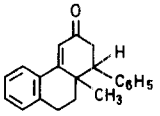
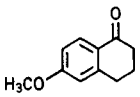
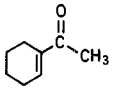
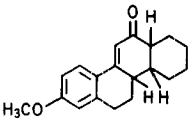
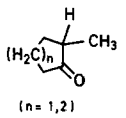
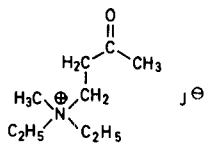
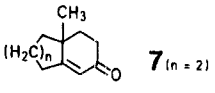
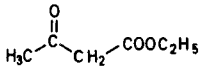
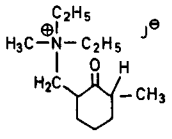
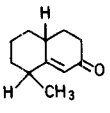
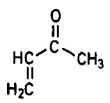
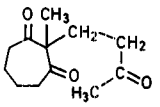
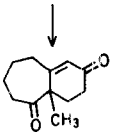
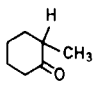
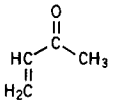
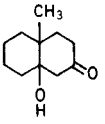
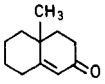
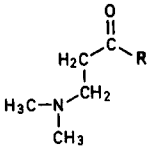
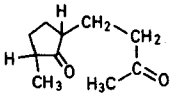
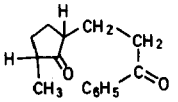
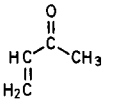
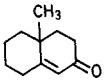
Entry	Nucleophile	Electrophile	Product	Yield (%)	Reference
1				43	1
2				34	1
3				46	1
4				42	1
5	 (n = 1,2)		 **7** (n = 2)	25–40	2
6				60	2
7				44–48	18
				45	18

Table 1. Continued

Entry	Nucleophile	Electrophile	Product	Yield (%)	Reference
8				52	17
			 **7**	85	17
9		 (R = CH_3, C_6H_5)	 or 	40 76	19 31
10		 	 **7**	49	20

Quite often, yields of the desired annelation product (e.g. **3**), when isolated directly, have been quite low[17]. This may be due not only to the possibility of dialkylation of the starting ketone, but also the reactivity of the octalone product **3**. For example, the γ-protons of an α,β-unsaturated ketone are often more acidic than the α-protons of the starting ketone[9]. Thus when the intermediate keto alcohol **2** dehydrates to octalone **3**, an acid-base reaction can take place between the original enolate and the octalone product to produce the enolate anion of **3**, which can itself undergo annelation. As a result of this complication, it has been found that yields are considerably improved when either the initial Michael adduct, **1**, or the keto alcohol **2** is first isolated, and then cyclized and/or dehydrated to give the desired octalone **3** in a separate step using less stringent conditions.

One such method has employed very mild conditions for the Michael addition of a relatively acidic nucleophile (e.g., a 1,3-diketone, a formyl ketone, or a β-keto ester) to produce the initial adduct, followed by cyclization and dehydration[18,21–24] using amine salts under conditions very similar to those generally used in Knoevenagel condensations[25] (see Table 1, entry 7).

2-Methyl-2-(3′-oxobutyl)-cycloheptane-1,3-dione[18,26]:
A mixture of 2-methylcycloheptane-1,3-dione (18 g, 0.13 mol), anhydrous methanol (100 ml), 85% methyl vinyl ketone (9 g, 0.13 mol), and potassium hydroxide (2 pellets) is stirred for 1 h at 50–60° and then for 3 h at reflux temperature. The mixture is freed of solvent in vacuo and the residual liquid extracted with chloroform. After washing with a small amount of water, the organic layer is dried and removed. Fractional distillation of the residual liquid gives 4.5 g of starting dione (b.p. 96–156°/5 torr) and 15–16 g (b.p. 150–160°/4.5 torr) of a main fraction which is redistilled to afford pure product; yield: 12–13 g (44–48%); b.p. 134–136°/1.5 torr.

Δ^7-1-Methylbicyclo[5,4,0]undecene-2,9-dione[18,26]:
To a stirred solution of 2-methyl-2-(3′-oxobutyl)-cycloheptane-1,3-dione (6.3 g, 0.03 mol) in dry ether (100 ml) cooled to 0°, pyrrolidine (2.4 ml, 0.03 mol) is added dropwise followed by acetic acid (1.8 ml,

[11] J. F. W. McOmie, Ed., *Protective Groups in Organic Chemistry*, Plenum Press, London, 1973.
[12] I. T. Harrison, S. Harrison, *Compendium of Organic Synthetic Methods*, Wiley-Interscience, New York, Vol. 1, 1971, Vol. 2, 1974.
[13] M. Tramontini, *Synthesis* **1973**, 703.
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[15] F. J. McQuillin, R. Robinson, *J. Chem. Soc.* **1938**, 1097.
[16] E. Wenkert, D. A. Berges, *J. Am. Chem. Soc.* **89**, 2507 (1967).
[17] J. A. Marshall, W. I. Fanta, *J. Org. Chem.* **29**, 2501 (1964).
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[19] E. M. Austin, H. L. Brown, G. L. Buchanan, R. A. Raphael, Jr., *Tetrahedron* **25**, 5517 (1969).
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[23] T. A. Spencer, H. S. Neel, D. C. Ward, K. L. Williamson, *J. Org. Chem.* **31**, 434 (1966).
[24] T. A. Spencer, H. S. Neel, T. W. Fletchner, R. A. Zayle, *Tetrahedron Lett.* **1965**, 3889.
[25] G. Jones, *Org. React.* **15**, 204 (1967).
[26] All procedures in this review should be carried out under an inert atmosphere such as argon or nitrogen.

0.03 mol). The reaction mixture is stirred at 0° for 2 h and then at room temperature for 3 h. The solvent is removed, the residual brown liquid taken up in ether (20 ml) and transferred to a column of alumina. Elution initially with a mixture of benzene and petroleum ether (40–60°) and then with benzene furnishes crystalline material; yield: 2.6 g (45%); m.p. 71–72°.

Probably the most generally useful procedure for monoketones was developed by Marshall and Fanta[17], and involves Michael addition of the ketone enolate to the vinyl ketone followed by cyclization to the keto alcohol in a single step[27]. The intermediate keto alcohol is then isolated and dehydrated with acid or base to produce the desired product (see Table 1, entry 8).

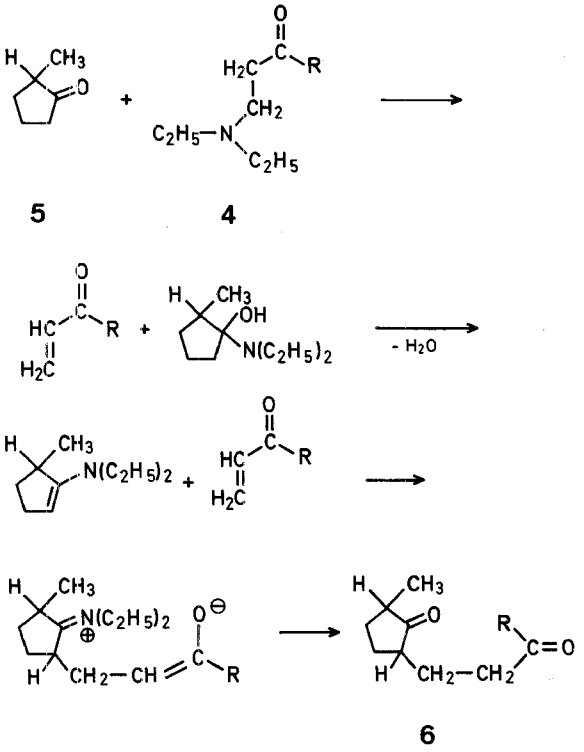
***cis*-9-Hydroxy-10-methyl-2-decalone**[17,26]:
A solution of 3 *N* ethalonic sodium ethoxide (3 ml) in 2-methylcyclohexanone (56 g) maintained at −10° is efficiently stirred and methyl vinyl ketone (35 g) is added over a 6 h interval. As the addition is completed, the reaction mixture becomes very thick (almost solid) and stirring is continued with difficulty. The reaction mixture is allowed to stand at −10° for an additional 6 h and the cold mass is transferred with ether and sodium chloride solution to a separatory funnel and thoroughly extracted with ether. The combined extracts are washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to a volume of 0.7 l. This volume is maintained by adding hexane as the ether is removed by evaporation on a steam bath until crystallization commences. The first crop affords white needles; yield: 35 g (39%); m.p. 120–121°. A second crop is also obtained; yield: 13 g (15%); m.p. 104–112°.

10-Methyl-2-oxo-$\Delta^{1(9)}$-octalin (7)[17,26]:
A sample of the ketol (7.50 g) is distilled with steam from 100 ml of 10% aqueous potassium hydroxide. The distillate (1 l) is saturated with sodium chloride and thoroughly extracted with ether. The extracts are dried over sodium sulfate and distilled affording the colorless octalone; yield: 5.83 g (86%); b.p. 82–83°/0.7 torr. Comparable yields are obtained when 100 ml of 10% aqueous oxalic acid is used in the dehydration either with or without steam distillation of the product.

More recently, it has been found that high yields of the octalone product may be obtained under conditions of mild acid catalysis (see Table 1, entry 10)[20]. In fact, there has been at least one case reported in which acid catalysis was successful where basic catalysis was not[28].

10-Methyl-2-oxo-$\Delta^{1(9)}$-octalin (7)[20,26]:
A mixture of 2-methylcyclohexanone (45 g, 0.4 mol), methyl vinyl ketone (36 g, 0.5 mol), and conc. sulfuric acid (0.3 ml) in benzene (100 ml) is refluxed for 16 h. The solution is cooled and diluted with hexane (100 ml). After washing with 5% aqueous potassium hydroxide (100 ml), the solution is dried, then concentrated on a rotary evaporator. Distillation of the residue affords the octalone; yield: 32.8 g (49%); b.p. 112–115°/5 torr.

Finally, it has been discovered that the Michael reaction can be induced to proceed under neutral conditions (see Table 1, entry 9)[19,29–31]. This procedure, dubbed the "thermal-Michael" reaction has been shown to proceed via an enamine[19]. A Mannich base[13] (**4**) is heated in the presence of a ketone, such as 2-methylcyclopentanone (**5**) to produce the Michael adduct **6**, in good yield, by the mechanism shown below. Further discussion of enamine alkylations will be deferred until later.



2-Methyl-5-(3′-oxobutyl)-cyclopentanone (6)[31,26]:
A stirred solution of diethylamino-2-butanone (8.58 g) in 2-methylcyclopentanone (17.3 g) is refluxed at 140° for 1.25 h, cooled, neutralized with acetic acid, and diluted with ether. The ethereal solution is washed with brine and dried (magnesium sulfate), then concentrated and distilled to provide a colorless oil; yield: 4.01 g (40%); b.p. 122–126°/10 torr.

3. Regiochemistry of Addition to Unsymmetrical Ketones

In a very simple case of an unsymmetrical ketone, 2-methylcyclohexanone, alkylation under either acid or base catalysis usually occurs regioselectively at the more highly substituted position to provide the octalone having an angular methyl group, as in **7**, below[2,17,20]. Exceptions to this generality can usually be rationalized as a result of severe steric interference at the more highly substituted α-carbon atom, as illustrated in the accompanying example[32].

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[28] J. E. McMurry, L. C. Blaszczak, *J. Org. Chem.* **39**, 2217 (1974).
[29] G. L. Buchanan, A. C. W. Curran, R. T. Wall, *Tetrahedron* **25**, 5503 (1969).
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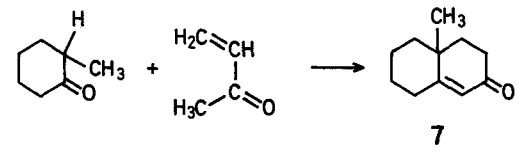
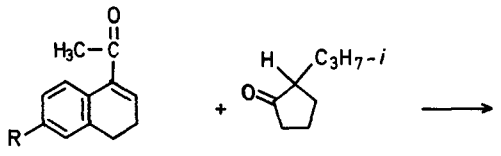
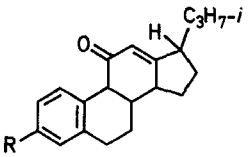
[31] H. L. Brown, G. L. Buchanan, A. C. W. Curran, G. W. McLay, *Tetrahedron* **24**, 4565 (1968).
[32] A. J. Birch, R. Robinson, *J. Chem. Soc.* **1944**, 503.
[33] R. A. Kretchmer, E. D. Mihelich, J. J. Waldron, *J. Org. Chem.* **37**, 4483 (1972).
[34] R. M. Coates, R. L. Sowerby, *J. Am. Chem. Soc.* **93**, 1027 (1971).
[35] G. Stork, *Pure Appl. Chem.* **17**, 383 (1968).
[36] H. O. House, M. Gall, H. D. Olmstead, *J. Org. Chem.* **36**, 2361 (1971).



7

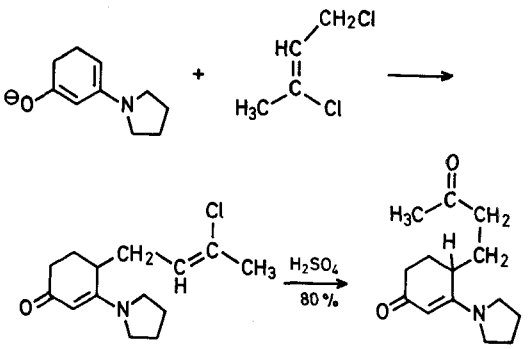




One way to insure regiospecificity in an alkylation sequence is to generate regiospecific enolates by, for example, conjugate reduction of an α,β-unsaturated system or by cleavage of a specific enol ether or ester under non-equilibrating conditions. These procedures have been adequately discussed elsewhere[9,33-37], and so will not be dealt with at length here. One point must be emphasized, however, and that is that by whatever means a regiochemically specific enolate is generated, (unless it happens to be the only isomer present in significant amounts at equilibrium) subsequent reactions (e.g. alkylation with an alkyl halide or a Michael acceptor) must be carried out under non-equilibrating conditions. In other words, aprotic conditions should be maintained; furthermore, the presence of a carbon acid (such as a ketone) can cause equilibration of the enolate and concomitant lowering of yield if the rate of proton transfer is comparable to, or faster than, the rate of alkylation.

Many polycyclic ring systems such as decalones and ketosteroids undergo regiospecific or regioselective alkylations which may or may not be analogous to those of a substituted monocyclic ketone. These regiochemical tendencies have been adequately covered elsewhere[9,38,39].

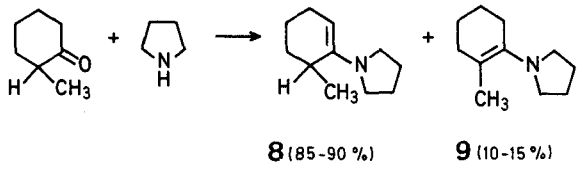
Quite recently, it has been observed that γ-alkylation can be achieved for enamino ketones, as shown below[40,41]. This is in contrast to the normal tendency of α,β-unsaturated system to undergo α- and/or α'-alkylation[9,42]. Furthermore, cleavage of the vinyl chloride group with sulfuric acid (*The Wichterle Reaction*, see Section 6.1.) did not cleave the enamine group or cause unwanted byproducts[40].



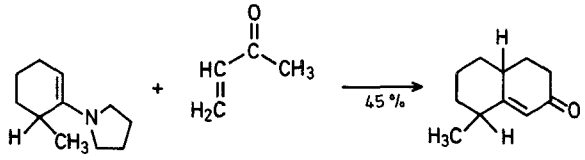
Other methods for controlling regiochemistry in the alkylation are via the use of enamines, activating or directing groups, and blocking groups, each of which is discussed briefly below.

3.1. Annelations with Enamines

The utilization of enamines in annelation sequences has been thoroughly discussed elsewhere[9,43-49]. It should be emphasized, however, that the regiochemistry *opposite* to that observed under standard Robinson conditions *(vide supra)* is obtainable via enamines[47]. The procedure takes advantage of the preferential formation of enamine **8** over **9**; this preference is the result of steric repulsion between the pyrrolidine and vinyl methyl portions of **9**[45]. Alkylation of enamine **8** with methyl vinyl ketone occurs smoothly to form 8-methyl-2-oxo-$\Delta^{1,9}$-octalin, as shown below[47]. Note that the analogous regiochemical preference observed in the "Thermal-Michael" reaction of 2-methylcyclohexanone mentioned above, is due to a similar preference for the formation of the less highly substituted enamine[19].



8 (85-90 %) **9** (10-15 %)



8

8-Methyl-2-oxo-$\Delta^{1(9)}$-octalin[47,26]:
To a solution of the pyrrolidine enamine of 2-methylcyclohexanone (8 g, 0.0485 mol) in benzene (200 ml) is added methyl vinyl ketone (4 g, 0.057 mol). The mixture is then refluxed for 24 h. A buffer

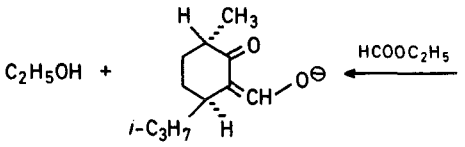
[37] G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **90**, 4462, 4464 (1968).
[38] J.-M. Conia, *Rec. Chem. Prog.* **24**, 43 (1963).
[39] H. O. House, *Rec. Chem. Prog.* **28**, 99 (1967).
[40] T. A. Bryson, R. B. Gammill, *Tetrahedron Lett.* **1974**, 3963.
[41] M. Yoshimoto, N. Ishida, T. Hiraoka, *Tetrahedron Lett.* **1973**, 39.
[42] G. Stork, R. Danheiser, *J. Org. Chem.* **38**, 1775 (1973).
[43] M. E. Kuehne, *Synthesis* **1970**, 510.
[44] J. Smuszkovicz, *Adv. Org. Chem.* **4**, 1 (1963).
[45] A. G. Cook, Ed., *Enamines: Synthesis, Structure, and Reactions*, Marcel Dekker, New York, 1969.
[46] K. Blaha, O. Cervinka, *Adv. Heterocycl. Chem.* **6**, 147 (1966).
[47] G. Stork, et al., *J. Am. Chem. Soc.* **85**, 207 (1963).
[48] G. Stork, M. E. Jung, *J. Am. Chem. Soc.* **96**, 3682 (1974).
[49] G. Stork, S. Danishefsky, M. Ohashi, *J. Am. Chem. Soc.* **89**, 5459 (1967).

solution made up of acetic acid (25 ml), water (25 ml), and sodium acetate (12.5 g) is then added and refluxing is continued for 4 h. Separation of the layers, extraction of the aqueous layer with benzene, and washing the combined extracts with 10% hydrochloric acid and then aqueous sodium hydrogen carbonate gives, after removal of the benzene at atmospheric pressure and distillation, the product; yield: 3.58 g (45%); b.p. 102–104°/2 torr.

Several of the more recently developed annelation procedures utilizing alkyl halides as alkylating agents have been shown to proceed with enamines as well as enolates, and will be mentioned in turn *(vide infra)*.

3.2. Annelations Using Activating or Directing Groups

It was previously mentioned that alkylation of 1,3-diketones with a Michael acceptor can be accomplished under very mild conditions, such that the 3′-oxobutyl Michael adduct intermediate can be isolated. A similar situation can be realized with monoketones by first condensing them with an activating group to form a β-dicarbonyl compound, followed by condensation with an appropriate alkylating agent

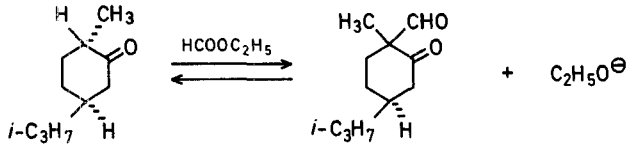


10

under mild conditions (see Table 2). Most common among these activating groups are the ethoxycarbonyl group[50–52] and the hydroxymethylene (formyl) group[53,54]. The former can be obtained by condensation of the ketone with diethyl carbonate while the latter can be obtained by condensation of the ketone with ethyl formate[55,57].

The hydroxymethylene group is also commonly used as a directing group to promote preferential alkylation at the less substituted position, as shown in Table 2, entry 4, which is taken from Corey and Nozoe's synthesis of helminthosporal[54]. On the one hand, acylation at C-6 of carvomenthone produces a β-keto aldehyde which under the reaction conditions loses a proton to form its enolate salt **10**. Reversion to starting material does not occur in this isomer. On the other hand, acylation at C-2 results in compound **11**, where enolization is not possible, and which will therefore, under the reaction conditions, revert to starting material. The net result, then, is formation of **10**.

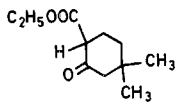
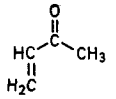
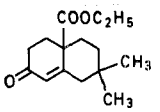
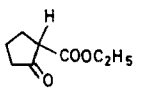
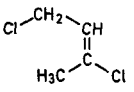
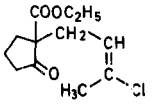
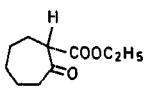
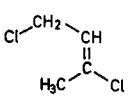
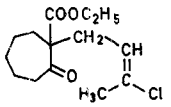
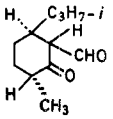
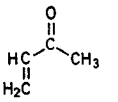
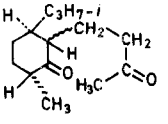
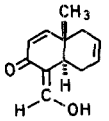
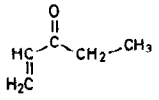
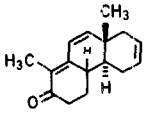
As shown in Table 2, entry 4, alkylation of **10** with methyl vinyl ketone followed by alkaline cleavage of the formyl group, produces the Michael adduct resulting from alkylation at the less substituted position.



carvomenthone **11**

2-Hydroxymethylene-7-methoxy-1-oxo-tetralin[57,26]:
Ethyl formate (12.0 ml, 0.148 mol) is added with stirring to a suspension of alcohol-free sodium methoxide (4.92 g, 0.0912 mol) in anhydrous benzene (50 ml). After 30 min at room temperature, the mixture is cooled in an ice bath. A solution of 7-methoxy-1-oxo-tetralin (5.0 g, 0.0284 mol) in dry benzene (75 ml) is then added

Table 2. Annelations using Activating or Directing Groups

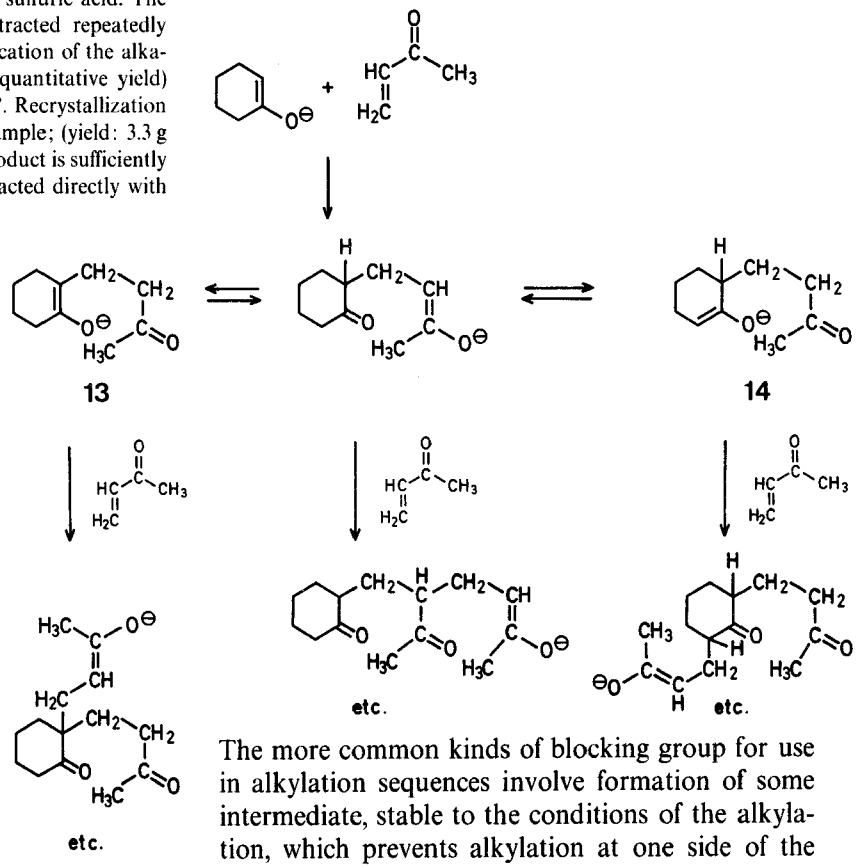
Entry	Nucleophile	Electrophile	Product	Yield (%)	Reference
1				55	51
2				68	50
3				48	52
4				49	54
5				50	53

dropwise over a period of 1 h, and the reaction mixture is stirred at room temperature for an additional hour, during which time the sodium salt of the product precipitates. The reaction mixture is finally cooled and acidified with cold, dilute sulfuric acid. The benzene layer is washed with water, and extracted repeatedly with 2 *N* potassium carbonate solution. Acidification of the alkaline extracts and ether extraction gives 5.8 g (quantitative yield) of a crude oil that crystallizes on standing at 0°. Recrystallization of this material from ether furnishes a pure sample; (yield: 3.3 g (57%); m.p. 33–34°). However the total crude product is sufficiently pure for further operations, and is normally reacted directly with methyl vinyl ketone without recrystallization.

6-Methoxy-3-oxo-1,2,3,9,10,10a-hexahydrophenanthrene[57, 26]: A mixture of the crude hydroxymethylenetetralone (4.9 g, 0.024 mol) and methyl vinyl ketone (2.58 g, 0.0369 mol) is cooled to 0° and treated with 5 drops of triethylamine. The reaction mixture is cooled in ice for 1 h and then allowed to stand at room temperature for 3 days. At the end of this time, the mixture is taken up in ether, washed repeatedly with sodium carbonate, and evaporated to dryness. A solution of the crude oily product (6.5 g) in methanol (200 ml) and water (200 ml) containing potassium hydroxide (4 g) is refluxed under nitrogen for 8 h, cooled, diluted with water, and extracted with ether. Removal of the solvent, followed by crystallization from di-*n*-butyl ether, or from methanol, gives the product; yield: 4.9 g (89%); m.p. 111–112°.

3.2. Annelations Using Blocking Groups

Blocking groups may be employed in any alkylation sequence to prevent dialkylation and/or to effect regiochemical specificity. As previously mentioned, a complication of the Robinson annelation is the possibility of di- or polyalkylation. This is a result of the similar acidities of the starting ketone, the initial Michael adducts, etc., as shown by the series of equations below. Before or after tautomerization of an initial Michael adduct (i.e.: to **13** or **14**), alkylation with a second molecule of methyl vinyl ketone could occur to form any of a number of di- or polyalkylated products. Woodward, et al.[53], have demonstrated the use of the hydroxymethylene group as not only an activating group but also as a blocking group to minimize dialkylation, as shown in Table 2, entry 5. The angular formyl group is easily cleaved by base (*vide supra*) after completion of the Michael reaction. This series of reactions was used in Woodward's classic synthesis of cholesterol[53].

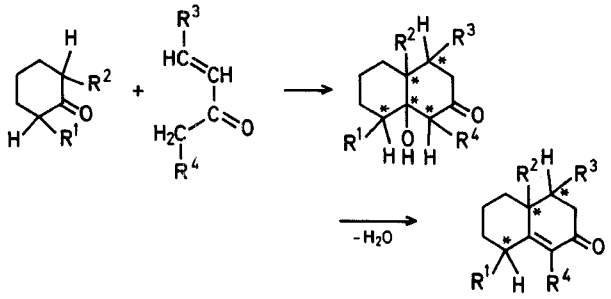


The more common kinds of blocking group for use in alkylation sequences involve formation of some intermediate, stable to the conditions of the alkylation, which prevents alkylation at one side of the carbonyl group, and which is also easily removable, or which may be converted into some other desired functionality. Such blocking groups include thioacetals[58, 59] and benzylidene groups[60], along with several protecting groups which are formed by condensation of an appropriate nucleophile with a hydroxymethylene (formyl) ketone. The latter include the isopropoxymethylene[61], *N*-methylanilinomethylene[62, 63], piperonylidinomethylene[64], and *n*-butylthiomethylene[65] groups. Of these, the latter is probably the most versatile and the one most often employed.

[50] V. Prelog, M. Zimmermann, *Helv. Chim. Acta* **32**, 2360 (1949).
[51] J. D. Metzger, M. W. Baker, R. J. Morris, *J. Org. Chem.* **37**, 789 (1972).
[52] R. D. Sands, *J. Org. Chem.* **28**, 1710 (1963).
[53] R. B. Woodward, et al., *J. Am. Chem. Soc.* **74**, 4223 (1952).
[54] E. J. Corey, S. Nozoe, *J. Am. Chem. Soc.* **85**, 3527 (1963).
[55] A. P. Krapcho, J. Diamanti, C. Cayen, R. Bingham, *Org. Synth.* **47**, 20 (1967).
[56] S. Boatman, T. M. Harris, C. R. Hauser, *Org. Synth.* **48**, 40 (1968).
[57] R. B. Turner, D. E. Nettleton, Jr., R. Ferebee, *J. Am. Chem. Soc.* **78**, 5923 (1956).
[58] R. B. Woodward, et al., *J. Chem. Soc.* **1957**, 1131.
[59] B. Gaspert, T. G. Halsall, and D. Willis, *J. Chem. Soc.* **1958**, 624.
[60] W. S. Johnson, *J. Am. Chem. Soc.* **65**, 1317 (1943).
[61] W. S. Johnson, H. Posvic, *J. Am. Chem. Soc.* **69**, 1361 (1947).
[62] A. J. Birch, R. Robinson, *J. Chem. Soc.* **1944**, 501.
[63] D. J. France, J. J. Hand, M. Los, *Tetrahedron* **25**, 4011 (1969); *J. Org. Chem.* **35**, 468 (1970).
[64] A. J. Birch, *J. Chem. Soc.* **1943**, 661.
[65] R. E. Ireland, J. A. Marshall, *J. Org. Chem.* **27**, 1615 (1962).

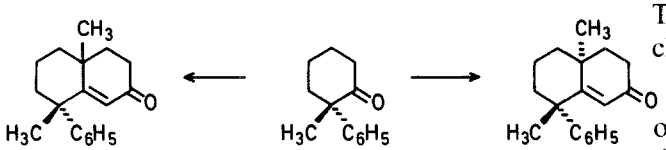
4. Stereochemistry

It is possible in an annelation sequence to generate no less than five chiral centers in a keto alcohol, but the multiplicity is usually reduced to three or less (if R^1, R^2, or $R^3 = H$) upon dehydration, as shown below. The stereochemical outcome of the creation of these chiral centers in the annelation product can and will either make or break a successful synthetic route.



Since the carbon atom to which R^1 is attached in the octalone is epimerizable under the conditions of cyclization and/or dehydration, it is sufficient to point out that it will usually assume the equatorial configuration[9,66,67]. The chirality of the carbon to which R^2 is attached is created in the initial alkylation step, has been the subject of the most study, and has been thoroughly discussed elsewhere[4,68-71].

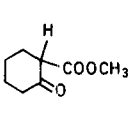
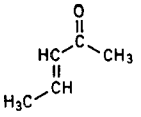
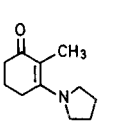
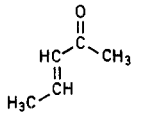
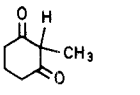
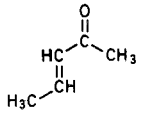
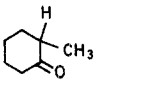
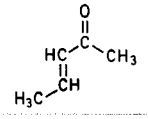
A particularly informative and illustrative example of stereochemical control in a dialkylation sequence involving an annelation has been provided by Ireland and Kierstead[72], in which the stereoselective conversion of 2-methyl-2-phenylcyclohexanone to either octalone **15** or **16** could be accomplished by reversing the order of the alkylation sequence.



15 **16**

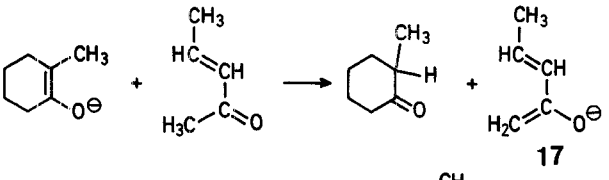
The stereochemistry at the carbon to which R^3 is attached is also determined during the initial alkylation. Instances in which $R^3 \neq H$ have only occurred in sequences involving vinyl ketones as the electrophilic component, and in the cases in which the stereochemistry at this center have been studied, R^2 has been a methyl group[73-77]. Table 3 summarizes these studies. As can be seen, varying the reaction conditions can produce drastic changes in the ratio of *cis* and *trans* substituted products.

Table 3. Stereochemistry at C-4 of the Octalone Annelation Product

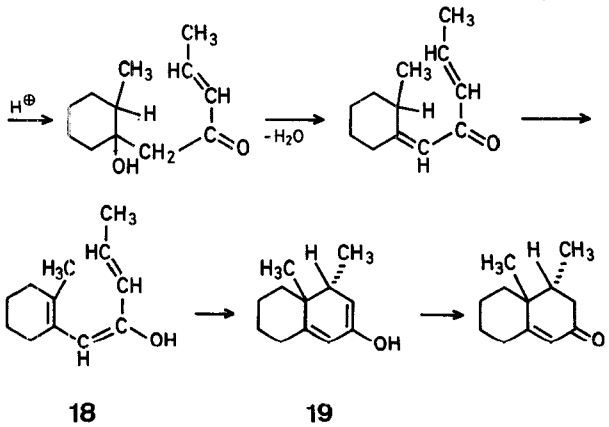
Entry	Nucleophile	Electrophile	*cis*:*trans* ratio	Reference
1			0.52–3.08	77
2			1-all *trans*	74
3			0.17	75
4			>19:1[a] <1:19[b]	76

[a] Solvent dioxan.
[b] Solvent dimethyl sulfoxide.

The most striking example of stereochemical control has been provided by Scanio and Starrett[76] (Table 3, entry 4); alkylation of the sodium enolate of 2-methylcyclohexanone with methyl propenyl ketone in dioxan solvent produced the *cis*-dimethyloctalone in >95% isomeric purity, while changing the solvent to dimethyl sulfoxide produced the epimeric *trans*-dimethyloctalone again in >95% isomeric purity! To account for this observation, these authors have proposed a new mechanism for the annelation when carried out in dimethyl sulfoxide, as shown below. The mechanism shown involves a disrotatory ring closure (i.e., **18**→**19**) similar to one which was observed by Ramage and Sattar[78] (**20**→**21**) to produce a similar *trans*-dimethyl arrangement.



17



18 **19**

[66] D. Caine, F. N. Tuller, *J. Org. Chem.* **34**, 222 (1969).
[67] E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962.
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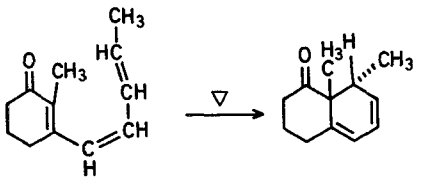


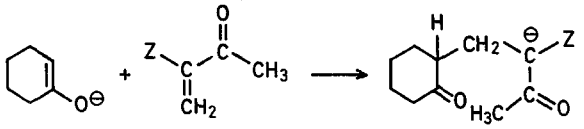
20 **21**

If this mechanism is in fact operable, it seems likely that it would not be applicable to more acidic nucleophiles, such as formyl ketones or β-keto esters. These reagents would be more likely to undergo a Michael reaction considerably faster than the type of acid-base reaction outlined above for the formation of the crossed enolate **17**.

Finally, it should be mentioned that the stereochemistry of the ring fusion of the ketoalcohol (when isolated) seems to be dependent upon the nature of R^2. In cases where the angular substituent (R^2) is methyl[17] or acetoxy[21], the ring fusion is *cis*; whereas if $R^2=H$, the ring fusion is *trans*[17]. When the keto alcohol is isolated, and R^4 is methyl, it may be either *cis* or *trans* to the bridgehead hydroxy group.

5. Annelations using Stabilized Electrophiles as Michael Acceptors

Stork and Ganem[79] have pointed out that the problems outlined above regarding di- and polyalkylation in a Robinson annelation sequence using a simple vinyl ketone might be minimized or even eliminated by utilizing an α-substituted vinyl ketone (i.e., **22**) in which the substituent is able to stabilize the initial Michael adduct (**23**). Thus tautomerizations of the initial adduct would be energetically unfavorable, and di- and polyalkylation could be minimized.



22 **23**

A requirement of this modification of the standard Robinson procedure is that the substituent should be easily removable. Perhaps the simplest of the possibilities for fulfilling these requirements is a methyleneacetoacetic acid derivative, **22**, Z=COOR. These compounds are well known to undergo Michael addition with ketone enolates[10], and were first applied in an annelation sequence by Peak and Robinson[80], then later by Wieland and Miescher[81]. Some of the results of these studies are listed in Table 4 (entries 1–6). Yields for this procedure were generally low[80,81], however it is not clear whether the low yields come as a result of deficiencies inherent in the reagents, or whether they simply are yields typically obtained in annelation reactions using experimental procedures commonly in use at that time.

Stork and Ganem[79] have very recently introduced another reagent of the type **22**, $Z=Si(C_2H_5)_3$, and have demonstrated its usefulness in annelations (see Table 4, entries 6–8). In the hope of carrying out the Michael reaction under non-equilibrating conditions, these authors have shown that α-silylvinyl ketones undergo Michael addition under *aprotic* conditions, (under which methyl vinyl ketone polymerizes most readily). The initial report indicated that equilibration of a regiochemically unstable enolate occurred faster than Michael addition, but subsequent reports[82,83] indicate that equilibration can be minimized by rigorous exclusion of moisture, or by changing solvent.

It should be noted that it is not necessarily a difference in basicities which accounts for the difference in behavior of α-silylvinyl ketones and simple unsubstituted ketones, as has been postulated[79]. Such a postulate rests on the assumption that a ketone enolate such as **23**, $Z=Si(C_2H_5)_3$, is less basic (i.e. the conjugate acid is more acidic) than a simple ketone. An alternative postulate could be that polymerization and di- or polyalkylation are retarded simply as a result of steric hindrance.

2-Triethylsilyl-1-buten-3-ol[85,26]:
To clean magnesium shavings (1.5 g) covered with dry tetrahydrofuran (10 ml, distilled from lithium aluminum hydride) is added enough dibromoethane (0.2–0.4 ml) to start the solvent refluxing. While boiling, the contents of the flask are treated with a solution of α-bromovinyltriethylsilane[79] (5 g, 22.6 mmol) in tetrahydrofuran (5 ml) at a rate sufficient to maintain reflux. When addition is complete, the brown-colored solution is heated externally for 15 minutes then quenched *at reflux* with freshly distilled acetaldehyde [1.5 g in tetrahydrofuran (5 ml)]. After cooling, the pot is acidified with 1 *N* hydrochloric acid (25 ml) and extracted twice with ether. The combined extracts (100 ml) are washed 3 times with water, once with saturated salt solution, dried (potassium carbonate) and concentrated to give a yellow oil; yield: 3.3 g (80%).

2-Triethylsilyl-1-buten-3-one (22, $Z=Si[C_2H_5]_3$)[85,26]:
The allylic alcohol (3.3 g, 17.8 mmol) is dissolved in acetone (60 ml), cooled in ice, and treated dropwise with a standard solution of Jones reagent (4.5 ml) until the reddish chromic acid color persists. This excess reagent is destroyed with a little isopropanol. Water (100 ml) and ether (200 ml) are added and the contents of the flask stirred until all the chromium salts have dissolved. The aqueous layer is then decanted and extracted again with fresh ether. The combined organic extracts (350 ml) are washed twice with water, once with ice-cold 0.05 *N* sodium hydroxide solution, once with saturated salt solution, and dried (potassium carbonate). Filtration, evaporation of the ether, and distillation affords a colorless liquid; yield: 2.8 g (85%); b.p. 83°/7 torr.

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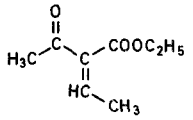
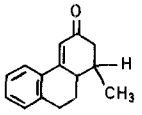
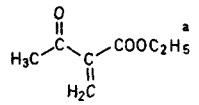
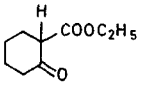
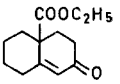
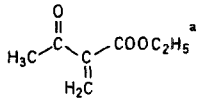
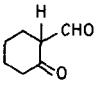
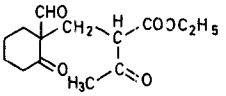
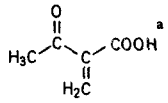
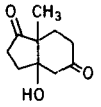
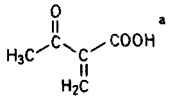
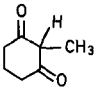
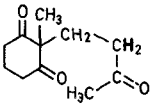
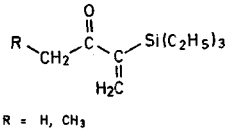
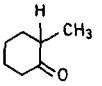
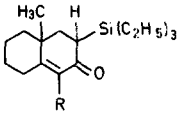
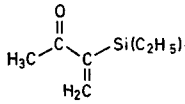
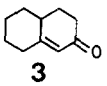
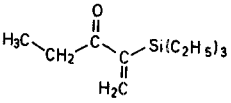
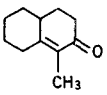
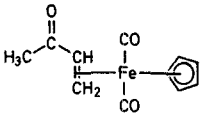
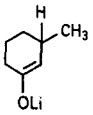
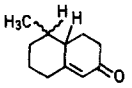
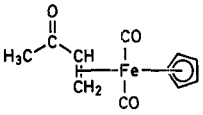
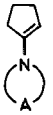
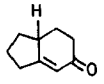
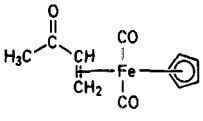
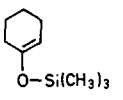
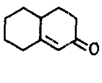
[79] G. Stork, B. Ganem, *J. Am. Chem. Soc.* **95**, 6152 (1973).

Table 4. Annelations using Stabilized Electrophiles

Entry	Electrophile	Nucleophile	Product	Yield (%)	Reference
1				36	80
2				–	81
3				37	81
4				–	81
5				–	81
6	 R = H, CH_3			60	79
7			 **3**	80	79
8				70	79
9				49	84
10				61	84
11				65	84

[a] Prepared *in situ* via condensation of the appropriate acetoacetic acid (derivative) with formaldehyde.

[80] D. A. Peak, R. Robinson, *J. Chem. Soc.* **1937**, 1581.
[81] P. Wieland, K. Miescher, *Helv. Chim. Acta* **33**, 2215 (1950).
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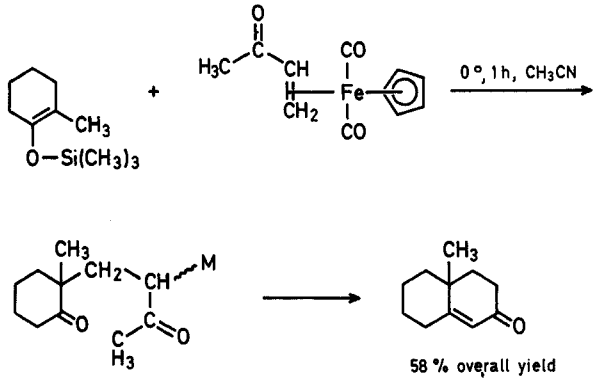
[86] G. Stork, H. J. E. Loewenthal, P. C. Mukharji, *J. Am. Chem. Soc.* **78**, 501 (1956).

$\Delta^{1,9}$-2-Octalone (3)[85, 26]:

To a solution of methyllithium (1.2 mmol) in dry dimethoxyethane (5 ml, distilled from lithium aluminum hydride) is added cyclohexanone enol silylether (0.187 g, 1.1 mol). After the addition, the reaction mixture was refluxed for 15 min, and then cooled to −78°. A solution of 2-triethylsilyl-1-butene-3-one (**22**, R = Si[C_2H_5]$_3$; 0.220 g, 1.2 mmol) is added, and the solution is warmed to room temperature, and let stir for 12 h. The reaction mixture is quenched with water (10 ml) and extracted with ether (70 ml). The ether

extract is washed four times with water, once with saturated salt solution, dried with potassium carbonate and concentrated in vacuo. The residue is taken up in 5% sodium methoxide/methanol (5 ml) and refluxed for three h. The reaction mixture is poured into ether (70 ml), washed four times with an equal volume of water, once with a saturated salt solution, dried over potassium carbonate and concentrated in vacuo. The residue is freed of triethylsilanol and methoxytriethylsilane by heating in a Kugelrohr oven (75°/0.2 torr) to give the product; yield: 0.12 g (80%).

Very recently, Rosan and Rosenblum[84] have reported the use of a methyl vinyl ketone-metal complex in an annelation sequence (see Table 4, entries 9–11). The iron-enone complex undergoes Michael addition with regiochemically unstable enolates without equilibration. It has also been shown to undergo Michael reaction with enamines. Perhaps the most potentially useful observation, however, is that the complex will react with a silyl enol ether to give the Michael adduct under completely neutral conditions. Cyclization of the initial adduct with concomitant loss of the metal group could be accomplished either by treatment with 2% potassium hydroxide in methanol or with basic alumina in refluxing dichloromethane.



6. Annelations Using Electrophiles with Masked Carbonyl Functions

An approach to the attachment of 3'-oxobutyl side chains on ketones for use in an annelation sequence has been to use an alkylating agent (e.g., an alkyl halide) which has a protected, or latent, carbonyl group[11,12] in the molecule. Table 5 lists several examples of alkylating agents which have been used for this purpose.

Perhaps the most simple of these is a β-haloacetal, such as is shown in Table 5, entries 1–3. Stork has pointed out that halides of this type are relatively unreactive, and also have a strong tendency to undergo elimination under the basic conditions of the reaction[3], factors which have no doubt contributed to its infrequent use.

Some time ago, Stork, et al.[86], utilized 3-benzyloxybutyl bromide (Table 5, entry 4) as a 3'-oxobutyl equivalent. This reagent suffers, as Stork points out[3], from the disadvantage that an extra chiral center is introduced during the alkylation, a fact which would often mean obtention of diastereomeric products.

The procedures which are outlined below involve alkylation of the nucleophilic substrate with an *allylic* halide, which accomplishes three useful purposes. First, alkylation should proceed at a rate fast enough to allow alkylation with regiochemically unstable enolates before equilibration can occur. Second, elimination as a side reaction should be minimized. Third, the 3'-carbon atom is trigonal, and therefore achiral, eliminating the problems of diastereoisomerism in the alkylation products.

Table 5. Annelations using Electrophiles with Masked Carbonyl Functions

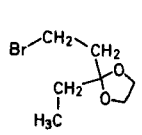
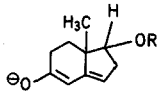
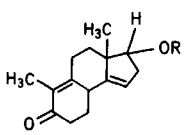
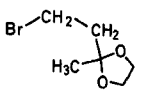
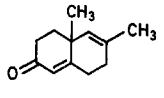
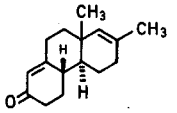
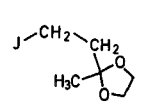
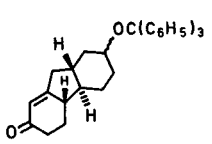
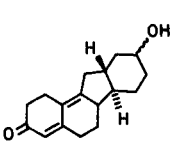
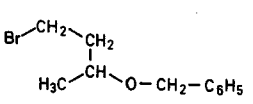
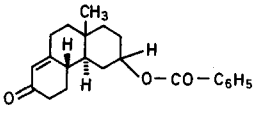
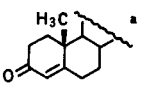
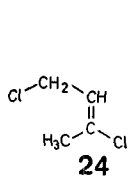
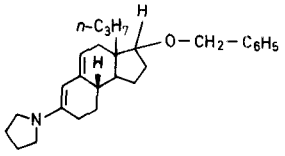
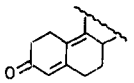
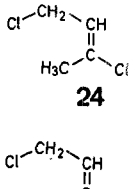
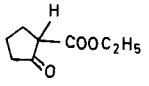
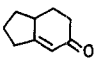
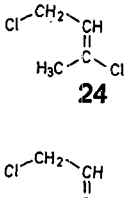
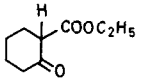
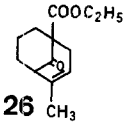
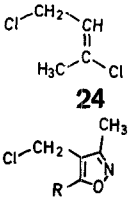
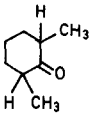
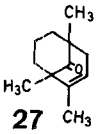
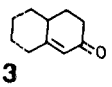
Entry	Electrophile	Nucleophile	Product	Yield (%)	Reference
1				–	88
2				–	3
3				30	89
4				–	86

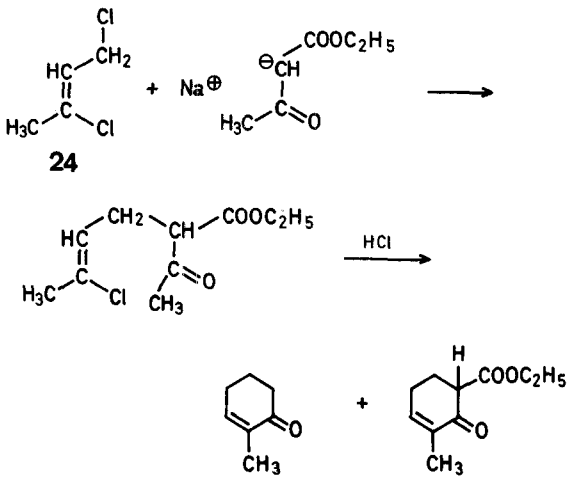
Table 5. Continued

Entry	Electrophile	Nucleophile	Product	Yield (%)	Reference
5	 **24**			–	90
6	 **24**	 (excess)	 **25**	43	50
7	 **24**		 **26**	–	91
8	 **24**		 **27**	59	66, 92
9			 **3**	–	49, 93, 94

[a] After several transformations.

6.1. The Wichterle Reaction

A widely used 3′-oxobutyl equivalent is 1,3-dichloro-2-butene (**24**) (see Table 2, entries 2 and 3, and Table 5, entries 5–8). This reagent was first used by Wichterle in the cyclohexenone synthesis illustrated below[87]. Since that time, use of this reagent in an annelation sequence has been commonly referred to as the Wichterle reaction[9].



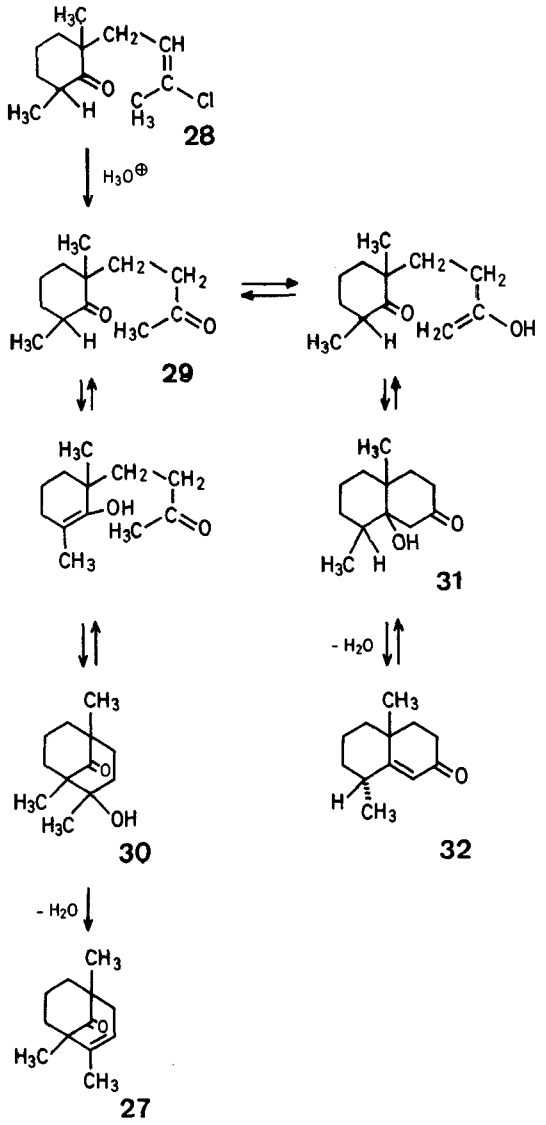
2-(3′-Chloro-2′-butenyl)-cyclopentanone[50, 26]:
To a solution of sodium (1.56 g, 68 mmol) in dry ethanol (80 ml) at 0° is added 2-ethoxycarbonylcyclopentanone (15.6 g, 100 mmol) with constant stirring. After one hour a solution of 1,3-dichloro-2-butene (8.5 g, 68 mmol) in dry ethanol (20 ml) is added slowly, and the mixture is stirred for 44 h at 0°. The mixture is neutralized at 0° with dilute sulfuric acid and the alcohol distilled off in vacuo. The residue is taken up in ether and worked up as usual. Distillation of the neutral portion produces 4.8 g of starting material (b.p. 100–105°/11 torr) and 11.3 g (68%) of the alkylated β-keto ester, b.p. 81–87°/0.1 torr. The latter material is refluxed for 4 h with concentrated hydrochloric acid (25 ml) and glacial acetic acid (40 ml). The workup gives an oil; yield: 7.3 g (91%, 62% overall).

5,6,7,8-Tetrahydroindan-5-one (25)[50, 26]:
To the crude, undistilled, ice-cold 2-(3′-chloro-2′-butenyl)-cyclopentanone (7.3 g, 42.3 mmol) is added carefully 90% sulfuric acid (12 ml), and the mixture is then let stand for 15 h at room temperature after the evolution of hydrogen chloride has ceased. The mixture is poured on to ice and extracted with ether. Distillation produces a colorless oil; yield: 4.1 g (71%); b.p. 107–112°/11 torr. The total yield based on 1,3-dichloro-2-butene is 43%.

The chief drawback to the use of this procedure is the fact that extremely harsh acid hydrolysis is required to generate the side chain carbonyl. Quite often these harsh conditions lead to unwanted side products, such as **26** and **27**, (see Table 5, entries 7 and 8) sometimes as the major annelation product[66, 91, 92]. These products are formed as a result

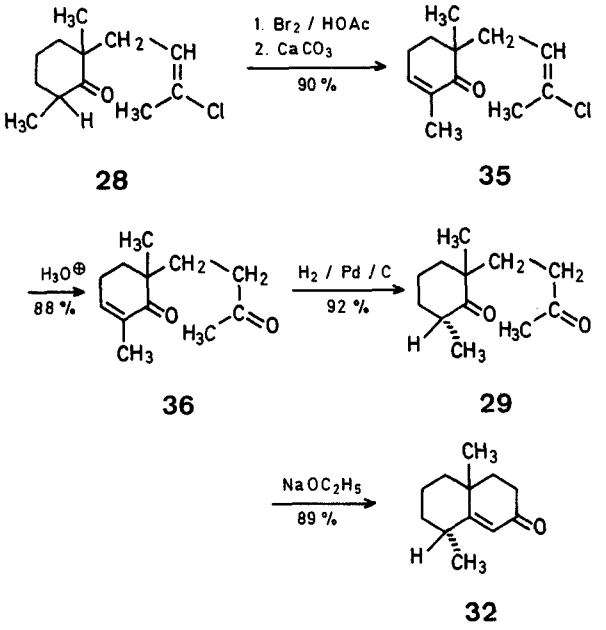
[87] O. Wichterle, *Collect. Czech. Chem. Commun.* **12**, 93 (1947). O. Wichterle, J. Prochazka, J. Hofman, *Collect. Czech. Chem. Commun.* **13**, 300 (1948).
[88] Z. G. Hajos, et al., *J. Org. Chem.* **32**, 3008 (1967).
[89] M. J. Green, et al., *J. Chem. Soc. Chem. Commun.* **1970**, 234.
[90] L. Velluz, et al., *Tetrahedron Lett.* **1961**, 127.
[91] W. G. Dauben, J. W. McFarland, *J. Am. Chem. Soc.* **82**, 4245 (1960).
[92] J. A. Marshall, D. J. Schaeffer, *J. Org. Chem.* **30**, 3642 (1965).

of enolization of the endocyclic ketone carbonyl and aldolization as shown in the series of equations below.

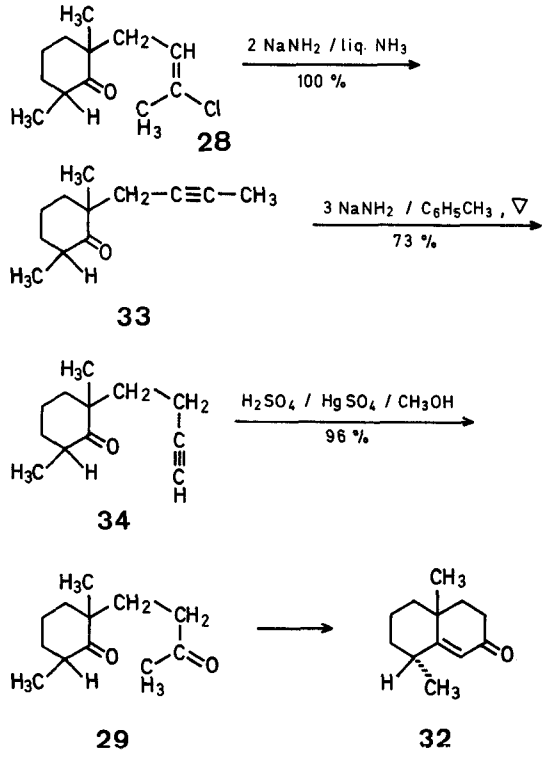


It seems likely that reversible formation of both keto alcohols **30** and **31** occurs, but under the strongly acidic reaction conditions, dehydration of **31** to **32** is either itself reversible or considerably slower than the irreversible dehydration of **30** to **27**. The net result, then, is the gradual accumulation of ketone **27**. Formation of keto alcohols such as **30** in Robinson annelations has long been known[95], even under relatively mild conditions, but it should be pointed out that under the normal (mild acid or base) conditions of the ring closure, dehydration of keto alcohol **30** is much less likely to occur, and so the enone **32** normally accumulates as the major product[66,92].

Enone **32** is a potentially useful starting material for terpenoid natural product synthesis, and two methods have been developed to circumvent the synthetic problems outlined above[66,92]. Parenthetically, it should be noted that annelation of 1,6-dimethylcyclohexanone with methyl vinyl ketone under basic conditions was unsuccessful. Marshall and Schaeffer[92] have developed the scheme outlined below, which involves bromination-dehydrobromination of ketone **28** to enone **35**, followed by strong acid treatment (Wichterle conditions) to hydrolyze the vinyl chloride[92]. Reduction of enedione **36** provided the dione **29**, which was cyclized to the desired octalone, **32**, in 65% overall yield (from **28**).



Caine and Tuller subsequently showed that the vinyl chloride side chain of **28** can be dehydrohalogenated and then isomerized to the terminal acetylene **34** with strong base. Hydration of the alkyne **34** produces the desired diketone **29**, which can be cyclized as before to octalone **32** in 62% overall yield from **28**[66].



2,6-Dimethyl-2-(2′-butynyl)-cyclohexanone (33)[66,26]:
Sodium amide (0.06 mol) is prepared by adding freshly cut sodium (1.38 g) to liquid ammonia (150 ml) containing anhydrous iron(III) chloride (~0.1 g) and the reaction mixture is stirred until the sodium amide precipitate is completely formed. A solution of 2,6-dimethyl-2-(γ-chlorocrotyl)-cyclohexanone (6.42 g, 0.03 mol) in anhydrous ether (25 ml) is added with stirring and followed by an additional 25 ml of ether. The resulting suspension is stirred for 3 h at reflux and stirring is continued while the ammonia is allowed to evaporate. When the reaction mixture reaches room temperature, 10% aqueous hydrochloric acid (30 ml) is added slowly and the mixture is stirred for 10 min. The layers are then separated, and the aqueous layer is saturated with sodium chloride and extracted with three 50 ml portions of ether. The combined etheral portions are washed with brine and dried over sodium sulfate. Concentration under reduced pressure gives a pale yellow oil which on distillation gives **33**; yield: 5.31 g (99%); b.p. 63–65°/0.04 torr.

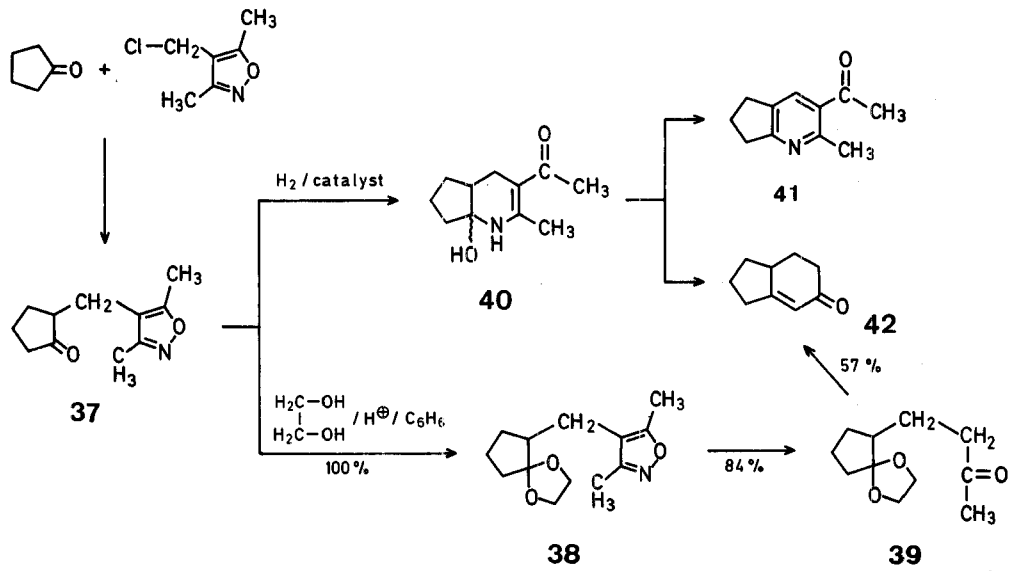
2,6-Dimethyl-2-(3-butynyl)-cyclohexanone (34)[66,26]:
Sodium amide (0.06 mol) is prepared using sodium (1.38 g) and liquid ammonia (20 ml) as described previously. Dry toluene (30 ml) is added and the ammonia is removed by distillation. A solution of **33** (3.56 g, 0.02 mol) in dry toluene (30 ml) is added and the mixture is heated to reflux. The black suspension is refluxed with stirring for 12 h and allowed to cool to room temperature. Aqueous hydrochloric acid (30 ml, 10%) is added slowly and the mixture is stirred for 10 min. The layers are separated, and the aqueous layer is saturated with sodium chloride and extracted with three 50 ml portions of ether. The combined organic portions are washed with brine and dried over sodium sulfate. Concentration under reduced pressure gives a light yellow oil which on distillation yields **34**; yield: 2.61 g (73%); b.p. 65–67°/0.04 torr.

2,6-Dimethyl-2-(3-oxobutyl)-cyclohexanone (29)[66,26]:
A mixture composed of water (6.8 ml), concentrated sulfuric acid (0.5 g), mercury(II) sulfate (0.1 g), methanol (12.5 ml), and **34** (2.0 g) is stirred at room temperature for 1.5 h. The reaction mixture is then poured into water (75 ml) and extracted with ether (30 ml). The aqueous layer is saturated with sodium chloride and extracted with three 50 ml portions of ether. The combined ethereal extracts are washed with brine and dried over sodium sulfate. Concentration under reduced pressure gives a colorless oil which on distillation gives the product **29**; yield: 2.11 g (96%); b.p. 86–88°/0.05 torr.

***trans*-8,10-Dimethyl-2-oxo-2,3,4,5,6,7,8,10-octahydronaphthalene (32)**[92,26]:
A solution containing the dione **29** (22.5 g, 0.115 mol) and sodium ethoxide (from 3.0 g, 0.013 mol, of sodium) in ethanol (500 ml) is heated at 45–50° for 1 h. The cooled solution is poured into water and extracted several times with ether. The combined organic layers are washed with brine, dried with magnesium sulfate and concentrated in vacuo. Distillation of the residue gives the product; yield: 18.3 g (89%); b.p. 90–99°/0.3 torr.

6.2. The Isoxazole Annelation

The isoxazole annelation, (Table 5, entry 9), as first introduced by Stork et al.[49,93], and later improved upon by Scott, Banner, and Saucy[94], has been shown to be applicable to sequences involving alkylation by either enolates or enamines[47,49]. Furthermore, the mild conditions required for unmasking of the carbonyl[94] give it distinct advantages over the Wichterle reaction. The only drawback to the original procedure as outlined by Stork et al.[49,93] is that the dihydropyridine intermediate **40**, involved in the deprotection/ring closure step can undergo aromatization (e.g., **40**→**41**)[93,96]. This side reaction can be avoided by acetalization of the endocyclic ketone **37** before reducing/hydrolyzing the isoxazole ring, as shown below[94].



2-[(3,5-Dimethyl-4-isoxazolyl)-methyl]cyclopentanone (37)[96,26]:
A solution of the pyrrolidine enamine of cyclopentanone (15.0 g, 0.109 mol)[47] and 3,5-dimethyl-4-chloromethylisoxazole (10.0 g, 0.0687 mol) in dioxan (60 ml) is heated under reflux for 17 h. Water (15 ml) is added to the above mixture and refluxing is continued for an additional hour. After being cooled the solution is poured into ice/water (450 ml) and extracted with ether. The organic layer is washed successively with 5% hydrochloric acid and 5% sodium hydrogen carbonate solution and water and then dried over magnesium sulfate. The solvent is removed in vacuo and the residue is distilled under reduced pressure to give **37**; yield: 5.8 g (44%); b.p. 138–148°/0.7 torr.

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)-methyl]cyclopentane (38)[94,26]:
To a solution of 2-[(3,5-dimethyl-4-isoxazolyl)-methyl]cyclopentanone (25.0 g, 0.13 mol) in ethylene glycol (50 ml) and benzene (300 ml) is added *p*-toluenesulfonic acid monohydrate (3.0 g, 16 mmol). The resulting solution is degassed and heated at reflux, with azeotropic removal of water (water-jacketed Dean-Stark trap), for 16 h. The cooled mixture is washed twice with saturated sodium hydrogen carbonate solution and three times with water and saturated brine and dried with magnesium sulfate. The benzene

solutions are concentrated to produce crude acetal **38** in quantitative yield (suitable for further reaction). The crude, acetal may be distilled to give **38** as a colorless liquid; yield: 26 g (85%), b.p. 125–129°/0.4 torr.

1,1-Ethylenedioxy-2-(3′-oxobutyl)-cyclopentane (39)[94,26]:
To a solution of **38** (5.0 g, 21 mmol) in 3.2% ethanolic potassium hydroxide solution (100 ml) is added 10% palladium on carbon catalyst (100 mg) and the resulting mixture is hydrogenated at atmospheric pressure and room temperature. After 8 h, the uptake of hydrogen has ceased. The catalyst is removed by filtration and washed with fresh ethanol. The filtrates are concentrated at reduced pressure to approximately 30 ml. To this solution (of vinylogous amide) is added 20% potassium hydroxide solution (100 ml) and the resulting mixture is degassed and heated at reflux overnight. The cooled solution is extracted with benzene. The benzene solutions are washed with saturated brine and dried (magnesium sulfate). Solvent removal provides the crude keto-acetal which is sufficiently pure for further reaction. Distillation gives **39** as a colorless liquid; yield: 3.52 g (83%); b.p. 85–90°/0.35 torr.

2,3,7,7a-Tetrahydroindan-5(6*H*)-one (42)[94,26]:
To a solution of crude keto-acetal **39**, prepared from isoxazole acetal **38** (5.0 g), in methanol (60 ml) is added 4 *N* hydrochloric acid (6 ml) and the resulting mixture is heated at reflux for 3 h. The solution is cooled, poured into water, and extracted with benzene. The combined benzene solutions are washed with saturated sodium hydrogen carbonate solution and saturated brine, dried (magnesium sulfate), and concentrated in vacuo. The resulting colorless oil is dissolved in 2% methanolic sodium hydroxide (50 ml). The resulting solution is heated at reflux for 3 h, cooled, diluted with water, and extracted with benzene. The benzene extracts are washed with saturated brine and dried (magnesium sulfate). Solvent removal and distillation gives **42** as a colorless liquid; yield: 1.64 g (57%); b.p. 60–68°/0.25 torr.

7. Annelations Involving Oxidation of Alkenyl Side Chains

Most of the preceding examples of annelations via alkylation/deprotection have introduced the 3′-carbon of the side chain in the oxidation state of a ketone carbonyl, so that only a "hydrolysis" is theoretically involved in the deprotection step. Recently, there have been introduced two procedures by which the 3′-carbon of the side chain is attached in the oxidation state of a double bond, and then subsequently oxidized up to a ketone to be cyclized.

The first of these to be considered is the vinylsilylallyl iodide reagent **43** (see Table 6, entries 1 and 2). This reagent was shown to be successful in alkylations using both enamines and enolates as nucleophiles. Also, regiochemically unstable enolates were shown to undergo alkylation before equilibration[48].

Epoxidation of vinyl silane **44** followed by acid-catalyzed conversion of the intermediate epoxide **45** to dione **46** is accomplished by treatment with *m*-chloroperbenzoic acid in 90% yield. Thus the overall yield from the enolate of 2-methylcyclohexanone is 80%.

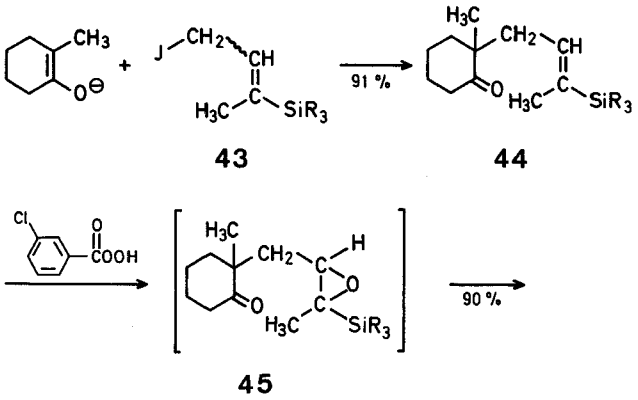
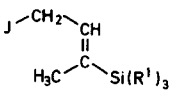
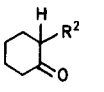
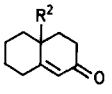
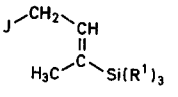
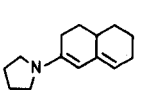
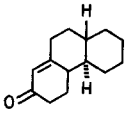
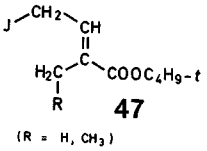
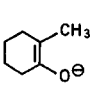
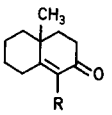
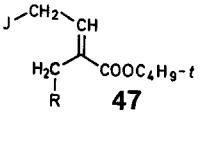
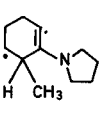
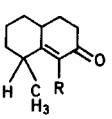


Table 6. Annelations Involving Side Chain Oxidation

Entry	Electrophile	Nucleophile	Product	Yield (%)	Reference
1				80	48
2				–	48
3	 **47** (R = H, CH_3)			75	97
4	 **47**			43	97

Trimethyl-(3-hydroxy-1-propynyl)-silane[98,26]:
To a stirred solution of propargyl alcohol (5.6 g, 0.1 mol) in dry tetrahydrofuran (200 ml; distilled from lithium aluminum hydride) cooled to −78° is added via syringe over 20 min a solution of *n*-butyllithium in hexane (125 ml of 1.6 *M* solution). The solution is allowed to stir at −78° for 25 min after addition, then the trimethylchlorosilane (21.8 g, 0.2 mol) is added all at once. The solution is allowed to warm to room temperature over a 1 h period, then poured into very dilute aqueous hydrochloric acid. The layers are separated and the aqueous layer extracted several times with ether. The ethereal extract is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give the crude material; yield: 17.4 g. Distillation gives the pure product; yield: 11.5 g (90%); b.p. 87°/25 torr.

***(Z)*-Trimethyl-(3-hydroxy-1-iodo-1-propenyl)-silane**[98,26]:
To a stirred solution of lithium aluminum hydride (8.1 g, 0.213 mol) and sodium methoxide (23 g, 0.426 mol) in dry tetrahydrofuran (500 ml) at room temperature is added dropwise a solution of the silyl propargyl alcohol (27.3 g, 0.213 mol) in tetrahydrofuran (50 ml) at a rate which caused the tetrahydrofuran to reflux gently. After addition, the solution is refluxed for 3 h, then cooled to −78°. The iodine (108 g, 0.426 mol) in tetrahydrofuran (200 ml) is added over a 1 h period. The solution is stirred at −78° for 3.5 h, then allowed to warm to room temperature over 1 h. Saturated aqueous ammonium chloride is added slowly. The salts are filtered and washed well with hot tetrahydrofuran (500 ml). Ether is added and the organic layer washed with saturated aqueous sodium thiosulfate until the iodine color is discharged. The ethereal solution is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 49.2 g of crude material. Distillation gives a slightly tan colored liquid; yield: 36.9 g (68%); b.p. 62°/0.08 torr.

***(E)*-Trimethyl-(3-hydroxy-1-methyl-1-propenyl)-silane**[98,26]:
To a stirred mixture of copper(I) iodide (26.04 g, 0.14 mol) in ether (150 ml) cooled to 0° is added a solution of methyllithium in ether (175 ml of 1.6 *M* solution). The alcohol (7.0 g, 28 mmol) in ether (15 ml) is added dropwise over a 15 min period. The solution is stirred at 0° for 3.5 h. Saturated aqueous ammonium chloride is added slowly to destroy the excess lithium dimethylcuprate. The salts are filtered and washed well with ether. The layers are separated and the aqueous layer extracted with ether several times. The ethereal extract is washed with 1 *N* hydrochloric acid, water, saturated aqueous sodium thiosulfate, and brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 4.3 g of crude material. Distillation gives the pure product; yield: 3.90 g (96%); b.p. 85–87°/9 torr.

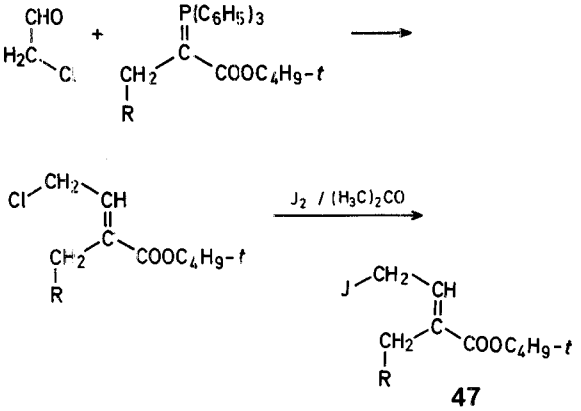
***(E)*-Trimethyl-(3-chloro-1-methyl-1-propenyl)-silane**[98,26]:
A stirred mixture of triphenylphosphine (26.2 g, 0.1 mol) and the alcohol (14.4 g, 0.1 mol) in tetrachloromethane (20 ml, 31 g, 0.2 mol) is heated under a nitrogen atmosphere. At ~40°, all the triphenylphosphine goes into solution and as the temperature reached ~80°, a white solid, triphenylphosphine oxide, precipitates. The solution is heated at a bath temperature of 85° for 1 h and then cooled to room temperature. Hexane is added and the white solid filtered. The hexane solution is evaporated in vacuo and the resulting liquid-solid mixture is again filtered and washed well with hexane. The hexane solution is again evaporated in vacuo and the residue filtered through 40 g silica gel with hexane. Evaporation of the hexane solution in vacuo gives 11.1 g of crude material. Distillation gives the pure product; yield: 9.7 g (60%); b.p. 55–56°/12 torr.

***(E)*-Trimethyl-(3-iodo-1-methyl-1-propenyl)-silane (43)**[98,26]:
A stirred solution of the chloride (162.5 mg, 1 mmol) and sodium iodide (180 mg, 1.2 mmol) in 2-butanone (15 ml) is heated at 50° for 1 h. The solution is cooled to room temperature, the solid filtered and washed well with acetone. All solvent is removed in vacuo and the residue taken up in ether. The ethereal solution is washed with water, saturated aqueous sodium thiosulfate, and brine, dried over sodium sulfate, filtered, and evaporated in vacuo to give 202 mg (79%) of a clear slightly yellow liquid; yield: 202 mg (79%). The compound could be distilled (bulb-to-bulb) at a bath temperature of 60°/20 torr.

2-Methyl-2-(3-trimethylsilyl-2-butenyl)-cyclohexanone (44)[98,26]:
To a stirred solution of triphenylmethane (13 mg) in tetrahydrofuran (30 ml) at room temperature is added a solution of methyllithium (1.8 ml of a 1.8 *M* solution, 3.2 mmol) to give a red color. Neat 2-methylacetoxycyclohexene (247 mg, 1.6 mmol) is added via a weighed syringe until the pink color just disappeared. To this is added the allylic iodide **43** (406 mg, 1.6 mmol) in tetrahydrofuran (10 ml). The solution is allowed to stir at room temperature for 20 h. It is then poured into brine, and extracted several times with ether. The ethereal extract is washed with aqueous sodium thiosulfate solution and brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 413 mg of a yellow liquid. Chromatography on silica gel (30 g), eluting with benzene, gives a clear liquid; yield: 346 mg (91%); b.p. 45°/0.02 torr.

2-Methyl-2-(3-oxobutyl)-cyclohexanone (46)[98,26]:
To a stirred solution of the vinylsilane **44** (100 mg, 0.42 mmol) in dichloromethane (50 ml) is added rapidly a solution of *m*-chloroperbenzoic acid (95 mg, 0.55 mmol) in dichloromethane (10 ml) at room temperature. After allowing the solution to stir for 4 h, T.L.C. analysis shows only a trace of starting vinylsilane **44**. Excess peracid is destroyed with 10% aqueous sodium sulfite. A solution of 10% aqueous sodium carbonate is added and the layers separated. The aqueous layer is extracted several times with dichloromethane. The organic extract is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give 86.5 mg of crude material. Chromatography on silica gel (9 g), eluting with 6:1 hexane/ether gives, in order of elution, 8.3 mg starting vinylsilane **44** and 66 mg of the dione **46** (89%; 94% based on unrecovered starting material).

The second reagent to be considered which requires side chain oxidation is the iodotiglate **47** (see Table 6, entries 3 and 4). This reagent was also shown to be successful as an alkylating agent for both enamines and enolates. Furthermore, regiochemically unstable enolates (e.g., **48**), generated in tetrahydrofuran, were shown to undergo alkylation with no prior equilibration of the enolate[97].



47

[92] G. Stork, J. E. McMurry, *J. Am. Chem. Soc.* **89**, 5463 (1967).
[94] J. W. Scott, B. L. Banner, G. Saucy, *J. Org. Chem.* **37**, 1664 (1972).
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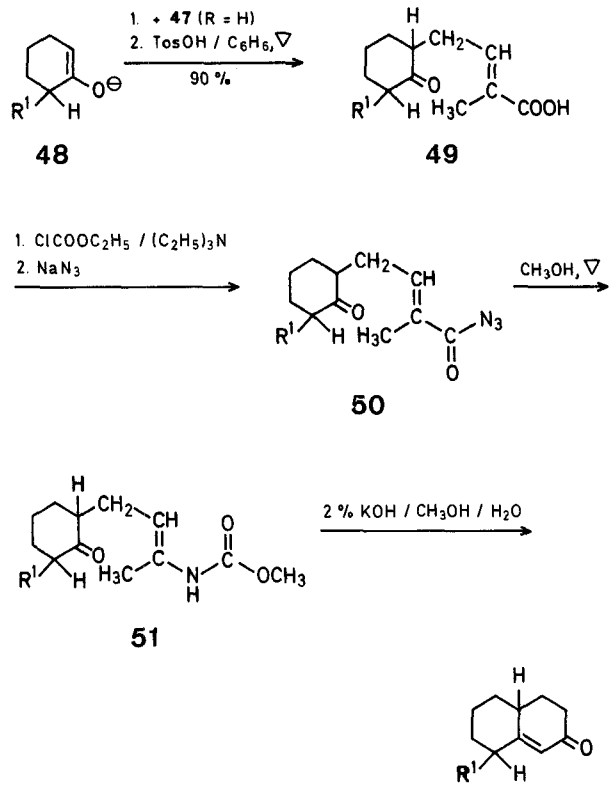
[96] G. Stork, M. Ohashi, H. Kamachi, H. Kakisawa, *J. Org. Chem.* **36**, 2784 (1971).
[97] P. L. Stotter, K. A. Hill, *J. Am. Chem. Soc.* **96**, 6524 (1974).
[98] M. E. Jung, *Ph. D. Thesis*, Columbia University, 1973. The author is indebted to Dr. Jung for supplying these details.
[99] J. Weinstock, *J. Org. Chem.* **26**, 3511 (1961).



The γ-iodotiglate **47** was prepared from the γ-chloro analog, which was prepared via a variant of the Wittig reaction, as shown. The oxidation of the side chain to the "masked carbonyl" vinyl carbamate **51** was carried out under mildly basic conditions via acyl azide **50** using the Weinstock modification[99] of the Curtius degradation. Hydrolysis of carbamate **51** and concomitant cyclization/dehydration of the intermediate dione to the enone may be accomplished in one step. The overall yield for conversion of the α,β-unsaturated acid **49** to 8-methyl-2-oxo-2,3,4,5,6,7,8,10-octahydronaphthalene is 83%.

***t*-Butyl 2-(Triphenylphosphoranylidene)-propanoate**[100, 26]:
To a solution of triphenylphosphine (170 g, 0.65 mol) in benzene (1300 ml) is added *t*-butyl 2-iodopropanoate (170 g, 0.655 mol). The solution is stirred at room temperature for 3 days and then filtered to remove the phosphonium salt (181 g, 54%, m.p. 162–164°). The solvent is reduced in volume to approximately 750 ml and is then heated at 50° for another 3 days. Filtration gives additional crop of phosphonium salt (126 g, total 307 g, 91.5%). The crude phosphonium salt is not further purified but is directly converted to the phosphorane. The crude phosphonium salt (159 g, 0.29 mol) was added to water (600 ml) and benzene (1000 ml). The slurry is treated with a solution of potassium hydroxide (30 g, 0.535 mol) in water (100 ml). The reaction mixture is stirred at room temperature for 30 min. The organic layer is removed and the aqueous layer extracted once more with benzene. The combined organic extracts are washed with brine, dried with magnesium sulfate, filtered, and the solvent removed in vacuo to give the crude phosphorane; yield: 112 g (99%); m.p. 164–167°. The crude phosphorane can be used directly in the Wittig reactions.

***t*-Butyl 4-Chloro-2-methyl-*trans*-2-butenoate**[100, 26]:
To a solution of the phosphorane (10.0 g, 25.7 mmol) in dry dichloromethane (50 ml) is added chloroacetaldehyde (2.55 g, 32.5 mmol) in dry dichloromethane (30 ml). The reaction is exothermic. The reaction mixture is heated at reflux for 19 h and the solvent is removed in vacuo and replaced with pentane. The pentane slurry is stirred and heated at reflux for 1 h and then cooled and filtered to remove most of the triphenylphosphine oxide. Removal of the solvent leaves a residue containing some triphenyl phosphine oxide. Distillation gives the product; yield: 4.2 g (86%); b.p. 67–69°/0.8 torr.

***t*-Butyl-4-iodo-2-methyl-*trans*-2-butenoate (47)**[100, 26]:
To a stirred mixture of sodium iodide (18 g, 120 mmol) in acetone (150 ml; which had been dried over molecular sieves) is added the *t*-butyl chlorotiglate (10 g, 52.5 mmol) in acetone (10 ml). A white precipitate forms immediately, and the mixture is stirred for 15 min at room temperature. The solvent is removed in vacuo, and the residue is taken up in ether/water. The organic layer is washed with brine containing a little sodium thiosulfate, dried with sodium sulfate, and condensed in vacuo to produce the crude products; yield: 14.6 g (96%). This material is suitable for use in the alkylation step if used immediately. Distillation of the residue provided purified material; yield: 12.8 g (86%); bath temperature 80°/0.005 torr, which could be stored indefinitely at −20°.

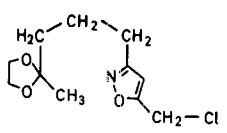
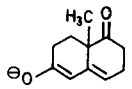
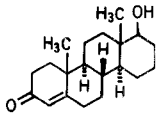
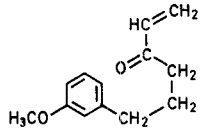
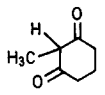
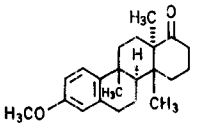
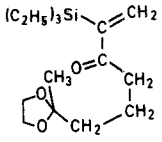
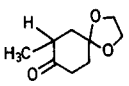
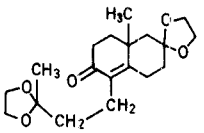
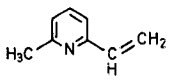
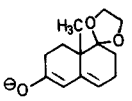
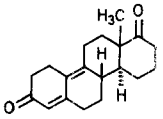
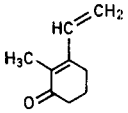
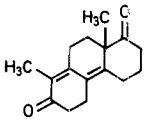
2-(3′-*t*-Butoxycarbonyl-2′-butenyl)-6-methylcyclohexanone[100, 26]:
To methyllithium in ether (8.0 ml, approximately 16 mmol) in dry tetrahydrofuran (30 ml, containing approximately 20 mg of triphenylmethane) is added 1-trimethylsilyloxy-6-methylcyclohexene (2.8 g, 15.2 mmol) dropwise until the red color just disappears. The enolate (**48**, R = CH_3) solution is cooled to 0° and treated with the iodotiglate (4.0 g, 14.1 mmol). The cooling bath is removed and the solution is allowed to stir for an additional 45 min and is then added to 10% aqueous sodium hydrogen carbonate and extracted with ether. The ethereal extract is washed with brine, dried over magnesium sulfate and evaporated in vacuo to give the product; yield: 3.6 g (95%). Short path distillation provides the pure product; yield: 3.4 g (90%); bath temperature, 110°/0.005 torr.

2-(3′-Carboxy-2′-butenyl)-cyclohexanone (49, R^1 = H)[100, 26]:
The *t*-butyl ester (6.4 g, 25.4 mmol) is dissolved in dry benzene (50 ml) containing approximately 25 mg of toluenesulfonic acid. The solution is heated at reflux for 18 h. The cooled solution is extracted several times with 5% sodium hydroxide solution. The aqueous layer is acidified with concentrated sulfuric acid, saturated with sodium sulfate, and extracted with ether. The ethereal solution is dried over magnesium sulfate, filtered, and evaporated in vacuo to give the product; yield: 4.5 g (92%); m.p. 85.5–86.5° (from hexane).

2-Oxo-2,3,4,5,6,7,8,10-octahydronaphthalene[100, 26] **(R^1 = H)**:
Using the procedure described by Weinstock[99], the acid (4.7 g, 24 mmol) is dissolved in 50% aqueous acetone and cooled to 0°. Triethylamine (4.5 g, 44.5 mmol) in acetone (45 ml) is added, followed by ethyl chloroformate (5.2 g, 48 mmol) in acetone (20 ml) and the solution is stirred at 0° for 30 min. Sodium azide (5.0 g, 77 mmol) in water (20 ml) is added slowly and the solution is stirred at 0° for 90 min. The solution is poured into ice water and extracted several times with ether. The ethereal extract is washed with brine, dried over magnesium sulfate, filtered and evaporated in vacuo to give the acyl azide; yield: 5.0 g (95%). The crude acyl azide (5.0 g, 22.6 mmol) is heated at reflux in methanol for 2 h, during which time nitrogen evolution is observed. The solvent is evaporated in vacuo to give the vinyl urethane; yield: 5.0 g (98%). The vinyl urethane (5.0 g, 22.6 mmol) is stirred at room temperature in methanol (60 ml, containing 15 ml of 10% aqueous potassium hydroxide) for 1 h. The solution is then heated at reflux for 2 h and stirred at room temperature for 1 h. The solution is diluted with brine and extracted several times with ether. The ethereal extract is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo to give the octalone; yield: 3.0 g (88%).

[100] K. A. Hill, private communication. The author is indebted to Dr. Hill and Dr. P. L. Stotter for supplying these experimental details.

Table 7. Bis-Annelations

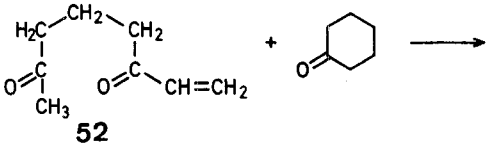
Entry	Electrophile	Nucleophile	Product	Yield (%)	Reference
1				23[a]	101
2				20[a]	102
3				73	79
4				18[a]	8
5				20–45	103

[a] The transformation illustrated involves some steps which are not involved in the annelation sequence.

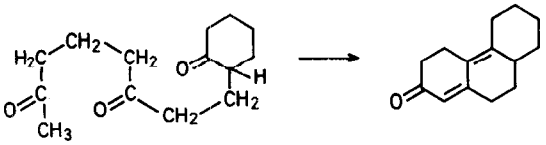
8. Bis-Annelations

An ingenious offshoot of the Robinson procedure, which will be mentioned only briefly here, is the so-called "bis-annelation" (see Table 7). In this procedure, the electrophilic reactant (e.g., the vinyl ketone, or alkyl halide) has incorporated within itself the potential for the formation of two new rings, instead of the one formed by a Robinson procedure. Danishefsky[8] has referred to this type of reagent as a "synthetic equivalent to oct-7-ene-2,6-dione" (**52**).

After initial Michael attack by a nucleophile, cyclization could lead to the formation of two new rings, as shown. Approaches to which this concept apply are utilizing a bis Robinson annelation. An alternative would of course be to use a Robinson-type annelation to form the first ring and another type of cyclization to form the second, or vice versa.



52



Bis-annelations have been invaluable in the synthesis of polycyclic ring systems, and it is beyond the scope of this review to even try to cover them. Table 7 provides a very few examples taken at random from the literature. The interested reader is referred to a recent paper by Danishefsky, Cain, and Nagel[8], which has an excellent discussion of bis-annelations, along with numerous references.

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