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Dihydrobenzenes in Synthesis in Terpene Related Areas

Arthur J. Birch

1-Methoxycyclohexa-1,4-dienes obtained by metal–ammonia reductions of anisole derivatives are useful in synthesis because of their nature both as enol ethers and as dienes. Dihalocarbene adducts give rise eventually either to tropones or to methylated cyclohexanones according to subsequent manipulations. Introduction of angular methyl groups can be accomplished efficiently in this manner. They readily directly form Diels–Alder adducts derived from the isomeric 1,3-dienes. These adducts can be ring-opened by acid to 4-substituted cyclohexenones, a procedure used in stereoselective syntheses of (±)-juvabione and of (±)-nootkatone. Synthetic capabilities of tricarbonylcyclohexadieneiron derivatives are introduced.

Instead of recounting only some finished syntheses I thought it might be more useful to terpene chemists interested in synthesis to draw attention to some general approaches which have been perhaps insufficiently used. The references given are only to my own work, which was in all cases the earliest in the area discussed. In a number of instances later work has been published by others.

The basis of the subject is the ready availability of cyclohexa-1,4-dienes and particularly the 1-methoxy derivatives from the reduction of aromatic compounds by metal–ammonia–alcohol combinations (*e.g.*, Birch and Subba Rao, 1972). This work was originally aimed at making 19-norsteroids, since the methoxydienes are enol ethers and can be hydrolyzed first to $\beta\gamma$- and to $\alpha\beta$-unsaturated cyclohexenones. The initial work culminated in the total synthesis of 19-nortestosterone (Birch, 1950a), the first totally synthetic potent androgen, and later led to analogs of other steroid hormones, including oral contraceptives. Direct reductions of aromatic rings or reductions followed by hydrolysis to ketones have been extensively used in connection with terpenoid synthesis, the first examples being concerned with piperitone and γ-curcumene (Birch and Mukherji, 1949). This is too well known to merit further discussion here except to note that the approach has largely eliminated the need for high pressure hydrogenations of aromatic rings and also permits a considerable degree of steric control.

Further to the production of cyclohexenones, copper-catalyzed Grignard reagent additions (Birch and Robinson, 1943; Birch and Smith, 1962; Kharasch and Tawney, 1941) to an enone system permit introduction of quaternary carbon atoms, including angular methyl groups. Such an introduction into, for example, a 2-octalone was early shown (Birch and Robinson, 1943; Birch and Smith, 1962) to result in a cis ring junction, which somewhat limits its applications in the terpene field. More recent modifications, using notably lithium copper dialkyl reagents, have shown considerable synthetic scope for the procedure.

The 1-methoxycyclohexa-1,4-dienes are at the same time vinyl ethers and dienes, and one or other or both of these features explains their reaction capabilities in synthesis. A general feature of their nature as vinyl ethers is the high reactivity of that double bond toward electrophilic reagents. One example is the acid hydrolysis shown in Figure 1. Another important feature is that if in consequence of this reactivity a new carbon–carbon bond is formed as part of a ring to the center carrying OMe, a ring bond is readily broken by reactions calculated to produce a carbonium ion on this particular carbon as a consequence of interaction with the unshared electrons on the oxygen. Two important synthetic examples of this type of fission will be quoted. The first consists of a very facile synthesis of tropone derivatives, exemplified by the synthesis of nezukone shown in Figure 2 (Birch and Keeton, 1968). The other is connected with the Diels–Alder reactions discussed later. Such reactions occur less readily or not at all in the absence of OR.

Reaction of the electron-deficient carbene occurs somewhat selectively in this case on the enol ether bond and much more selectively in cases where the second double bond is less activated by substitution. Removal of halide anion by a silver cation or by heating in quinoline provokes the ring fission shown. The intermediate oxonium salt undergoes hydrolysis and with double bond shifts and hydrogen bromide elimination the action of silver fluoroborate experimentally gives directly the tropone in high yield. Several other examples are shown in Figure 3 (Birch *et al.*, 1965). Although such syntheses could probably be carried out by standard ring expansions, brominations, dehydrobrominations, etc., the present procedure is a three-step one from an aromatic compound and is probably the easiest tropone synthesis available.

Dimethoxy derivatives can lead to cyclooctane derivatives or ring-closed derivatives of these, again in high yields (Figure 4) (Birch and Keeton, 1971; Birch *et al.*, 1964a).

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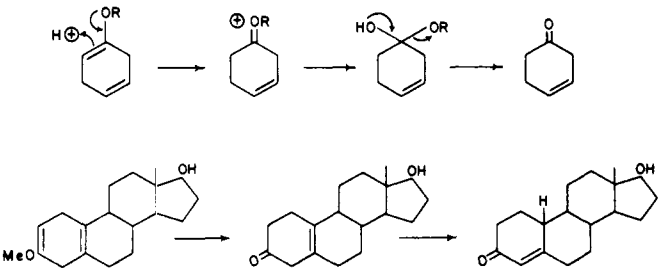

Figure 1. Acid hydrolysis of 1-methoxycyclohexa-1,4-dienes.

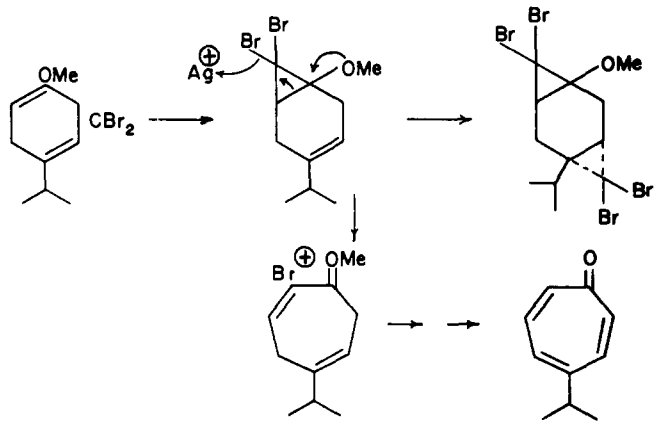

Figure 2. Synthesis of nezukone.

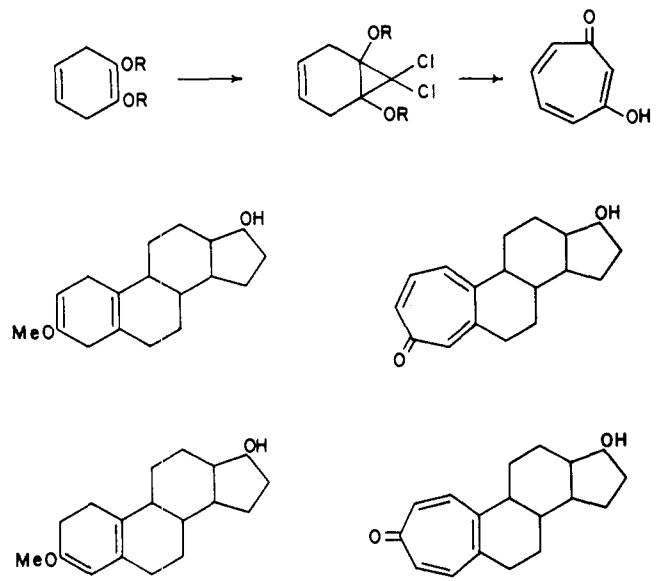

Figure 3. Tropone syntheses.

Tetrahydropyranyloxy precursors leading to hydroxycyclopropanes and the use of hydronaphthalenes give interesting systems containing fused seven-, six-, and three-membered rings (Birch and Keeton, 1971; Birch *et al.*, 1964a).

A feature of the metal–ammonia reductions is that they normally generate only one product and that the double bonds in this are in fixed and predictable relations to substituents because of the mechanism of the reaction. Introduction of a substituent onto a double bond is therefore a method of regiospecific introduction relative to other substituents. It has been used to indirectly introduce methyl next to a carbonyl, for example, and angular methyl groups. This approach is, in a number of cases, an indirect way of avoiding difficulties due to unwanted or mixed directions of formation of enolate anions or of enamines.

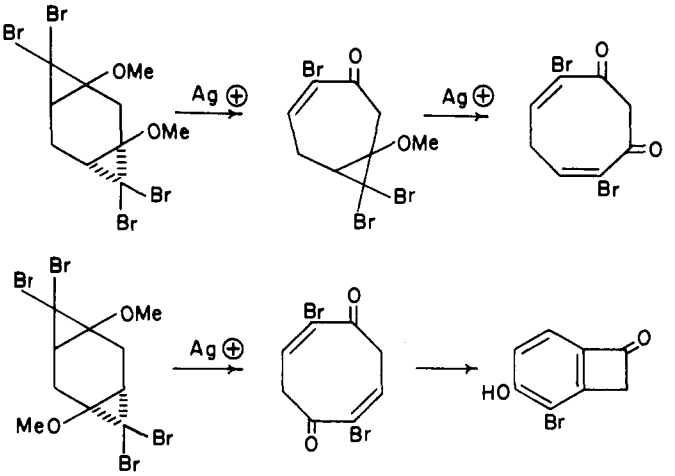

Figure 4. Dimethoxycarbene adducts in synthesis.

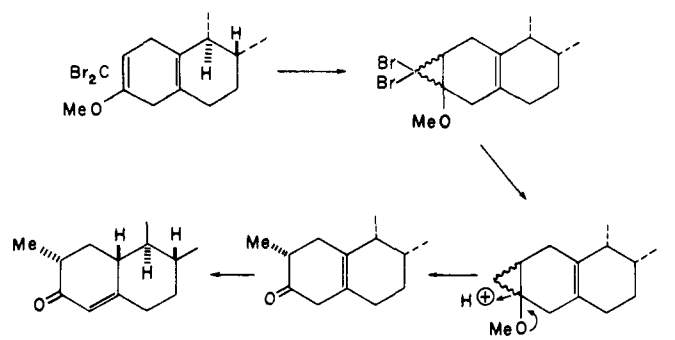

Figure 5. Synthesis of 2-methyl-19-nortestosterone.

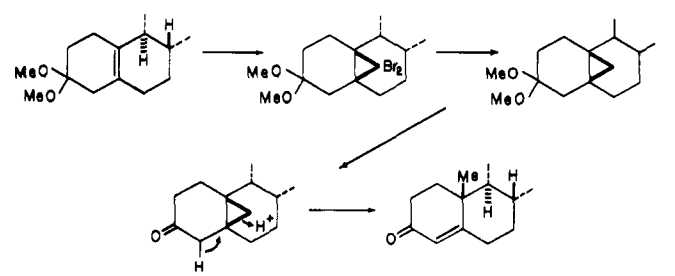

Figure 6. Synthesis of 19β-methyl steroids.

The first example, combining both capabilities, was in the steroid series (Birch *et al.*, 1964b). The introduction of a 2-Me into 19-nortestosterone *via* the precursor of the latter is shown in Figure 5. It depends on the great reactivity toward electrophilic reagents of the vinyl ether.

Both double bonds can be reacted in one experimental stage and two Me can be introduced, one of them the 19β-Me of the normal steroids. In order to introduce this Me alone, the greater reactivity of the vinyl ether bond can be used to remove it by forming a ketal with retention of the ability to generate a ketone on hydrolysis, as shown in Figure 6. Notably the presence of carbonyl causes predictable fission of the intermediate cyclopropane in one direction only. The procedure, in view of the ready availability of (+)-estrone by total synthesis, is probably the most efficient total synthesis of the nonaromatic steroid skeleton. This angular methylation procedure has been used with other stereoisomers of estrone (*e.g.*, Birch and Subba Rao, 1965).

By using the bisdibromocarbene adduct from dihydroestrone methyl ether, it has been found possible to expand ring A efficiently to cycloheptanone by a procedure related to the tropone synthesis discussed and to introduce the

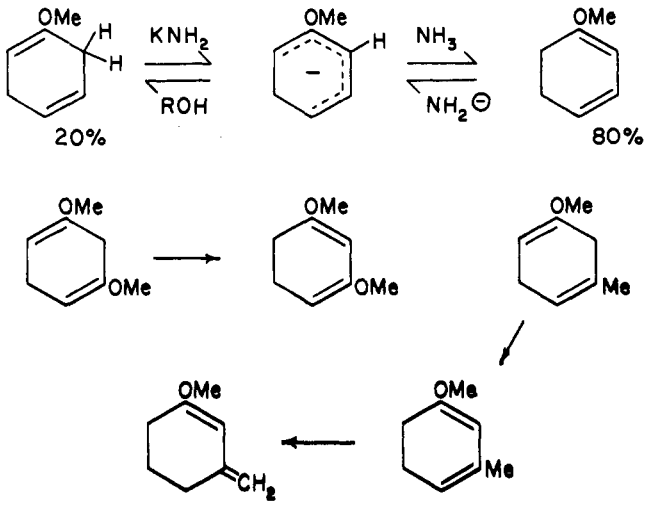

Figure 7. Isomerization of 1,4-cyclohexadienes.

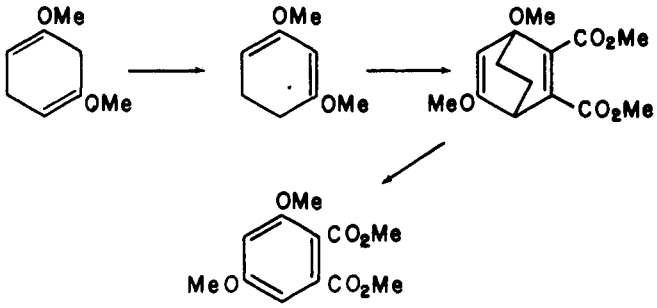

Figure 8. Synthesis of 3,5-dimethoxyphthalic acid dimethyl ester.

angular Me, giving A-homotestosterone (Birch and Subba Rao, 1966) in five stages from estrone methyl ether.

The nature of the cyclohexadienes as dienes immediately leads to consideration of the possibility of conjugating the bonds and then using Diels–Alder reactions. A frequent drawback to Diels–Alder reactions with cyclic dienes for many types of synthesis is that the products contain bridged rings, and it could be helpful if either one or two C–C bonds could be efficiently broken subsequently to give nonbridged products. Both of these overall types of sequences can be readily achieved, as noted later.

In discussing first the conjugation process, it was shown many years ago (Birch, 1945, 1950b) that 1-methoxycyclohexa-1,4-diène is quite acidic (at the 6 position) for a hydrocarbon acid and readily yields a salt with potassamide in liquid ammonia. This salt, and particularly that from 1,3-dimethoxycyclohexa-1,4-diene, can be alkylated *in situ*, with hydrolysis then giving a ketone or a diketone. One example is the reaction of the last salt with *m*-methoxyphenylethyl bromide, hydrolysis to the cyclohexan-1,3-dione, and then ring closure to a phenanthrene derivative used as a steroid intermediate (Birch and Smith, 1951). Another example is the isopropylation of the salt from 1-methoxycyclohexa-1,4-diene, followed by hydrolysis to 2-isopropylcyclohex-3-enone. This type of procedure has not been widely applied and may well have further uses.

If the base is only in a low molar proportion, the salt is reversibly protonated as shown in Figure 7, establishing equilibrium with the conjugated isomer (usually about 75–80%). Either isomer with excess base gives the same salt, which cannot only be alkylated but also kinetically protonated to the *unconjugated* isomer. The conjugated isomer can therefore largely be converted into the less stable unconjugated isomer. A discussion of the theoretical consequences of this distinction between products con-

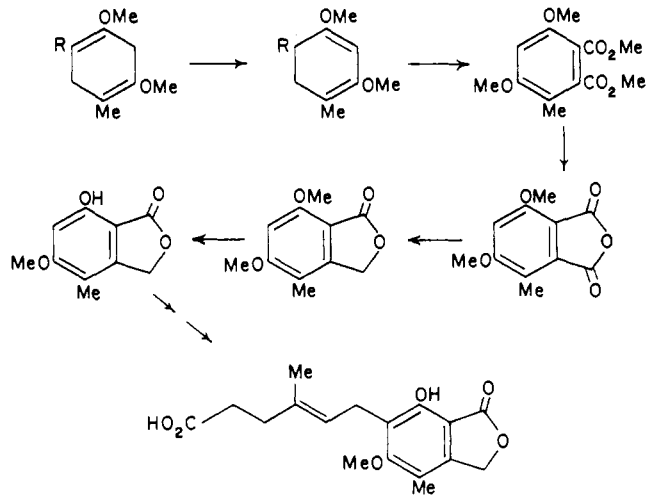

Figure 9. Synthesis of mycophenolic acid nucleus.

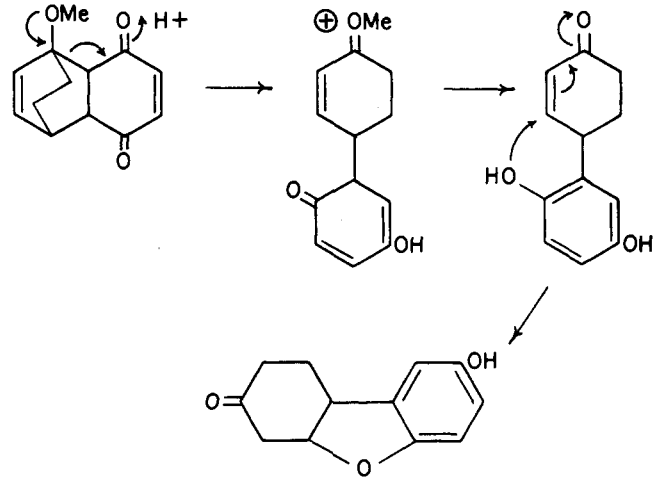

Figure 10. Ring opening in 1,4-ethylene bridged systems.

trolled by a rate and by an equilibrium position was the first in the area (Birch, 1947) and was taken further by Hughes and Ingold in the following year (Catchpole *et al.*, 1948). It was the theoretical basis of the first deconjugation of an $\alpha\beta$-unsaturated ketone for synthetic purposes (Birch, 1950c), a type of reaction later considerably used in terpenoid and steroid synthesis.

The experimental point is that the conjugated isomer is available in this way for Diels–Alder reactions in which the 1-methoxy derivatives are found to be particularly reactive. Conjugation in this way is not so successful with hydrocarbons lacking the OMe substituents, since disproportionation and dehydrogenation result.

Later work (Birch and Dastur, 1973a), based on an observation by Rogers (1969), showed that the methoxycyclohexa-1,4-dienes can be conjugated, probably in charge-transfer complexes, by Diels–Alder dienophiles themselves. The addition reaction can therefore be conducted directly on the 1,4-diene, frequently with yields of adduct of 85–90%, the severity of conditions required depending on the structure of the dienophile. The use of a catalyst of the type *in situ*, such as dichloromaleic anhydride, permits the Diels–Alder reaction to be carried out under uniformly mild conditions with other dienophiles.

There are two ways in which an unbridged product can finally be obtained. The first is independent of the presence of OMe, and is the well-known Alder–Rickert reaction (Alder and Rickert, 1937), exemplified by the synthesis of 3,5-dimethoxyphthalic acid (Figure 8). It is particularly useful in this series for the synthesis of compounds

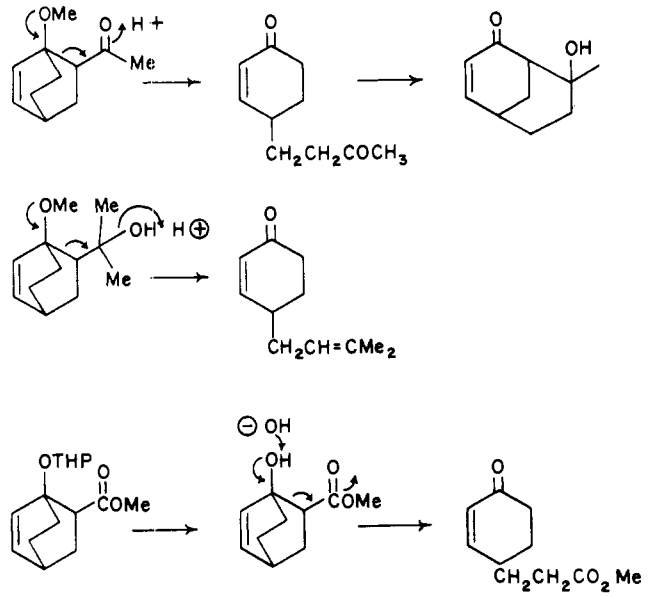

Figure 11. Examples of ring opening in bridged systems.

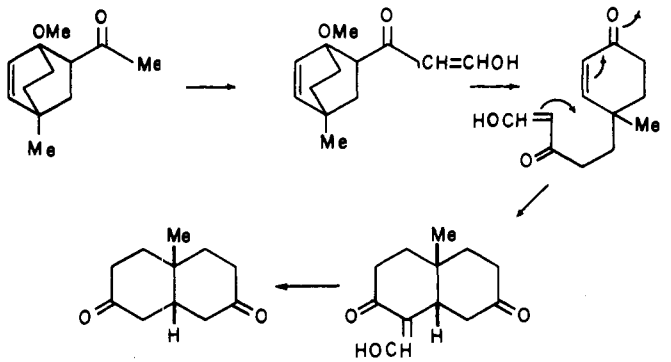

Figure 12. Michael type ring closure in ring-opened bridged system.

related to polyketides because of the orientations of substituents possible.

One example of its use is the synthesis of the nucleus of the partly terpenoid and partly polyketide mould metabolite mycophenolic acid (Figure 9) (Birch and Wright, 1969).

Although somewhat outside the scope of this talk, it may be noted that any 1,4-ethylene-bridged 1,4-dihydrobenzenes lose the bridge thermally in this way, the temperature required for the 1-methoxy derivatives being unusually low (~130°). Quinones can lead to polycyclic compounds, providing the initial adduct is aromatized or oxidized to give the appropriate intermediate bridged 1,4-dihydrobenzene structure (Birch and Powell, 1970; Birch *et al.*, 1964c).

The other method of obtaining unbridged compounds applies only in the 1-alkoxy series and depends on a crucial observation by my former student Dr. D. Butler (Figure 10) (Birch *et al.*, 1964d).

The reaction is readily explicable as a cleavage made possible by the stabilization of an intermediate carbonium ion through the unshared electrons on the oxygen. To stimulate the process, an initial carbonium ion generation is required in the side chain and this can be brought about as shown in Figure 11 (Birch and Hill, 1966a) or in other standard ways, such as the solvolysis of a secondary tosylate. In cases where a side chain carbonium ion is difficult to generate by the addition of a proton, as in adduct of acrylic ester or nitrile, the reaction can be produced by "pushing" electrons instead of "pulling" them (Birch and

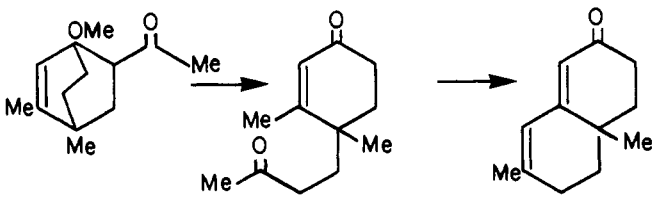

Figure 13. Ring closure on vinylogously activated methyl groups.

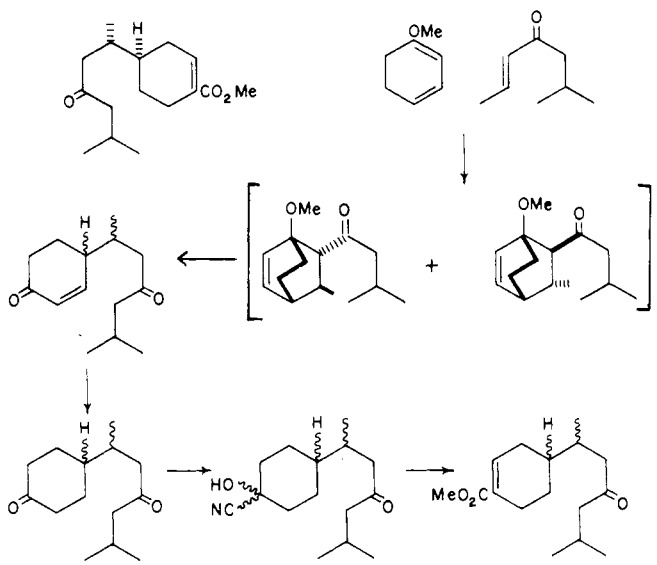

Figure 14. Synthesis of juvabione (mixture of diastereoisomers).

Hill, 1967). In that case a precursor such as a THP ether can be used initially in order to generate a bridgehead OH. Fission then occurs with base. Other competing reactions are not possible in any of these processes because of the situation of the OR at a bridgehead. Reactions are very rapid and very efficient with perchloric acid (1%) in acetic acid, giving diketones, etc., although subsequent ring closures occur readily, one of them shown (Figure 11).

Ring closures in the ketonic products of both aldol and Michael types can occur, some aspects of this being discussed in the Literature Cited. One example worth drawing to the attention of terpene chemists is the mode of inducing a very efficient occurrence of a Michael-type ring closure (Figure 12) (Birch and Hill, 1966b). In all such cases the resulting final ring junction is totally cis.

Another interesting example (Figure 13) (Birch *et al.*, 1973) involves a vinylogously activated Me group, where the intermediate diketone cannot be isolated from the acid-catalyzed ring opening since subsequent ring closure proceeds very rapidly. Using appropriate substituents, there are obvious applications in the terpene series.

Several syntheses have been based on this type of Diels–Alder and cleavage process which, in principle, gives a wide range of 4-substituted cyclohexenones.

One is the stereoselective synthesis (Birch *et al.*, 1970) of the insect hormone juvabione, which also leads to an assignment of stereochemistry. An interesting principle is involved in that the mixture of initial adducts obtained can be separated by distillation because of the differences in properties induced by proximities of groups. Their configurations can then be assigned by nmr spectra. This separation contrasts with the almost impossible task of separating by distillation or glc the diastereoisomers of juvabione itself. The process shown in Figure 14, based on the acid-catalyzed ring opening of the mixture of adducts, leads to a very simple nonselective synthesis of a mixture of diastereoisomers of juvabione.

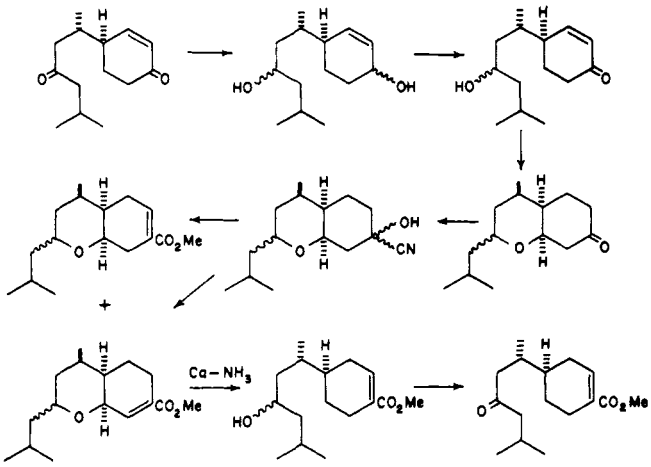

Figure 15. Stereoselective synthesis of juvabione.

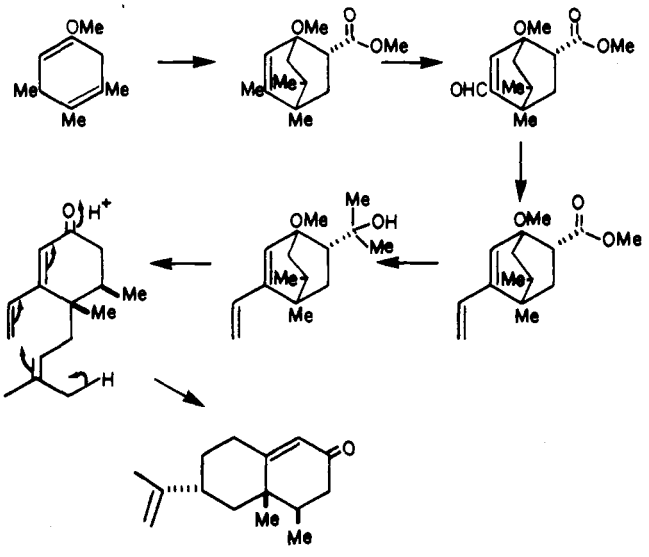

Figure 16. Synthesis of (±)-nootkatone.

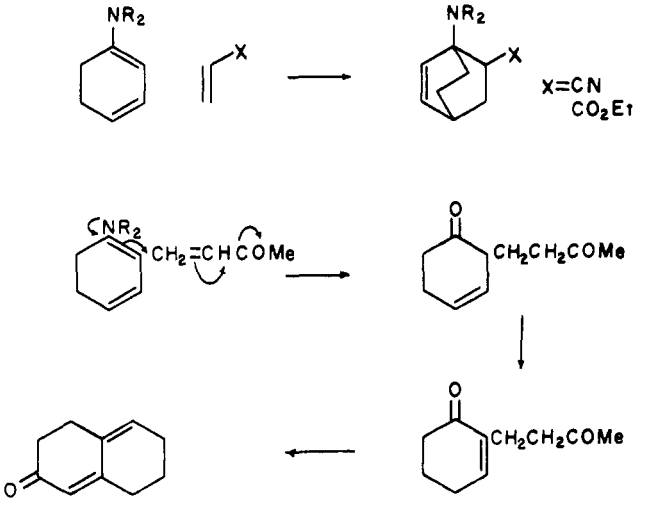

Figure 17. Reactions of cyclohexadienamines.

By separation of the correct adduct and ring opening, the stereoselective synthesis shown in Figure 15 was successfully accomplished. It is not necessary here to discuss the complications, which were needed in order to retain throughout the asymmetry due to the initial cyclohexenone structure, destroyed in the synthesis shown in Figure 14 by hydrogenation.

Another example of a completed synthesis is that of

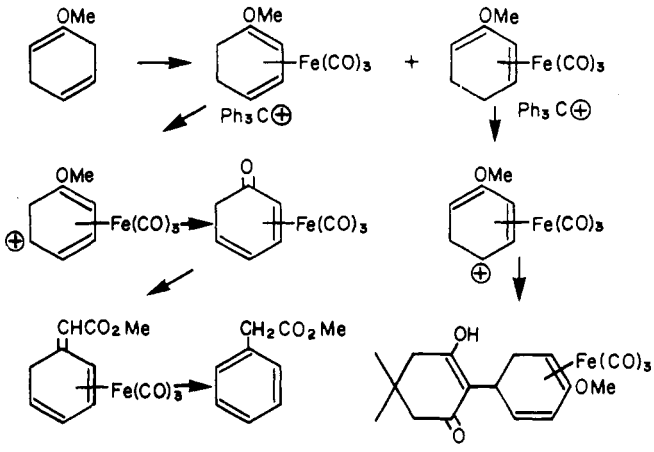

Figure 18. Reactions of cyclohexadiene tricarbonyliron complexes.

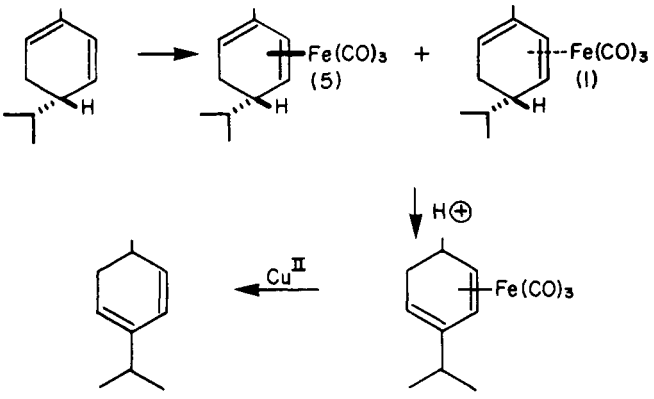

Figure 19. Tricarbonyliron complexes of α-phellandrene.

(±)-nootkatone (see Figure 16) (Birch and Dastur, 1973b). Two major points of interest may be noted. The first is that the stereochemistry of the initial Diels–Alder reaction leads predictably to the correct orientation of the adjacent Me groups, a major problem in synthesis of this ring system. The second is that the oxidation of the vinylic Me with selenium dioxide is efficient and specific because there are no other allylic positions which can be attacked.

With the ready availability of cyclohexadienamines by reduction of aromatic amines (Birch *et al.*, 1971), these interesting compounds, which can react both as dienes and as enamines, merit further consideration in the general area. Some characteristic reactions are shown in Figure 17. They share with other metal–ammonia products the characteristic of a predictable situation of substituents relative to the unsaturated system. This contrasts with mixtures normally obtained from unsymmetrically substituted ketones. Unlike the methoxydienes, however, isomerization during addition reactions is so easy that products do not always represent the starting dienamine, and this aspect requires further investigation. By the use of dimethyl acetylenedicarboxylate, a number of substituted and unsaturated cyclooctane derivatives can be obtained (Birch and Hutchinson, 1971).

A final topic I wish to note, although it is too large to discuss in detail, is that of tricarbonyliron complexes of cyclohexadienes, obtainable by reaction of the 1,4- or the 1,3-dienes with iron carbonyls. From the synthetic viewpoint, the usefulness is that certain functionalized and reactive intermediates can be obtained which undergo reactions not possible in uncomplexed compounds. In particular, stable carbonium salts can be obtained in different ways (Birch and Haas, 1971; Birch *et al.*, 1968) which undergo reactions with nucleophilic reagents. One reaction,

of many of this type, is shown in Figure 18. The reactions can also lead to completely stereospecific introduction of deuterium into "allylic" and other positions (Birch and Thompson, 1973). This could be useful for introducing labeling which is stereospecifically needed in a terpene derivative.

To close on a completely terpenoid note, α-phellandrene, which is the first natural substance I ever examined (Birch, 1937), produces the two stereosiomeric complexes, which are shown in Figure 19 (Birch and Thompson, 1973), without racemization. The action of acid, as in all such cases, results in equilibration to the thermodynamically more stable isomer, in this instance with a 2-isopropyl group. Removal of iron by the use of cupric chloride (Birch and Chauncy, 1973) regenerates α-phellandrene or leads to the new diene shown from the appropriate complex.

Since only cisoid dienes can complex with $Fe(CO)_3$, and since double bond migrations occur during complexing, the process offers opportunities to obtain finally thermodynamically less stable from the more stable transoid diene structures.

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Model Studies in Terpene Biosynthesis

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The carbonium ion rearrangements which are thought to lead from the cyclopropylcarbinyl pyrophosphates, presqualene and prephytoene pyrophosphate, to head-to-head terpenes are discussed. Ten carbon model compounds were used for solvolysis studies. Hydrolysis of *N*-methyl-4-(chrysanthemyloxy)pyridinium iodide gave artemisia triene, santolina triene, yomogi alcohol, santolina alcohol, artemisia alcohol, chrysanthemol, *trans*-2,7-dimethyl-3,6-octadien-2-ol, 2,7-dimethyl-2,6-octadien-4-ol, and *trans*-2,7-dimethyl-4,5-octadien-2-ol. Hydrolysis of *trans*-2,2-dimethyl-3-(2′-methylpropenyl)cyclobutyl tosylate and 2-[*trans*-2′-(2″-methylpropenyl)cyclopropyl]propan-2-yl *p*-nitrobenzoate gave 2-[*trans*-2′-(2″-methylpropenyl)cyclopropyl]propan-2-ol, *trans*-2,7-dimethyl-3,6-octadien-2-ol, and 2,7-dimethyl-2,6-octadien-4-ol. The properties of the carbonium ion intermediates are discussed in terms of product and stereochemical studies. Biosynthesis of head-to head terpenes is compared to the chemical results and a biosynthetic mechanism is proposed.

It is a pleasure for me to participate in this symposium as a way to express my gratitude to Bill Dauben as a colleague and a teacher. I am sure that all of you know that his scientific contributions span a wide range of chemical problems. Inevitably all of his students are exposed in depth to topics in such seemingly diverse areas as natural products, synthesis, carbonium ions, and photochemistry. This was a valuable experience for which I am particularly grateful.

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I would like to discuss the biosynthesis of a special class of terpenes—those in which two regular head-to-tail fragments have been joined by a head-to-head coupling. One example of a compound in this family is squalene, a C_{30} intermediate in the biosynthetic pathway to sterols, and another is phytoene, a C_{40} compound which has been implicated in biosynthesis of carotenoids. The symmetry of both molecules suggests that they were formed by joining two identical terpenoid units. These observations have been verified in experiments which clearly indicate that biosyntheses of squalene[1] and phytoene[2] require the coupling of two molecules of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, respectively.