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The Birch reduction in organic synthesis

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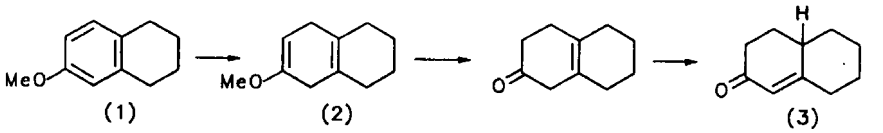
Abstract: The unique availability of substituted cyclohexa-1,4-and 1,3-dienes notably enol ethers, from Birch reduction of benzenes, permits many novel synthetic reactions of general utitility. Some principles are discussed.

The Birch Reduction has greatly increased the utility of benzenoid compounds in alicyclic synthesis[1]. It has had a less profound effect on heterocyclic synthesis[2]. It provides steric control in many situations. It is one of the most highly used[1,2] synthetic reactions in organic chemistry.

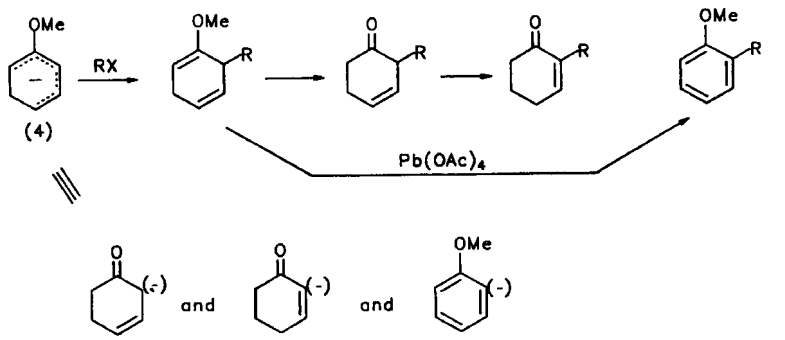
It was designed to make 19-norsteroid hormones[3]. The model reactions were carried out in 1943 using the A-B ring-structure of estrone methyl ether (1) converted via the dihydro- enol-ether (2) into the 19-nor A-B ring-structure (3) containing a cyclohexenone characteristic of most of the structure-specific sex hormones. This resulted in 1950 in the first totally synthetic androgenic anabolic sex hormone 19-nortestosterone[3]. This success led on to the 19-norprogestagens including the first oral contraceptives. It was initially the only process available to make them, and without it their advent would certainly have been greatly delayed.

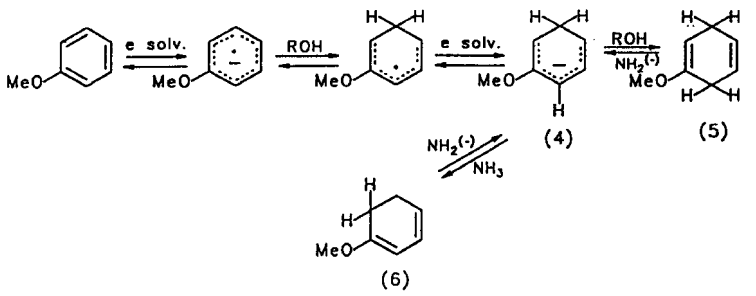


(1) (2) (3)

The basis of synthetic applicability is the availability for the first time of partially hydrogenated benzene derivatives, containing reactive double bonds regiospecifically oriented to substitution. In particular, it provides a wide series of enol-ethers in cyclohexadienes and cyclohexenes, formerly not available. Reductive alkylation provides another novel series..

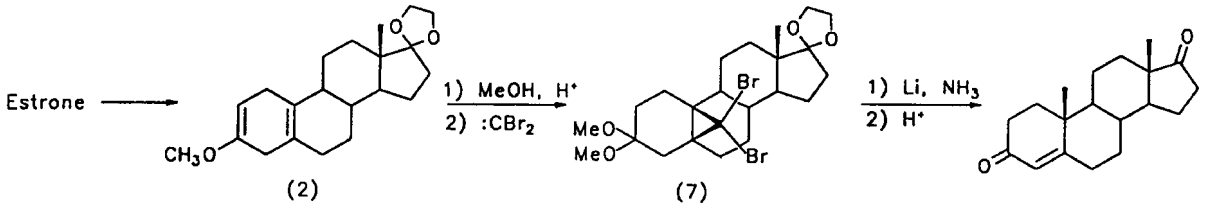
A range of experimental conditions can be set up[4], requiring careful choice for a specific purpose, based on theoretical understandings of the sequence of transformations. These include rates of reductions, double-bond conjugations and reactions of mesomeric anions. I developed this theory, including aspects of the addition of electrons to benzenoid compounds and the positions of reaction, especially with protons, of substituted radical-anions and mesomeric anions, e.g.[1,5] The need to explain why an unconjugated dihydrobenzene results, with the bonds regiospecifically oriented to various substituents, led me to distinguish for the first time in 1947, between the products of a reaction rate (kinetic)(5) and an equilibrium position (thermodynamic)(6)[6] involving the mesomeric anions(4). This distinction proved very general and led me in 1948 to the first calculated deconjugations of α,β-unsaturated ketones for synthetic purposes, like the total synthesis of the cholesterol ring-AB substitution pattern[7](7). The theories contributed to the general picture of reductions by dissolving metals: electron-addition equilibria and the influence of specific protonating agents on the nature of products. Equilibria and transformations could be produced through such anions, which included the ability, for the first time, to convert the "stable" conjugated diene(6) into the thermodynamically "less stable" unconjugated diene(5)[1,6]



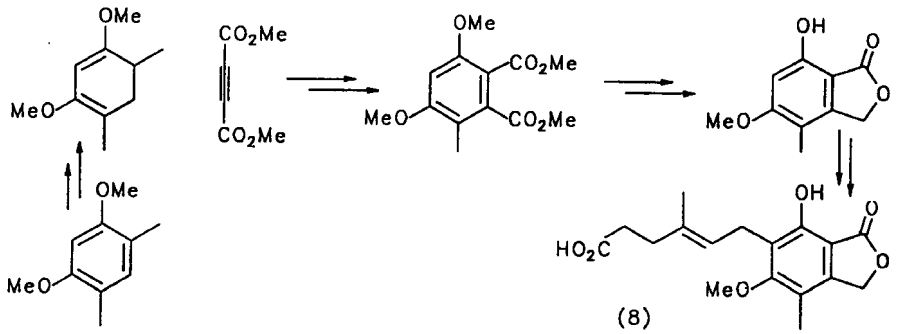


The positions of 2H additions on a monobenzene ring relative to substituents can now be predicted[1] (i.e. the double bond positions in the resulting products). The two double bonds can be reacted separately with other reagents, directly or indirectly. An important indirect method is to "cover-up" an enol-ether as a ketal, leaving only one C=C. An example of use is the simplest, stereospecific, total synthesis of non-aromatic steroids, by addition of dibromo-carbene to a 5(10) steroid double bond, as shown via (7), and subsequent highly efficient simple manipulations[8].

The mesomeric carbanion (4) can not only act as a "turntable" but can be reacted with electrophilic reagents, e.g. alkyl halides as shown[1].



We found that catalysts, like dicholoromaleic anhydride (charge-transfer)could bring about conjugation, notably *in situ* under neutral conditions during Diels-Alder reactions, permitting direct use of the unconjugated precursor with complete overall conversion. These Diels-Alder reactions proved especially important using the 1-methoxy dienes. The "lateral" approach of the diene and dienophile gives e.g.8, of predictable steric configuration in the products. This synthetic approach can generate one centre of a "difficult" configuration, because it is formed as one of a pair with overall control by two centres. With cyclic dienes the Diels Alder reaction results in production of two new C-C results in a bridged ring. To convert into non-bridged rings, there must be broken either two C-C (as in the Alder-Rickert reaction, to generate a new aromatic ring[9]) or one C-C. The first process is unique in synthetic consequences, because the adjustable substitution patterns of the dienes (eg. 1,3-OMe or Me) makes possible syntheses of many natural polyketide aromatic substitution patterns not obtainable by aromatic "substitution" reactions. We thus, for example, synthesised[10] our pharmacologically important mould product mycophenolic acid (8). Subba Rao e.g.[11] has provided many other examples of this use.



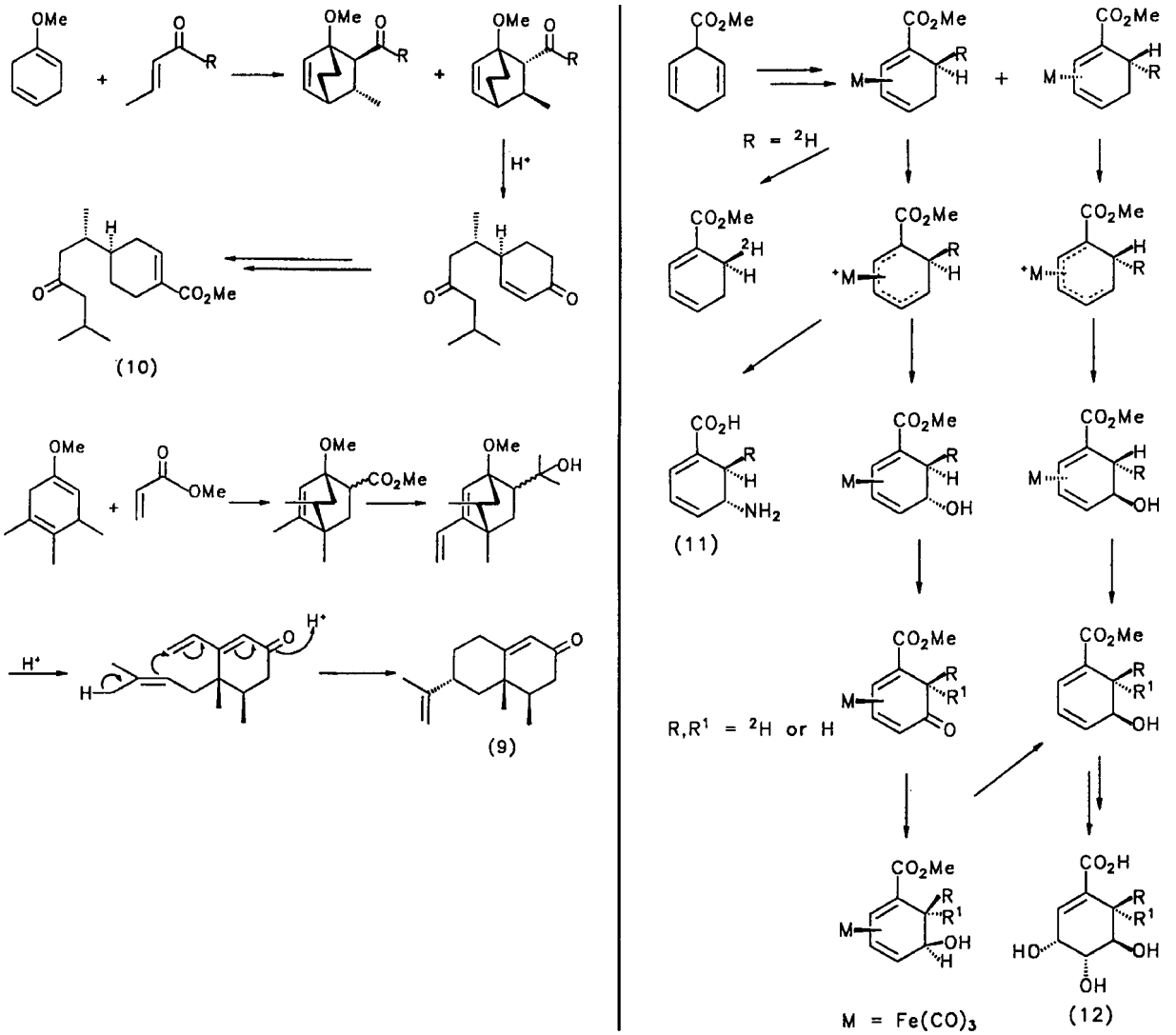
To break open a ring, fission of one C-C is made possible by a bridge-head OR in adducts from a 1-OR diene. The simplest method is by an acid-catalysed "retro-aldol" reaction, which, we discovered[12] rather than predicted as we did with our other reactions. Knowing its occurrence we could devise many syntheses. Subba Rao has shown e.g.[13] that it can provide the basis of other valuable transformations. I give two of our own examples here: nootkatone(9) and juvabione (10).

The steric problem with the former is the compressed orientation of two Me. If one Me is in a precursor, introduction of the second is in the unwanted (less compressed) orientation. An appropriate Diels-Alder reaction, however, leads through lateral control to an intermediate from which the synthesis can be completed[14].

A different type of case is the insect hormones juvabione (10). Here, the existence of a "floppy" side chain with an unsymmetrical ring makes very little physical difference between diastereoisomers so that their separation is a problem. In an intermediate bridged-ring Diels- Alder adduct, groups are forced together to produce different physical properties and separation of the diastereoisomers is possible[15]. Thus we devised a "stereoselective" synthesis. Many other species I cannot discuss. One is the simplest synthesis of many substituted tropones and cyclooctanones.

Another major novel field at which I can only glance I have styled 'inorganic enzyme chemistry'[16,17]. Notionally it has the "ideas" by which enzymes work, but not the methods employed. The approach assembles, activates and controls stereospecificity and enantiospecificity(100.00%). The organometallic complexes, mainly of $Fe(CO)_3$ exhibit unique capabilities in stoichiometric synthesis. The complexed metal sits over a ring-face which it totally distinguishes from the opposite one not only sterically but in reactivity. According to the mechanism, reaction can occur on carbon of the complexed cyclohexadiene either on the occupied face(proton, deuteron introduction, Friedel Crafts reaction) or on the opposite face, e.g. a nucleophile on a carbon of a complexed cation. The *d*-orbitals of Fe can activate on demand for either electrophilic or nucleophilic reactions. Any unsymmetrical diene(eg 1-OMe-) when complexed becomes chiral and the complex can be resolved. If this chiral complex is used in reactions it generates a new asymmetric centre on carbon of known absolute configuration.

I quote related examples: gabaculine[18](11) and shikimic acid[19](12), both derivable from the cation(13) [M=$Fe(CO)_3$]. The efficient generation of gabaculine(11), otherwise difficult of access, also defined the previously unknown absolute configuration. The shikimic acid case is more interesting, in



principle, using the symmetry control properties of the M group adduct. Although optical resolution is required, both enantiomers can be converted into either of the enantiomers of shikimic acid (that is a complete enantiomeric conversion can be carried out). Incorporation of ^{2}H can be carried out regio-and enantio-specifically in both cases directed by M on to the same face, also possible with gabaculine. Such enantiomeric introduction of ^{2}H or ^{3}H normally requires enzymic control, hence my nomenclature. To resemble even more closely the capabilities of enzymes, asymmetric generation rather than resolution is needed. Using 16-dehydropregnenolone acetate as catalyst, this has been achieved although with only 40% e.e.

Other metals used like Cr exert a different type of effect on the organic system due to the conformation of the complexed metals groups.

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